

Decision Letter (JCQ-2025-0029)

From:

To:

CC:

BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0029

Body: 17-Oct-2025

Dear Professor Seki:

Manuscript ID JCQ-2025-0029 entitled "An Update on Therapeutic Strategies for HER2-Mutated Non-Small Cell Lung Cancer" 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.

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.

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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).

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
Journal of Clinical Question
jcqc@gleampub.com

[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

Dear Authors,

I would like to thank you for your effort in preparing this comprehensive review, which addresses an important and timely topic.

The manuscript is well structured and informative. However, the Discussion section would benefit from further revision.

My comments follow

Major Revisions:

HER2 mutation: In my opinion, this paragraph is confusing. I suggest clearly dividing it into a first part providing an overview of both HER2 mutation and amplification/expression, followed by a second part focusing on mutations alone.

Please add a paragraph on safety/side effects after the ADC chapter.

Discussion: The first paragraph does not have a clear focus; I suggest removing it.

Discussion: Please expand the fourth paragraph (resistance). Moreover, I strongly recommend providing a reference for each point (currently, there is only one reference in the entire Discussion). I suggest including references from the aforementioned trials and adding new ones where appropriate.

Minor Revisions:

Introduction: Please cite a couple of strategies implemented by healthcare systems to improve molecular characterization in metastatic NSCLC.

Line 139: Please provide some examples of regions where T-Dx is not available.

Line 143: Please clarify what is meant by HER2-altered NSCLC (mutated? amplified?).

Please correct Table 2 (both tables are currently labeled "Table 1").

Reviewer: 2

Comments to the Author

Reviewer Comments

Manuscript ID: JCQ-2025-0029

Manuscript type: Review Article

Title: An Update on Therapeutic Strategies for HER2-Mutated Non-Small Cell Lung Cancer

Recommendation: Minor Revision

General Comments

This review provides a comprehensive and up-to-date overview of therapeutic advances for HER2-mutated non-small cell lung cancer (NSCLC). The manuscript is accurate, well-organized, and supported by relevant literature. However, the current version mainly focuses on descriptive summaries of each agent, while the central clinical question — "What is the optimal treatment strategy for HER2-mutant NSCLC: ADCs or TKIs?" — remains insufficiently addressed.

To enhance the clinical relevance and readability of the paper, I recommend the authors clarify their perspective and strengthen the integrative aspects of the review as outlined below.

Major Comments

1. Clarify the authors' standpoint on the optimal treatment strategy (P2, L26–29)

The following statement is critical to the manuscript's conceptual core:

"Although ADCs currently dominate the treatment landscape, evolving TKIs and combination strategies are expected to reshape therapeutic sequencing and facilitate more personalized, biomarker-driven care for HER2-altered NSCLC."

Please expand this into a concise treatment algorithm or schematic diagram summarizing the authors’ proposed strategy for HER2-mutant NSCLC. Indicate the rationale for therapeutic sequencing (ADCs vs TKIs) according to mutation subtype (especially exon 20 insertions) and treatment line (1st-line, post-progression, trial options).

2. Prioritization and cost-effectiveness of treatment regimens (P4, L58–60)

The section summarizing ICI-chemotherapy combinations and cost data is informative but would benefit from further interpretation. Please discuss the relative ranking of each regimen from a per-patient-per-month (PPM) perspective, integrating both efficacy and cost-effectiveness. A brief comparative table summarizing “efficacy–toxicity–cost” would add significant clinical value.

3. Comparison of diagnostic assays for HER2 alterations (P5, L74–76)

This is an important point that deserves expansion. Please include a summary table of the major diagnostic techniques used to detect HER2 mutations and exon 20 insertions in daily practice (e.g., PCR, NGS, FISH, IHC). List their sensitivity, specificity, and sample type (tissue vs liquid biopsy), and provide a brief comment on which method is currently the most clinically recommended.

4. Clarify the HER2 signaling mechanism (P6, L78–82)

To aid reader comprehension, please include a schematic illustration of the HER/ErbB receptor family signaling pathways, highlighting how HER2 exon 20 insertions activate downstream MAPK and PI3K-AKT pathways.

5. Add a comparative table summarizing regulatory approval status across regions (P12 and P17, Table 1)

Please indicate the approval status of each agent (e.g., T-DXd, T-DM1, Rezetecan, RC48, etc.) under the major regulatory authorities — FDA, EMA, and PMDA — to enable an international comparison. A supplementary table showing which drugs are currently approved in each region would be extremely informative for global readers.

In addition, please verify the consistency between Table 1 and Table 2, and clearly specify their respective reference positions in the main text. Importantly, the table currently labeled as “Table 1” on P17 appears to be a typographical error and should likely be “Table 2.” Please correct this labeling and ensure that the corresponding insertion point in the text is clearly indicated. For all seven agents listed in this table, kindly append the same type of regulatory-approval summary (FDA/EMA/PMDA etc.), so that clinicians in different regions can easily recognize which agents are currently available for clinical use in their own practice settings.

6. Present the authors’ concept of personalized treatment algorithms (P18, Discussion)

The statement —
“As clinical data mature, personalized treatment algorithms will increasingly leverage both targeted TKIs and ADCs...”
— should be supported by a visualized treatment framework or flowchart. Please summarize the authors’ proposed personalized algorithm according to treatment line (1st/2nd/3rd) and biomarker profile (mutation subtype, HER2 overexpression, etc.).

7. Visualize resistance mechanisms (P19, Discussion)

The discussion on resistance mechanisms is highly valuable but remains textual. Please provide a diagram summarizing resistance pathways, including HER2 extracellular domain alterations, bypass pathway activation (MET, KRAS), drug efflux mechanisms, and secondary kinase domain mutations. This would improve both educational and practical clarity.

Minor Comments

P2, L18: Check whether the abbreviations “ADCs” and “TKIs” require spelling out at first mention, according to the journal’s author guidelines.

Ensure consistency of abbreviations throughout (e.g., T-DXd vs TDXd). Verify that all figure and table numbers (Table 1, Table 2) are correctly referenced within the main text.

Summary

Overall, this is a solid and timely review that successfully summarizes the therapeutic landscape of HER2-mutant NSCLC. By addressing the above points — particularly the inclusion of clear algorithms, comparison tables, and visual schematics — the paper will become significantly more clinically instructive and practice-oriented. With these revisions, I believe the manuscript will provide meaningful guidance for both clinicians and researchers in the field.

Date Sent: 17-Oct-2025

Author's Response to Decision Letter for (JCQ-2025-0029)**An Update on Therapeutic Strategies for HER2-Mutated Non-Small Cell Lung Cancer****Dear Editor and Reviewers,**

We sincerely thank you for your valuable time, constructive feedback, and insightful comments on our manuscript. We greatly appreciate the reviewers' thoughtful observations, which have been instrumental in improving the clarity, precision, and clinical depth of our work. In this revised version, we have carefully addressed every comment and suggestion. Below, we provide a detailed, point-by-point response to each comment. All corresponding modifications have been incorporated into the manuscript, with changes clearly highlighted.

Response to the Associate Editor's Comments

Comment 1: Check grammar and flow for minor errors.

Response: We have thoroughly reviewed and edited the entire manuscript to correct grammatical issues and improve sentence flow, ensuring readability and professional consistency.

Comment 2: Ensure all abbreviations are defined on first use in both abstract and main text.

Response: All abbreviations (e.g., ADCs, TKIs, NSCLC) have been verified and are now defined upon first appearance in both the abstract and the main text.

Comment 3: Add ORCID IDs for authors if available.

Response: ORCID IDs have been added for all authors where available.

Response to Reviewer 1

We thank Reviewer 1 for the positive evaluation and helpful suggestions that have strengthened our manuscript. We have revised the text extensively in accordance with each comment.

Major Revisions

Comment 1: In my opinion, this paragraph is confusing. I suggest clearly dividing it into a first part providing an overview of both HER2 mutation and amplification/expression, followed by a second part focusing on mutations alone.

Response: The section has been reorganized into two distinct parts: (1) an overview of HER2 alternation; and (2) a focused discussion on HER2 mutations. This revision enhances logical flow and reader comprehension. (Line 84-109)

Comment 2: Add a paragraph on safety/side effects after the ADC chapter.

Response: A new paragraph summarizing the safety and side effect profiles of HER2-targeted ADCs focused on two major agents of T-DXd, and T-DM1, especially on the ILDs. The detailed contents (line 206-222).

Comment 3: Discussion: The first paragraph does not have a clear focus; I suggest removing it. Response: We appreciate this suggestion. The first paragraph of the Discussion has been deleted to strengthen the clarity, focus, and coherence of the section.

Comment 4: Discussion: Please expand the fourth paragraph (resistance). Moreover, I strongly recommend providing a reference for each point (currently, there is only one reference in the entire Discussion). I suggest including references from the aforementioned trials and adding new ones where appropriate.

Response: We appreciate the reviewer's comment on this point. The resistance section has been thoroughly expanded and supported with additional references from recent clinical trials and reviews. "Although ADCs such as T-DXd often induce more durable and profound responses compared with TKIs, the development of resistance remains inevitable. Primary and acquired resistance mechanisms to T-DXd have been increasingly characterized in both preclinical and clinical studies. These include alterations in the HER2 extracellular domain that impair antibody binding or internalization, loss of HER2 expression or heterogeneity of HER2 amplification, and activation of compensatory signaling pathways such as MET, KRAS, and PI3K/AKT.53-55 In addition, upregulation of ATP-binding cassette drug efflux pumps may decrease intracellular payload accumulation, contributing to reduced cytotoxic efficacy. In contrast, resistance to HER2-directed TKIs often involves secondary HER2 kinase domain mutations that diminish drug binding affinity, HER3 co-activation or dimerization, and histologic transformation to a less HER2-dependent phenotype (e.g., HER2-low or HER2-negative disease).57 Notably, cross-resistance between ADCs and TKIs appears to be incomplete, suggesting a rationale for sequential or combinatorial therapeutic strategies. For example, patients who progress on T-DXd may still derive benefit from subsequent TKI therapy, or vice versa, depending on the dominant molecular resistance mechanisms identified at progression. Emerging agents, including trastuzumab deruxtecan and the novel HER2-selective TKI zongertinib, have demonstrated prolonged durations of response and favorable safety profiles in early-phase trials, comparable to or exceeding those of T-DXd. These findings underscore the importance of molecular re-profiling at progression and rational sequencing of HER2-targeted therapies to overcome resistance and optimize long-term disease control."

Minor Revisions

Comment 1: Introduction: Please cite a couple of strategies implemented by healthcare systems to improve molecular characterization in metastatic NSCLC.

Response: We appreciate the reviewer's valuable comment. In the revised manuscript, we have added a description of healthcare system-level strategies that have been implemented to improve molecular characterization in metastatic NSCLC. Specifically, we now mention the adoption of reflex molecular testing protocols, in which pathologists automatically initiate biomarker testing at the time of diagnosis to reduce delays and improve detection of actionable alterations. In addition, we highlight the establishment of standardized precision oncology workflows that promote coordination among oncologists, pathologists, and molecular laboratories to optimize tissue acquisition, testing efficiency, and integration of results into clinical decision-making. These additions have been incorporated into the Introduction section to address the reviewer's comment.

Comment 2: Line 139: Please provide some examples of regions where T-Dx is not available.

Response: We appreciate the reviewer's comment. Specific examples of regions where T-Dx is not available have been added to the manuscript. The revised text now reads: "While Trastuzumab Deruxtecan (T-Dx) has been approved in more than 60 countries for advanced NSCLC, it remains unavailable in certain low- and middle-income regions, such as parts of sub-Saharan Africa and Southeast Asia, where regulatory approval or reimbursement has not yet been established."

Comment 3: Line 143: Please clarify what is meant by HER2-altered NSCLC (mutated? amplified?).

Response: We appreciate the reviewer's insightful comment. The term HER2-altered NSCLC in our manuscript refers to patients with either HER2 mutations or HER2 amplification/overexpression. To improve clarity, we have revised the text to read: "patients with HER2-altered advanced NSCLC, including those harboring exon 20 insertions and overexpression."

Comment 4: Please correct Table 2 (both tables are currently labeled "Table 1").

Response: Thank you for your comment on this point. The table labels have been corrected and are now properly listed as Table 2 and Table 3, each with the appropriate titles.

Response to Reviewer 2

We greatly appreciate Reviewer 2's thorough evaluation and valuable recommendations, which have notably enhanced the scientific depth and clinical applicability of our review.

Major Comments

1. Clarify the authors' standpoint on the optimal treatment strategy (P2, L26–29) The following statement is critical to the manuscript's conceptual core: "Although ADCs currently dominate the treatment landscape, evolving TKIs and combination strategies are expected to reshape therapeutic sequencing and facilitate more personalized, biomarker-driven care for HER2-altered NSCLC." Please expand this into a concise treatment algorithm or schematic diagram summarizing the authors' proposed strategy for HER2-mutant NSCLC. Indicate the rationale for therapeutic sequencing (ADCs vs TKIs) according to mutation subtype (especially exon 20 insertions) and treatment line (1st-line, post-progression, trial options).

Response: We appreciate the reviewer's thoughtful comment and suggestion. Several new agents have only recently been approved by the FDA. At present, there is not enough clinical evidence to determine the optimal treatment sequence for HER2-altered NSCLC. We have clarified this point in the revised manuscript. ADCs are currently considered the standard therapeutic option. Emerging TKIs and combination strategies may help refine treatment sequencing as more data become available. However, because the evidence is still limited and evolving, creating a concise schematic for treatment strategy by line of therapy is not yet feasible.

2. Prioritization and cost-effectiveness of treatment regimens (P4, L58–60) The section summarizing ICI-chemotherapy combinations and cost data is informative but would benefit from further interpretation. Please discuss the relative ranking of each regimen from a per-patient-per-month (PPPM) perspective, integrating both efficacy and cost-effectiveness. A brief comparative table summarizing "efficacy-toxicity-cost" would add significant clinical value.

Response: We appreciate the reviewer's insightful comment and suggestion. In response, we have added a new subsection discussing the efficacy, toxicity, and cost-effectiveness of available treatment options. However, after reviewing the original literature, detailed per-regimen data on PPPM cost and comparative cost-effectiveness were not consistently reported. Moreover, ICI-based combinations fall outside the primary focus and scope of this review, which centers on HER2-altered NSCLC and targeted approaches. Therefore, while a detailed comparative table could not be included, we have provided a concise narrative summary to reflect the current evidence and highlight the need for future cost-effectiveness analyses.

3. Comparison of diagnostic assays for HER2 alterations (P5, L74–76) This is an important point that deserves expansion. Please include a summary table of the major diagnostic techniques used to detect HER2 mutations and exon 20 insertions in daily practice (e.g., PCR, NGS, FISH, IHC). List their sensitivity, specificity, and sample type (tissue vs liquid biopsy), and provide a brief comment on which method is currently the most clinically recommended.

Response: We appreciate the reviewer's insightful comment on this point. As noted, HER2 testing in non-small cell lung cancer (NSCLC) relies on complementary laboratory methods. Next-generation sequencing (NGS) on tissue DNA is the most comprehensive and guideline-recommended first-line approach, accurately detecting HER2 point mutations and exon 20 insertions with near-perfect sensitivity and specificity (Table 1). NGS using circulating tumor DNA (ctDNA) from plasma, also known as a liquid biopsy, provides a non-invasive alternative for rapid or serial testing; however, its sensitivity is lower (approximately 70–80%), and negative results should be confirmed with tissue testing when feasible. Targeted polymerase chain reaction (PCR) assays, including the amplification-refractory mutation system (ARMS), competitive allele-specific TaqMan PCR (castPCR), and droplet digital PCR (ddPCR), demonstrate excellent analytical sensitivity and specificity for known HER2 hotspot variants but may fail to detect rare or novel alterations, making them best suited for focused screening rather than comprehensive profiling. Fluorescence in situ hybridization (FISH) remains the reference method for identifying ERBB2 gene amplification (copy-number gain) and is valuable when amplification status influences therapeutic decisions or to confirm NGS results. Finally, immunohistochemistry (IHC) assesses HER2 protein overexpression but shows limited concordance with ERBB2 genomic alterations, serving instead as a complementary test to evaluate protein expression rather than mutations or insertions.

4. Clarify the HER2 signaling mechanism (P6, L78–82) To aid reader comprehension, please include a schematic illustration of the HER/ErbB receptor family signaling pathways, highlighting how HER2 exon 20 insertions activate downstream MAPK and PI3K-AKT pathways.

Response: We appreciate the reviewer's comment on this point. We included a new schematic diagram (Figure 1) illustrating the HER/ErbB signaling cascade

5. Add a comparative table summarizing regulatory approval status across regions (P12 and P17, Table 1) Please indicate the approval status of each agent (e.g., T-DXd, T-DM1, Rezatecan, RC48, etc.) under the major regulatory authorities, FDA, EMA, and PMDA, to enable an international comparison. A supplementary table showing which drugs are currently approved in each region would be extremely informative for global readers. For all seven agents listed in this table, kindly append the same type of regulatory-approval summary (FDA/EMA/PMDA etc.), so

that clinicians in different regions can easily recognize which agents are currently available for clinical use in their own practice settings.

In addition, please verify the consistency between Table 1 and Table 2, and clearly specify their respective reference positions in the main text. Importantly, the table currently labeled as “Table 1” on P17 appears to be a typographical error and should likely be “Table 2.” Please correct this labeling and ensure that the corresponding insertion point in the text is clearly indicated.

Response: Thank you for your comment on this point. We have prepared Supplementary Table 1 to summarize the FDA, EMA, and PMDA approvals for the agents. As Reviewer 1 pointed out, the table labels have been corrected and are now properly listed as Table 2 and Table 3, with the appropriate insertions noted in the manuscript.

6. Present the authors’ concept of personalized treatment algorithms (P18, Discussion) The statement — “As clinical data mature, personalized treatment algorithms will increasingly leverage both targeted TKIs and ADCs...” — should be supported by a visualized treatment framework or flowchart. Please summarize the authors’ proposed personalized algorithm according to treatment line (1st/2nd/3rd) and biomarker profile (mutation subtype, HER2 overexpression, etc.).

Response: We appreciate the reviewer’s constructive comment and suggestion. We agree that a visualized treatment framework would enhance clarity. However, due to the limited and evolving clinical evidence, it is not feasible to propose a robust and validated personalized treatment algorithm at this stage. The available data are insufficient to support treatment sequencing by line of therapy or biomarker subtype with strong evidence. We have clarified this limitation in the revised manuscript and emphasized that such a framework will be more appropriate once additional data from ongoing and future studies become available.

7. Visualize resistance mechanisms (P19, Discussion) The discussion on resistance mechanisms is highly valuable but remains textual. Please provide a diagram summarizing resistance pathways, including HER2 extracellular domain alterations, bypass pathway activation (MET, KRAS), drug efflux mechanisms, and secondary kinase domain mutations. This would improve both educational and practical clarity.

Response: We appreciate the reviewer’s constructive comment and suggestion. In response, we have added a comprehensive table summarizing the key mechanisms of resistance to HER2-targeted therapies, including HER2 structural alterations, bypass pathway activation (e.g., MET, KRAS), drug efflux mechanisms, and secondary kinase domain mutations. This table provides a clear and concise overview to enhance both educational and practical understanding.

Minor Comments

P2, L18: Check whether the abbreviations “ADCs” and “TKIs” require spelling out at first mention, according to the journal’s author guidelines.

Response: Thank you for your comment. We have verified that all abbreviations are clearly defined at their first mention (e.g., ADCs, TKIs, etc.).

Ensure consistency of abbreviations throughout (e.g., T-DXd vs TDXd).

Response: We appreciate the reviewer’s comment. The abbreviation has been standardized throughout the manuscript to T-DXd for consistency.

Verify that all figure and table numbers (Table 1, Table 2) are correctly referenced within the main text.

Response: Thank you for your comment on this point. The table labels have been corrected and are now properly listed as Table 1 and Table 2, each with the appropriate titles.

We truly appreciate the reviewers’ insightful feedback and the Editor’s guidance, which have significantly enhanced the manuscript’s quality and clinical relevance. We hope that our revisions fully address all concerns and meet the journal’s expectations for publication.

Sincerely,
Nobuhiko Seki
Division of Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan.
e-mail: nseki@med.teikyo-u.ac.jp