Journal of Clinical Question

Decision Letter (JCQ-2026-0020)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0020

Body: 10-Jun-2026

Dear Dr Chin:

Manuscript ID JCQ-2026-0020 entitled "KRAS-Targeted Therapy in Non–Small Cell Lung Cancer: Current Standards, Resistance Mechanisms, and Emerging Therapeutic Strategies" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

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Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author
The manuscript addresses an important and clinically relevant topic. However, I believe that several important findings from the literature are not sufficiently reflected in the discussion and interpretation of the available evidence, particularly with regard to sotorasib.

First, the discussion of overall survival could be strengthened by incorporating recent real-world evidence comparing sotorasib with docetaxel in previously treated KRAS G12C-mutated NSCLC.

Karim et al. (2026), using data from the UK Cancer Drugs Fund early access program, reported a significant reduction in mortality for patients receiving sotorasib compared with docetaxel in the second-line and beyond setting (hazard ratio [HR] 0.633; 95% CI 0.536–0.749; P < 0.001). Similarly, Johnson et al. (2024), using the US Flatiron database, reported a mortality HR of 0.62 (95% CI 0.41–0.93) in the second-line setting and 0.65 (95% CI 0.49–0.87) in the second-line and beyond population.

I believe these studies warrant discussion within the manuscript. Importantly, the observed survival benefit is not inconsistent with findings that can be derived from CodeBreaK 200: Substantial crossover occurred in the trial, with 59 patients in the docetaxel arm subsequently receiving sotorasib (46 through protocol-defined crossover and 13 through commercial access; de Langen et al., 2023, page 6, left column). Furthermore, Supplementary Table S5 shows that sotorasib reduced the risk of progression-free survival events by 34% compared with docetaxel (HR 0.66), while fatal progression-free survival events occurred less frequently in the sotorasib arm than in the docetaxel arm (22/144 (15.3%) vs 33/134 (24.6%) events). I think the manuscript would benefit from incorporating this evidence, as it refelects the current knowledge on the ability of sotorasib to reduce mortality.

Second, the manuscript does not discuss the patient-reported outcomes from CodeBreaK 200, which are highly relevant when evaluating the overall clinical value of treatment options in this setting.

Waterhouse et al. (2024) reported that patients treated with sotorasib experienced substantially lower treatment burden than those receiving docetaxel. Patients receiving sotorasib were significantly less bothered by treatment-related side effects (odds ratio [OR] 5.7) and experienced lower symptom severity across multiple domains, including pain (OR 2.9), aching muscles (OR 4.4), aching joints (OR 4.2), and mouth or throat sores (OR 4.3). Overall, sotorasib maintained quality of life while improving clinical efficacy outcomes relative to docetaxel. These findings represent an important component of the benefit-risk assessment and deserve consideration in the discussion.

Third, the manuscript would benefit from a more comprehensive review of the comparative evidence between sotorasib and adagrasib. The currently available evidence suggests broadly similar efficacy between the two KRAS G12C inhibitors, while several analyses indicate a more favorable safety profile for sotorasib.

For example, Chopra et al. (2025), using a matching-adjusted indirect comparison methodology, reported comparable efficacy outcomes between the two agents but a more favorable safety profile for sotorasib. These findings are broadly consistent with other emerging comparative datasets, including the real-world analysis presented by Barsouk et al. (2026). Given the clinical importance of treatment tolerability in this population, I believe that the safety differences reported across studies deserve mention.

Finally, the discussion regarding patients with brain metastases could be expanded. Although adagrasib has often been preferentially used in patients with CNS involvement, the totality of currently available evidence does not demonstrate a clear efficacy advantage over sotorasib in this subgroup.

In the matching-adjusted indirect comparison by Chopra et al. (2025), no statistically significant efficacy differences were observed between the two agents. Likewise, the real-world analysis reported by Barsouk et al. (2026) does not provide evidence of superior outcomes with adagrasib despite its more frequent use among patients with brain metastases. Overall, the currently available evidence suggests similar efficacy between the two agents in this population, with point estimates generally favoring sotorasib.

In summary, I believe that the manuscript would be strengthened by incorporating these additional data sources and by providing a more comprehensive discussion of the available evidence regarding overall survival, patient-reported outcomes, safety, and comparative effectiveness of sotorasib and adagrasib. Such additions would help ensure that readers receive a balanced overview of the current evidence base and its implications for clinical practice.

Karim N, et al. Real-world comparative effectiveness of sotorasib versus docetaxel monotherapy in second line and beyond for advanced or metastatic non-small cell lung cancer: A national database analysis from England. Lung Cancer. 2026 May 28;217:109469. doi: 10.1016/j.lungcan.2026.109469. Epub ahead of print. PMID: 42229337.

References :

Johnson M, et al. Real-world comparative effectiveness of sotorasib versus docetaxel in second line and beyond among patients with advanced non-small cell lung cancer (NSCLC). Lung Cancer. 2024 Nov;197:107960. doi: 10.1016/j.lungcan.2024.107960. Epub 2024 Sep 19. Erratum in: Lung Cancer. 2025 Mar;201:108440. doi: 10.1016/j.lungcan.2025.108440. PMID: 39369609.

Waterhouse DM, et al. Patient-reported outcomes in CodeBreaK 200: Sotorasib versus docetaxel for previously treated advanced NSCLC with KRAS G12C mutation. Lung Cancer. 2024 Oct;196:107921. doi:

10.1016/j.lungcan.2024.107921. Epub 2024 Aug 6. PMID: 39303400.

Chopra D, et al. Matching-Adjusted Indirect Comparison of Sotorasib Versus Adagrasib in Previously Treated Advanced/Metastatic Non-Small Cell Lung Cancer Harboring KRAS G12C Mutation. Adv Ther. 2025 Sep;42(9):4300-4317. doi: 10.1007/s12325-025-03259-8. Epub 2025 Jun 21. PMID: 40542959; PMCID: PMC12394275.

Barsouk A, Yaskolko M, Sussman JH, Sun L, Cohen RB, Aggarwal C, Langer CJ, Marmarelis ME. Sotorasib vs adagrasib in the 2L+ setting: Outcomes in a large, multi-institutional, real-world database of KRAS-G12C mutated mNSCLC. Journal of Clinical Oncology. 2026;44(16_suppl):8608. Presented at the 2026 ASCO Annual Meeting.

Reviewer: 2

Comments to the Author
A very well-written manuscript; however, there are shortcomings. The KRAS field is rapidly evolving, and the information delivered is clearly "obsolete." Secondly, bear in mind that there are also paramount relevant reviews on the subject:
1. Riedl et al. Emerging landscape of KRAS inhibitors in cancer treatment. Cancer Cell, March 9, 2026.
2. Bright et al. Response and resistance to RAS inhibition in cancer. Cancer Discovery 2025.
3. Riedl et al. Genomic landscape of clinically acquired resistance alterations in patients treated with KRASG12C inhibitors. Ann Oncol 2025.
4. Perurena et al. Combinatorial strategies to target RAS-driven cancers. Nature Reviews Cancer 2024.
5. Tanaka and Ebi. Mechanisms of resistance to KRAS inhibitors: cancer cell's strategic use of normal cellular mechanisms to adapt. Cancer Science 2024.
6. Molina-Arcas-Downward. Exploiting the therapeutic implications of KRAS inhibition on tumor immunity. Cancer Cell 2024.
Update the information; also look at the ASCO 2026 presentations. Several oral KRASG12D and pan-RAS(ON) inhibitor communications were presented at ASCO in June 2026. See O'Reilly et al. on daraxonrasib. N Engl J Med 2026; combination of eliromrasib plus daraxonrasib in Wei et al. Cancer Discovery 2026. See Alonso et al. Cancer Cell 2026, etc.
Novel KRASG12D inhibitors were presented at ASCO, such as RNK08954 and GFH375. See an article on RNK08954 in Cancer Discovery, May 2026.
MRTX1135 development has been interrupted by BMS, as described in the Cancer Discovery article. It also contains relevant information with regard to Revolution Medicine's KRASG12D inhibitor and GFH375, and immune response in the Discussion on RNK08954.
The older KRAS G12C inhibitors (sotorasib, adagrasib) will become "offshore," overcome by more efficient agents already in phase 1, 2, and 3 trials.
In the text, please include the name of fulzerasib, approved in China in 2024. Please keep in consideration that the KROCUS study of fulzerasib plus cetuximab was published in April. Gregorc et al. Lancet Oncology 2026.

Date Sent: 10-Jun-2026

Author's Response to Decision Letter for (JCQ-2026-0020)

KRAS-Targeted Therapy in Non–Small Cell Lung Cancer: Current Standards, Resistance Mechanisms, and Emerging Therapeutic Strategies

Dear Editor and Reviewers,
We sincerely thank you for the careful evaluation of our manuscript and for the constructive comments. We have revised the manuscript thoroughly in response to the reviewers' suggestions and believe that these revisions have improved the methodological clarity, clinical interpretation, and overall presentation of the work. A detailed point-by-point response is provided below, with all changes incorporated into the revised manuscript.

Reviewer: 1
Comment 1
First, the discussion of overall survival could be strengthened by incorporating recent real-world evidence comparing sotorasib with docetaxel in previously treated KRAS G12C-mutated NSCLC.Karim et al. (2026), using data from the UK Cancer Drugs Fund early access program, reported a significant reduction in mortality for patients receiving sotorasib compared with docetaxel in the second-line and beyond setting (hazard ratio [HR] 0.633; 95% CI 0.536–0.749; P < 0.001). Similarly, Johnson et al. (2024), using the US Flatiron database, reported a mortality HR of 0.62 (95% CI 0.41–0.93) in the second-line setting and 0.65 (95% CI 0.49–0.87) in the second-line and beyond population.
I believe these studies warrant discussion within the manuscript. Importantly, the observed survival benefit is not inconsistent with findings that can be derived from CodeBreaK 200: Substantial crossover occurred in the trial, with 59 patients in the docetaxel arm subsequently receiving sotorasib (46 through protocol-defined crossover and 13 through commercial access; de Langen et al., 2023, page 6, left column). Furthermore, Supplementary Table S5 shows that sotorasib reduced the risk of progression-free survival events by 34% compared with docetaxel (HR 0.66), while fatal progression-free survival events occurred less frequently in the sotorasib arm than in the docetaxel arm (22/144 (15.3%) vs 33/134 (24.6%) events). I think the manuscript would benefit from incorporating this evidence, as it refelects the current knowledge on the ability of sotorasib to reduce mortality.
Response: We thank the reviewer for highlighting the importance of the recent real-world survival analyses. We agree that the overall survival findings from CodeBreaK 200 should be interpreted in the context of the study design and post-progression treatment patterns. Accordingly, we revised the discussion to clarify that, although CodeBreaK 200 did not demonstrate a statistically significant overall survival difference in the intention-to-treat analysis, the trial was primarily designed for progression-free survival and substantial crossover from docetaxel to sotorasib occurred. We also retained the randomized PFS benefit and objective response rate advantage of sotorasib over docetaxel.
In addition, we incorporated the recent real-world studies from the United Kingdom Cancer Drugs Fund early-access programme and the US Flatiron database, which reported lower mortality among patients treated with sotorasib than among those treated with docetaxel in previously treated KRAS G12C-mutated NSCLC. We acknowledge in the revised text that residual confounding cannot be excluded in observational analyses; nevertheless, these findings support the clinical relevance of sotorasib in routine practice.
The revised text reads: "Randomized evidence was provided by CodeBreaK 200, in which sotorasib significantly improved PFS versus docetaxel (median, 5.6 vs 4.5 months; HR, 0.66) and achieved a higher ORR (28.1% vs 13.2%).35 Although no statistically significant OS difference was observed in the intention-to-treat analysis, this finding should be interpreted cautiously because the trial was designed primarily for PFS and substantial crossover to sotorasib occurred in the docetaxel group. Consistent with the randomized PFS benefit, recent real-world studies from the United Kingdom and the United States reported lower mortality among patients treated with sotorasib than with docetaxel.36,37 While residual confounding cannot be excluded, these findings support the clinical relevance of sotorasib in routine practice."

Comment 2
Second, the manuscript does not discuss the patient-reported outcomes from CodeBreaK 200, which are highly relevant when evaluating the overall clinical value of treatment options in this setting. Waterhouse et al. (2024) reported that patients treated with sotorasib experienced substantially lower treatment burden than those receiving docetaxel. Patients receiving sotorasib were significantly less bothered by treatment-related side effects (odds ratio [OR] 5.7) and experienced lower symptom severity across multiple domains, including pain (OR 2.9), aching muscles (OR 4.4), aching joints (OR 4.2), and mouth or throat sores (OR 4.3). Overall, sotorasib maintained quality of life while improving clinical efficacy outcomes relative to docetaxel. These findings represent an important component of the benefit-risk assessment and deserve consideration in the discussion.
Response: We agree that patient-reported outcomes are an important component of the overall benefit-risk assessment, particularly when comparing an oral targeted therapy with docetaxel in the post-platinum setting. We have therefore added the CodeBreaK 200 patient-reported outcome findings to the revised discussion.

The manuscript now states: “Patient-reported outcomes from CodeBreaK 200 also favored sotorasib, with lower treatment burden and less symptom worsening than docetaxel while maintaining overall quality of life.35 These findings strengthen the overall benefit-risk profile of sotorasib in the post-platinum setting.”

Comment 3
Third, the manuscript would benefit from a more comprehensive review of the comparative evidence between sotorasib and adagrasib. The currently available evidence suggests broadly similar efficacy between the two KRAS G12C inhibitors, while several analyses indicate a more favorable safety profile for sotorasib. For example, Chopra et al. (2025), using a matching-adjusted indirect comparison methodology, reported comparable efficacy outcomes between the two agents but a more favorable safety profile for sotorasib. These findings are broadly consistent with other emerging comparative datasets, including the real-world analysis presented by Barsouk et al. (2026). Given the clinical importance of treatment tolerability in this population, I believe that the safety differences reported across studies deserve mention.
Response: We appreciate this important suggestion. We have expanded the discussion to address the absence of direct randomized comparisons and to summarize the available indirect and real-world comparative evidence. The revised text acknowledges that efficacy appears broadly similar between sotorasib and adagrasib, whereas available comparative analyses suggest that sotorasib may have a more favorable tolerability profile, including fewer treatment-related adverse events and treatment modifications.
The revised text reads: “No randomized trial has directly compared sotorasib with adagrasib. Available indirect and real-world analyses suggest broadly similar efficacy, whereas sotorasib may have a more favorable tolerability profile, including fewer treatment-related adverse events and treatment modifications.38,39”

Comment 4
Finally, the discussion regarding patients with brain metastases could be expanded. Although adagrasib has often been preferentially used in patients with CNS involvement, the totality of currently available evidence does not demonstrate a clear efficacy advantage over sotorasib in this subgroup. In the matching-adjusted indirect comparison by Chopra et al. (2025), no statistically significant efficacy differences were observed between the two agents. Likewise, the real-world analysis reported by Barsouk et al. (2026) does not provide evidence of superior outcomes with adagrasib despite its more frequent use among patients with brain metastases. Overall, the currently available evidence suggests similar efficacy between the two agents in this population, with point estimates generally favoring sotorasib.
Response: We agree that the discussion of CNS involvement required further clarification. We have revised the manuscript to acknowledge the documented intracranial activity of adagrasib while avoiding the implication that this establishes comparative superiority over sotorasib. The revised discussion states: “Although adagrasib has demonstrated intracranial activity, current comparative evidence does not establish superior efficacy over sotorasib in patients with brain metastases.38,40 Treatment selection should therefore consider CNS disease status, expected toxicity, comorbidities, prior therapy, and drug availability.”
Reviewer: 2
Comment 1
Update the information; also look at the ASCO 2026 presentations. Several oral KRASG12D and pan-RAS(ON) inhibitor communications were presented at ASCO in June 2026. See O’Reilly et al. on daraxonrasib. N Engl J Med 2026; combination of eliromrasib plus daraxonrasib in Wei et al. Cancer Discovery 2026. See Alonso et al. Cancer Cell 2026, etc.
Response: We thank the reviewer for this important recommendation. We comprehensively updated the literature and conference evidence through June 2026 and expanded the discussion of emerging oral KRAS G12D- and pan-RAS(ON)-directed therapies. We note that the report by O’Reilly et al. in The New England Journal of Medicine evaluated daraxonrasib in metastatic pancreatic ductal adenocarcinoma, and the study by Alonso et al. in Cancer Cell addressed KRAS-targeted therapeutic strategies and resistance mechanisms in colorectal cancer. Because these studies were not conducted in NSCLC, they were not incorporated as direct clinical evidence for NSCLC treatment efficacy in the present review.
However, we added the study by Wei et al. in Cancer Discovery, which evaluated the combination of elironrasib plus daraxonrasib. This work provides preclinical evidence that dual RAS(ON) inhibition may achieve deeper and more durable suppression of oncogenic RAS signalling than either agent alone and may enhance antitumour immune activity. We have therefore included this study as mechanistic and translational rationale for future combination strategies, while clearly stating that clinical efficacy data for this combination in NSCLC are not yet available.

Comment 2
Novel KRASG12D inhibitors were presented at ASCO, such as RNK08954 and GFH375. See an article on RNK08954 in Cancer Discovery, May 2026.
Response: We appreciate this suggestion and have expanded the section on emerging KRAS G12D inhibitors. The revised manuscript now includes RNK08954 and GFH375, together with zoldonrasib and setidegrasib, as representative next-generation approaches targeting KRAS G12D. For RNK08954, we incorporated both the phase Ia Cancer Discovery report and the subsequent ASCO 2026 NSCLC update. The revised text describes its selective oral KRAS G12D-inhibitory mechanism, the early phase Ia activity signal, and the updated NSCLC cohort, in which the ORR was 38.5% and the DCR was 94.9%; median duration of response was not reached, whereas PFS data remained immature. For GFH375, we added the available early-phase NSCLC data to the clinical-evidence table and narrative discussion. We also reviewed the ASCO 2026 abstract, which reported additional activity in cholangiocarcinoma and colorectal cancer. Because the latter presentation did not report an NSCLC cohort, these data were not incorporated into the NSCLC efficacy table but are acknowledged as supporting the broader clinical development of this KRAS

G12D inhibitor.

Comment 3
MRTX1135 development has been interrupted by BMS, as described in the Cancer Discovery article. It also contains relevant information with regard to Revolution Medicine's KRASG12D inhibitor and GFH375, and immune response in the Discussion on RNK08954.
Response: We thank the reviewer for this helpful comment. We expanded the discussion of emerging KRAS G12D-directed and RAS(ON)-targeted therapies by incorporating available evidence on the Revolution Medicines development platform, including zoldonrasib and daraxonrasib, as well as early clinical data for GFH375. We also added discussion of the RNK08954 phase Ia report in Cancer Discovery, including its preclinical findings suggesting modulation of the tumour immune microenvironment and enhanced antitumour immune activity. These immunological observations are presented as hypothesis-generating translational findings that require further clinical validation. Because the discontinued Mirati/BMS KRAS G12D program was not previously included in our manuscript, we did not add a separate detailed discussion of this agent. Instead, the revised section focuses on actively developing KRAS G12D inhibitors and emerging RAS(ON)-directed strategies with currently available clinical or translational evidence.

Comment 4
The older KRAS G12C inhibitors (sotorasib, adagrasib) will become "offshore," overcome by more efficient agents already in phase 1, 2, and 3 trials.
Response : We agree that the therapeutic landscape is evolving rapidly, with multiple mutant-selective, protein-degrading, and RAS(ON)-directed agents now in phase I–III development. We therefore revised the conclusion to emphasize that sotorasib and adagrasib represent the first generation of clinically established KRAS G12C inhibitors and that newer agents may potentially improve the depth, durability, tolerability, or breadth of RAS inhibition.
However, we did not state that sotorasib and adagrasib have become obsolete or have already been surpassed. At present, the newer agents remain predominantly supported by early-phase, single-arm data, and no direct randomized evidence has established superiority over approved KRAS G12C inhibitors. The revised text therefore adopts a balanced position: sotorasib and adagrasib remain clinically relevant options, while next-generation KRAS G12C, KRAS G12D, and pan-RAS(ON) approaches may reshape treatment algorithms as comparative efficacy, long-term safety, and resistance data mature.

Comment 5
In the text, please include the name of fulzerasib, approved in China in 2024. Please keep in consideration that the KROCUS study of fulzerasib plus cetuximab was published in April. Gregorc et al. Lancet Oncology 2026.
Response: We thank the reviewer for this valuable suggestion. We added fulzerasib, also known as GFH925 or IBI351, to the KRAS G12C inhibitor section. The revised manuscript now states that fulzerasib is an orally administered, covalent, irreversible KRAS G12C inhibitor that received conditional approval from the National Medical Products Administration of China in August 2024 for adults with advanced KRAS G12C-mutated NSCLC after at least one prior systemic therapy.
We also added the pivotal phase II monotherapy data and included the KROCUS study by Gregorc et al. in The Lancet Oncology. The revised text describes the first-line fulzerasib-plus-cetuximab regimen and reports the confirmed ORR of 69%, DCR of 100%, and median PFS of 12.5 months. We further clarify that KROCUS was a single-arm phase Ib/II study and that randomized confirmation is required before this chemotherapy-free approach can be compared with established first-line regimens.

We thank the reviewer again for these highly valuable comments. The revised manuscript now provides a more current, balanced, and clinically relevant overview of the rapidly evolving KRAS therapeutic landscape.

Best Regards
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