Decision Letter (JCQ-2025-0024)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0024

Body: 12-Aug-2025

Dear Dr Tang:

Manuscript ID JCQ-2025-0024 entitled "Emerging Frontiers in the Treatment of Non-small Cell Lung Cancer: Innovations and Clinical Advances" 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 minor 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.
1. Access to https://mc.manuscriptcentral.com/jcq and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
3. Click "Manuscripts with Decisions" on Author Dashboard page.
4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

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).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

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 Isaacs
Editor in Chief,
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
1. Check grammar and flow for minor errors.
2. Ensure all abbreviations are defined on first use in both abstract and main text.
3. Add ORCID IDs for authors if available

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
This is a well-written, timely, and comprehensive review of recent advances in NSCLC treatment, particularly in immunotherapy, targeted therapies, and emerging cytotoxic strategies. It effectively summarizes key clinical trials and FDA approvals up to 2025, making it highly relevant for both clinicians and researchers. However, several areas could be improved to enhance clarity, cohesion, and readability:
Abstract
The abstract is dense and focuses heavily on summarizing therapeutic advances. Consider explicitly framing why this review is needed, highlighting the unmet clinical needs or controversies that justify its importance.
Data Presentation and Synthesis
Some sections are overloaded with trial data but lack integrative insights.
In the targeted therapy section, numerous trials are presented consecutively without connecting overarching themes or implications.
In the immunotherapy combinations section, several regimens are discussed, but the sequencing rationale and patient selection strategies could be clarified to guide clinical decision-making.
Emerging Agents
While agents such as telisotuzumab vedotin, plinabulin, and bispecific antibodies are mentioned, the discussion would benefit from:
Mechanistic context — briefly explain why these agents are promising in NSCLC.
Developmental stage — specify whether these are in Phase II, Phase III, or nearing regulatory submission to help readers gauge their maturity.

Reviewer: 2

Comments to the Author
The manuscript “Emerging Frontiers in the Treatment of Non-Small Cell Lung Cancer: Innovations and Clinical Advances” provides a comprehensive review of recent advances in NSCLC management, highlighting the continued role of platinum-based chemotherapy alongside breakthroughs in immunotherapy, targeted therapies, and novel agents. It discusses the impact of immune checkpoint inhibitors, perioperative strategies, and subcutaneous formulations that enhance patient convenience. The review also covers treatments for key oncogenic drivers (e.g., EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, HER2, NTRK) and explores emerging modalities such as antibody-drug conjugates, bispecific antibodies, and precision oncology approaches, emphasizing a shift toward personalized, multimodal care to improve patient outcomes. The manuscript offers significant value to clinicians and researchers by summarizing complex developments in a rapidly evolving field. However, several weaknesses need to be addressed before publication.
Comment 1: The Clinical Question Box contains long and complex sentences that reduce clarity. It should be rewritten and split into 2–3 shorter, concise statements for better readability.
Comment 2: While the manuscript summarizes trial outcomes effectively, it often lacks interpretation of clinical relevance. For example, the sections on subcutaneous immune checkpoint inhibitors and perioperative strategieswould benefit from explaining their practical impact on patient care, treatment adherence, and accessibility.
Comment 3: Figure 1 is referenced but not adequately described in the text, and no summary of its content is provided. Adding a clear legend or a brief discussion of its key points would improve its integration into the narrative.
Comment 4: Certain topics are repeated across multiple sections (e.g., perioperative immunotherapy strategies and CheckMate 816 results), leading to redundancy. Consolidating overlapping discussions would improve the manuscript’s logical flow and reduce reader fatigue.
Comment 5: The Author Contributions statement is vague and contains grammatical errors (e.g., “K.O. and H.K. worked on and revision”). This should be rephrased for clarity. Additionally, minor grammatical issues and overly complex sentences throughout the manuscript affect readability and should be addressed through careful language polishing.

Date Sent: 12-Aug-2025

Author's Response to Decision Letter for (JCQ-2025-0024)

Emerging Frontiers in the Treatment of Non-small Cell Lung Cancer: Innovations and Clinical Advances

Dear Editor and Reviewers,
We sincerely thank you for your valuable time and constructive feedback on our manuscript. We greatly appreciate the thorough evaluation and insightful suggestions, which have significantly improved the quality and clarity of our review. Below, we provide a detailed, point-by-point response to each comment. All suggested changes have been incorporated into the revised manuscript, and line numbers are indicated where applicable.

Editor Comment
1. Check grammar and flow for minor errors.
Response: We appreciate this comment. We have carefully reviewed the manuscript, corrected grammatical errors, and improved sentence flow to enhance readability.
2. Ensure all abbreviations are defined on first use in both abstract and main text.
Response: Thank you for highlighting this. All abbreviations are now defined upon first use in both the abstract and the main text.
3. Add ORCID IDs for authors if available
Response: ORCID identifiers for all authors have been added where available.

Reviewer: 1
Comment1: The abstract is dense and focuses heavily on summarizing therapeutic advances. Consider explicitly framing why this review is needed, highlighting the unmet clinical needs or controversies that justify its importance.
Response: We agree and have revised the abstract accordingly. "Non-small cell lung cancer (NSCLC), which accounts for about 85% of lung cancer cases, remains a leading cause of cancer-related mortality worldwide. Over the past decade, the advent of immunotherapies, targeted agents, and molecularly guided strategies has transformed the therapeutic landscape. However, significant challenges persist: many patients still present with advanced disease, and uncertainties remain regarding treatment sequencing, integration of novel therapies, and management of cases without actionable mutations. This review highlights the evolving role of chemotherapy within the modern multimodal treatment paradigm of NSCLC and underscores its enduring relevance amidst rapid therapeutic innovation. While platinum-based chemotherapy has historically been the cornerstone of treatment, its role is now increasingly dynamic, serving as a critical component of combination regimens alongside immunotherapies and targeted approaches. Advances such as immune checkpoint inhibitors and therapies directed at oncogenic drivers like EGFR, ALK, and ROS1 have significantly improved patient outcomes, yet chemotherapy remains essential, particularly for patients without actionable mutations. Emerging strategies, including perioperative immunotherapy, antibody-drug conjugates, bispecific antibodies, and novel cytotoxic agents, promise to further enhance efficacy. In addition, molecular personalization and the use of circulating tumor DNA are opening new avenues for precision oncology."

Comment 2: Some sections are overloaded with trial data but lack integrative insights. In the targeted therapy section, numerous trials are presented consecutively without connecting overarching themes or implications.
Response: We have reorganized and condensed this section to provide better integration: "Targeted therapy has revolutionized the management of NSCLC by tailoring treatment strategies to specific oncogenic drivers, thereby improving efficacy and reducing unnecessary toxicity. Across multiple genomic alterations, such as EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, NTRK, and HER2, novel inhibitors have consistently demonstrated enhanced progression-free survival, central nervous system penetration, and improved quality of life compared to conventional chemotherapy. While each mutation-driven therapy requires individualized selection based on molecular profiling, several shared principles emerge: early and comprehensive genomic testing is essential, CNS-active agents are increasingly prioritized, and resistance mechanisms frequently necessitate sequential targeted approaches or combination regimens. Furthermore, the expanding role of perioperative and adjuvant targeted therapies underscores a shift toward integrating precision medicine across disease stages. Together, these advancements highlight a unifying paradigm: harnessing molecular insights to deliver personalized, durable, and more effective treatment for patients with NSCLC."

Comment 3:In the immunotherapy combinations section, several regimens are discussed, but the sequencing rationale and patient selection strategies could be clarified to guide clinical decision-making.
Response: We have added a paragraph to improve clinical guidance: "In advanced NSCLC, the choice and sequencing of immunotherapy combinations are increasingly guided by tumor PD-L1 expression, histological subtype, and disease burden. Dual ICI regimens, such as nivolumab plus ipilimumab or

durvalumab plus tremelimumab, are preferred in patients without actionable driver mutations and with adequate performance status, particularly when a durable immune response is prioritized. For tumors with PD-L1 ≥1%, nivolumab–ipilimumab, as supported by CheckMate 227, offers significant long-term survival benefit, whereas for PD-L1 <1%, combinations like CheckMate 9LA or the POSEIDON triplet provide rapid disease control alongside durable responses. Chemo-immunotherapy combinations, such as those from KEYNOTE-189 and KEYNOTE-407, remain the standard backbone for most patients, especially when a quick tumor shrinkage is needed or when PD-L1 expression is low or absent. Sequencing strategies are also evolving: platinum-based chemotherapy may be frontloaded in high-tumor-burden cases to debulk disease before transitioning to ICI-dominant maintenance, while perioperative settings now leverage neoadjuvant chemo-immunotherapy regimens (e.g., CheckMate 816, AEGEAN) to enhance surgical outcomes and reduce relapse risk. This nuanced, biomarker-driven approach enables clinicians to tailor regimens to maximize efficacy while balancing toxicity risks and treatment durability."

Comment 4. While agents such as telisotuzumab vedotin, plinabulin, and bispecific antibodies are mentioned, the discussion would benefit from: Mechanistic context, briefly explain why these agents are promising in NSCLC. Developmental stage, specify whether these are in Phase II, Phase III, or nearing regulatory submission to help readers gauge their maturity.
Response: We appreicate the reviwers comment on this point. Response: We have expanded and reorganized the section:"Telisotuzumab vedotin, an ADC targeting c-Met, a receptor tyrosine kinase overexpressed in non-squamous NSCLC and associated with tumor progression and therapy resistance, has demonstrated promising activity. In the Phase 2 LUMINOSITY study, it showed encouraging efficacy in previously treated advanced NSCLC, achieving an overall response rate (ORR) of 34.6% in patients with high c-Met expression (≥ 50% IHC), with a manageable safety profile.80 By selectively delivering cytotoxic payloads to c-Met–positive cells, it enhances antitumor activity while sparing normal tissues."

Reviewer: 2
Comment 1: The Clinical Question Box contains long and complex sentences that reduce clarity. It should be rewritten and split into 2–3 shorter, concise statements for better readability.
Response: We appreciate this suggestion. Response: The Clinical Question Box has been rewritten: "Treatment selection for NSCLC is guided by molecular profiling, PD-L1 expression, tumor histology, and patient factors. Targeted therapies are preferred for tumors with actionable mutations like EGFR, ALK, ROS1, BRAF, MET, RET, KRAS G12C, HER2, or NTRK. If no mutations are found, PD-L1 levels guide therapy: ≥50% often leads to immunotherapy alone, while lower levels usually require chemo-immunotherapy. Chemotherapy choices depend on histology, with pemetrexed used for non-squamous tumors and taxanes or gemcitabine for squamous types. Patient fitness, comorbidities, and emerging biomarkers, such as circulating tumor DNA, further personalize treatment."

Comment 2: While the manuscript summarizes trial outcomes effectively, it often lacks interpretation of clinical relevance. For example, the sections on subcutaneous immune checkpoint inhibitors and perioperative strategieswould benefit from explaining their practical impact on patient care, treatment adherence, and accessibility.
Response: We appreicate the reviewer's comment on this point. We have added context on clinical implications: "Beyond clinical equivalence, these SC formulations have important practical implications for patient care. Shorter administration times can enhance treatment adherence by reducing patient burden and improving the overall treatment experience. They also increase accessibility, particularly in resource-limited or high-volume outpatient settings, by optimizing infusion chair turnover and reducing healthcare resource utilization. Moreover, SC delivery may be especially beneficial for patients with limited mobility or those living in remote areas, where minimizing hospital visits can significantly improve quality of life and facilitate continuity of care."

Comment 3: Figure 1 is referenced but not adequately described in the text, and no summary of its content is provided. Adding a clear legend or a brief discussion of its key points would improve its integration into the narrative.
Response: We have added a comprehensive legend and integrated discussion into the text: "Figure 1 summarizes the chronological advances in ICIs for NSCLC from 2015 to 2025. It highlights the progressive introduction of agents such as nivolumab, pembrolizumab, atezolizumab, durvalumab, and cemiplimab across various treatment settings, including first-line, perioperative, adjuvant, and neoadjuvant therapies."

Comment 4: Certain topics are repeated across multiple sections (e.g., perioperative immunotherapy strategies and CheckMate 816 results), leading to redundancy. Consolidating overlapping discussions would improve the manuscript's logical flow and reduce reader fatigue.
Response: We appreicate the reviewer's comment on this point. We have consolidated overlapping discussions to improve flow: "Beyond the established role of immunotherapy in advanced NSCLC, a breakthrough in early-stage disease came with the CheckMate 816 trial. This study evaluated neoadjuvant nivolumab combined with platinum-based chemotherapy before surgical resection. The regimen significantly increased the rate of pathologic complete response (24.0% vs. 2.2%) and improved event-free survival (EFS) (31.6 vs. 20.8 months) compared to chemotherapy alone. These benefits translated into durable survival outcomes, with a 5-year OS advantage presented at ASCO 2025."

Comment 5: The Author Contributions statement is vague and contains grammatical errors (e.g., "K.O. and H.K. worked on and revision"). This should be rephrased for clarity. Additionally, minor grammatical issues and overly complex sentences throughout the manuscript affect readability and should be addressed through careful language polishing.
Response: We appreicate the reviewer's comment on this point. The Author Contributions statement has been rewritten: "M.T. contributed to the study design, literature search, and manuscript drafting. Y.A.,

C.Z., X.Z., and Y.Y. contributed to data analysis and manuscript revision. All authors have read and approved the final manuscript and agree with its content and data.”

We are grateful for the reviewers’ constructive feedback, which has substantially improved the quality of our manuscript. We hope the revised version meets your expectations and look forward to your favorable consideration.

Sincerely,
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1. Response Letter.pdf PDF