Decision Letter (JCQ-2026-0021)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0021

Body: 10-Jul-2026

Dear Ms Zhang:

Manuscript ID JCQ-2026-0021 entitled "Factors potentially impacting the efficacy of programmed death (ligand) 1 inhibitors for treatment of 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.

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 S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author

Dear authors

Thank you for your efforts in this study.

This review article examines the factors that influence the effectiveness of PD-1/PD-L1 immune checkpoint inhibitors in patients with non-small cell lung cancer (NSCLC). The authors summarize evidence showing that treatment response is determined by a complex interaction of tumor-related, microenvironmental, therapeutic, and patient-specific factors.

The manuscript discusses key tumor microenvironment features, including CD8+ T-cell infiltration, progenitor exhausted T cells (Tpex), myeloid-derived suppressor cells, regulatory T cells, and neutrophils, highlighting how these immune components can either enhance or suppress responses to immunotherapy. It then reviews major tumor-intrinsic biomarkers such as PD-L1 expression, tumor mutational burden (TMB), and driver gene mutations, with particular emphasis on EGFR mutations, KRAS mutations, and co-mutations involving STK11, KEAP1, and TP53.

The review also evaluates treatment-related factors, including combinations of immunotherapy with chemotherapy, radiotherapy, antiangiogenic agents, and other immunotherapies. Additionally, it examines patient characteristics that may affect outcomes, such as age, performance status, cachexia, obesity, sex, smoking history, gut microbiota composition, antibiotic and proton pump inhibitor use, and glucocorticoid exposure.

The authors conclude that no single biomarker is sufficient to predict response to PD-(L)1 inhibitors. Instead, optimal patient selection will likely require integrating multiple biological, clinical, and molecular factors into a personalized treatment framework. The review highlights ongoing challenges, particularly the standardization of TMB assessment, management of EGFR-mutant disease, understanding KRAS co-mutation biology, and validating microbiome-based interventions to improve immunotherapy outcomes.

My comments:

This review addresses an important and clinically relevant topic: factors influencing the efficacy of PD-1/PD-L1 inhibitors in NSCLC. The manuscript is generally well organized and covers many of the major determinants of immunotherapy response, including tumor microenvironment, TMB, driver mutations, combination therapies, and patient-related factors. The inclusion of emerging topics such as gut microbiota, Tpex cells, STK11/KEAP1 co-mutations, and TMB standardization is a strength.

However, the manuscript would benefit substantially from a more systematic review methodology, stronger critical appraisal of the literature, improved balance between established evidence and emerging hypotheses, clearer discussion of conflicting findings, and refinement of language throughout.

Abstract

The abstract should more clearly state the methodology used to identify and evaluate the literature. The phrase "we systematically conducted an in-depth exploration" suggests a systematic review, yet no systematic review methodology is described anywhere in the manuscript. Either the authors should provide a formal systematic review methodology (including search strategy, databases, inclusion criteria, and study selection process) or revise the wording to describe the article as a narrative review. The current wording may be misleading.

The statement that the response rate remains unsatisfactory in "approximately 20% in unselected patient populations" requires clarification because the wording implies that only 20% of patients have unsatisfactory responses rather than approximately 20% responding to therapy. The sentence should be rewritten for precision.

The abstract would also benefit from a concluding sentence highlighting the main clinical implications and future directions.

Background

The introduction provides adequate clinical context but lacks a clear explanation of how the review was conducted. For a contemporary review article, readers should be informed whether literature selection was systematic or narrative. Databases searched, time periods covered, language restrictions, and article selection criteria should be described.

The authors should also better define the scope of the review. While they appropriately justify focusing on PD-(L)1 inhibitors, the review intermittently expands into broader immunotherapy discussions. A more explicit statement of scope would improve coherence.

The claim that objective response rates are approximately 20% in broader NSCLC populations should be updated with more nuanced discussion according to treatment line, PD-L1 expression level, and treatment regimen. Response rates vary substantially across clinical settings.

Tumor Microenvironment Section

This section is generally strong and scientifically current. However, the discussion remains largely descriptive.

The authors should incorporate a more critical discussion regarding the clinical utility of TME biomarkers. While CD8+ infiltration, Tpex cells, Tregs, MDSCs, and TANs are extensively described, the manuscript does not adequately address whether these biomarkers are reproducibly measurable, standardized, or clinically actionable.

For example, the section on Tpex cells presents them as promising predictive biomarkers but does not discuss the practical limitations of measuring Tpex populations in routine clinical settings.

The review would be strengthened by discussing why many TME biomarkers remain investigational despite strong biological rationale.

The authors should also consider discussing tertiary lymphoid structures (TLSs), which have emerged as important predictors of immunotherapy response and are only briefly mentioned later in the glucocorticoid section.

PD-L1 Expression Section

The discussion appropriately acknowledges limitations of PD-L1 as a biomarker. However, the review should more comprehensively discuss the variability among PD-L1 assays and the consequences for clinical decision-making.

The manuscript would benefit from a dedicated summary comparing:

22C3

SP263

SP142

Combined Positive Score (CPS)

Tumor Proportion Score (TPS)

The current discussion is too brief for such a clinically important biomarker.

The authors should also emphasize that PD-L1 remains the only widely adopted biomarker in routine clinical practice despite its imperfections.

Tumor Mutational Burden Section

The TMB section is one of the manuscript's strongest components. The discussion of standardization challenges is particularly valuable.

However, several improvements are recommended.

First, the authors should discuss more explicitly why enthusiasm for TMB has decreased in some clinical settings despite early positive trial results. Regulatory and clinical adoption of TMB has become increasingly controversial, and this should be reflected.

Second, the review should provide a balanced discussion of negative studies and limitations. Most evidence presented supports TMB, while less attention is devoted to studies demonstrating weak predictive value.

Third, the manuscript would benefit from discussing composite biomarkers integrating TMB, PD-L1, gene expression signatures, and immune infiltration rather than treating TMB largely as a standalone marker.

Driver Mutation Section

This is another strong section and appropriately highlights molecular heterogeneity.

However, the review currently devotes disproportionate attention to EGFR and KRAS while providing limited discussion of other clinically relevant driver alterations such as:

ALK

ROS1

RET

MET exon 14 skipping

HER2

BRAF

Given the title of the manuscript, a broader overview of oncogenic drivers affecting immunotherapy efficacy would be appropriate.

The discussion of EGFR subtypes is valuable but some conclusions appear stronger than the available evidence supports. For example, statements regarding differential immunogenicity between L858R and exon 19 deletion should be presented more cautiously because evidence remains somewhat inconsistent.

Similarly, the discussion of STK11 and KEAP1 mechanisms is detailed and informative, but the review should distinguish more clearly between preclinical mechanistic evidence and clinically validated predictive biomarkers.

Combination Therapy Section

The section comprehensively reviews chemotherapy, radiotherapy, antiangiogenic therapy, and dual checkpoint blockade.

However, the manuscript often presents positive findings without equivalent discussion of negative studies, failed trials, toxicity concerns, cost considerations, or patient-selection challenges.

For example, the discussion of chemoimmunotherapy should more thoroughly address:

Increased toxicity

Treatment discontinuation rates

Quality-of-life considerations

Economic burden

Similarly, radiotherapy combinations are discussed primarily through positive studies. More discussion is needed regarding unresolved questions surrounding radiation dose, sequencing, timing, and patient selection.

The authors should also consider including a dedicated subsection summarizing ongoing phase III trials likely to influence future practice.

Patient Characteristics Section

This section covers many clinically relevant variables but would benefit from greater critical evaluation.

Age

The authors appropriately acknowledge conflicting evidence. However, the speculation that poorer outcomes in elderly patients are attributable to performance status should be explicitly identified as a hypothesis rather than an evidence-based conclusion.

Obesity

The discussion of the obesity paradox is balanced, but the section should place greater emphasis on body composition measures such as sarcopenia, visceral adiposity, and muscle mass, which may be more informative than BMI alone.

Sex Differences

The manuscript discusses biological mechanisms but ultimately acknowledges inconsistent clinical

evidence. The conclusion that women generally demonstrate poorer responses to PD-(L)1 inhibitors may be overly definitive given the conflicting literature cited in the same section. The language should be softened.

Smoking

The discussion appropriately addresses smoking-associated immunogenicity but should more strongly emphasize that smoking is not clinically desirable despite its association with increased immunotherapy responsiveness. Some readers could misinterpret this section without appropriate contextualization.

Gut Microbiota

This section is timely and comprehensive. However, the review should more clearly distinguish between association and causation. Many microbiome findings remain exploratory and have not yet been translated into standard clinical practice.

The authors should also discuss challenges in microbiome standardization, reproducibility, geographic variation, dietary influences, and sequencing methodologies.

Glucocorticoids

This is a well-developed section. Nonetheless, it would benefit from discussion of indication bias. Patients receiving corticosteroids often have more advanced disease or worse clinical status, which may partially explain poorer outcomes observed in retrospective studies.

Summary and Future Prospects

The conclusion effectively synthesizes the major findings.

However, the manuscript should move beyond simply listing positive and negative factors. A stronger conceptual framework is needed.

Specifically, the authors should emphasize:

Integration of biomarkers rather than reliance on single biomarkers.

Multi-parameter predictive models.

AI-assisted prediction tools.

Spatial transcriptomics.

Single-cell sequencing.

Circulating tumor DNA biomarkers.

Dynamic biomarkers measured during treatment.

These topics are likely to represent the future direction of precision immuno-oncology.

Writing and Presentation

The manuscript requires moderate language editing by a fluent scientific English editor.

Examples include:

Inconsistent article usage.

Occasional awkward phrasing.

Repetitive sentence structures.

Overly long sentences.

Frequent use of speculative language without qualification.

Examples include phrases such as "we speculate" and several instances where causation is implied despite observational evidence.

The manuscript should also undergo a careful terminology review to ensure consistent use of:

PD-1

PD-L1

PD-(L)1

ICI

Immunotherapy

throughout the text.

Figures

The manuscript references multiple figures (Figures 1–6), but based on the text alone it is unclear whether they adequately synthesize information or merely illustrate concepts. The figures should be evaluated to ensure that they:

Add value beyond the text.

Are sufficiently detailed.

Include clear legends.

Clearly distinguish established evidence from emerging hypotheses.

Provide integrated models rather than isolated mechanisms.

Recommendation

The manuscript addresses an important topic and contains substantial contemporary literature, but it requires major revision before publication.

The highest-priority improvements are:

1. Clearly define and describe the review methodology.

2. Strengthen critical appraisal rather than predominantly descriptive reporting.

3. Provide more balanced discussion of controversies and negative studies.

4. Expand discussion of additional driver mutations beyond EGFR and KRAS.

5. Improve discussion of clinical applicability and biomarker implementation.

6. Refine language and reduce overly definitive conclusions where evidence remains uncertain.

7. Strengthen the future directions section by emphasizing integrated biomarker strategies and emerging technologies.

These revisions would substantially increase the scientific rigor, clinical relevance, and publishability of the review.

Reviewer: 2

Comments to the Author
This manuscript systematically summarizes the multidimensional factors affecting the efficacy of PD-1/PD-L1 inhibitors in non-small cell lung cancer (NSCLC). The logical structure is clear, and the figures are well-designed. However, as a high-quality review, it lacks literature support for several key academic statements. Additionally, the summary of predictive biomarkers could be more intuitive, and the discussion on cutting-edge tumor microenvironment (TME) mechanisms requires further depth.

Major Comments:
1. Lack of references for key statements: Several crucial mechanistic and clinical statements lack citations, undermining the manuscript's academic rigor. The authors should thoroughly review the entire manuscript and provide appropriate references. Examples include, but are not limited to, the following statements in Section 3.3:
"While classical drivers like EGFR are typically linked to an immunosuppressive TME, rationally designed combination regimens are showing potential to overcome this resistance."
"Conversely, the immunogenicity of KRAS-mutant tumors is predominantly defined by co-mutational status, with STK11 or KEAP1 co-mutations driving profound resistance and TP53 co-mutations often enhancing sensitivity."
"Previous views held that EGFR-mutant NSCLC is typically characterized by a 'cold' TME featuring low TMB and low CD8+ T-cell infiltration, which is associated with poor response to ICI monotherapy."

2. Addition of a comprehensive summary table: Although various factors are discussed in the text, an intuitive summary is missing. It is highly recommended to add a comprehensive table summarizing the biomarkers and clinical features discussed. Suggested columns include, but are not limited to: Biomarker/Factor, Clinical Role (Positive vs. Negative predictor), Brief Mechanism, Evidence/Specimen Data Support.

3. Integration of high-resolution multi-omics perspectives: The current discussion on TME heterogeneity is somewhat macroscopic. In Section 2 (TME factors), it is advised to incorporate recent insights from single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics. For instance, discuss the formation of Tertiary Lymphoid Structures (TLS) and the critical role of specific cell-cell communication networks in predicting immunotherapy benefits.

4. Update on novel combination strategies: In Section 4 (Combination therapy), alongside traditional anti-angiogenic and bispecific agents, please briefly introduce the strategy of combining Antibody-Drug Conjugates (ADCs) with PD-(L)1 inhibitors. This emerging approach is currently demonstrating significant potential in remodeling the TME in NSCLC.

5. Enhance the specificity of future directions: In Section 6.2 "Controversies and Directions", it is recommended that the authors propose 1-2 specific, novel trial design concepts to serve as potential breakthroughs for future research in this field.

Date Sent: 10-Jul-2026

Journal of Clinical Question

Author's Response to Decision Letter for (JCQ-2026-0021)

Factors potentially impacting the efficacy of programmed death (ligand) 1 inhibitors for treatment of non-small cell lung cancer

Response Letter

Dear Reviewers
We sincerely thank the reviewer for the careful and constructive evaluation. The manuscript has been revised to clarify its narrative-review methodology, strengthen critical appraisal, distinguish established clinical evidence from emerging mechanistic hypotheses, provide a more balanced discussion of conflicting findings, and improve the scientific language and terminology throughout.
Note: Page and line references correspond to the continuously line-numbered revised manuscript submitted with this response letter.

Reviewer 1
Comment 1: The abstract should more clearly state the methodology used to identify and evaluate the literature. The phrase "we systematically conducted an in-depth exploration" suggests a systematic review, yet no systematic review methodology is described anywhere in the manuscript. Either the authors should provide a formal systematic review methodology (including search strategy, databases, inclusion criteria, and study selection process) or revise the wording to describe the article as a narrative review. The current wording may be misleading.
The statement that the response rate remains unsatisfactory in "approximately 20% in unselected patient populations" requires clarification because the wording implies that only 20% of patients have unsatisfactory responses rather than approximately 20% responding to therapy. The sentence should be rewritten for precision.
The abstract would also benefit from a concluding sentence highlighting the main clinical implications and future directions.
Response: Thank you for this important observation. We agree that the previous wording could incorrectly imply a formal systematic review. Because the purpose of the article is an interpretive narrative synthesis rather than an exhaustive systematic review, the abstract and manuscript have been revised to identify the article explicitly as a narrative review, and the phrase “we systematically conducted an in-depth exploration” has been removed. A concise description of the literature-identification and selection approach has also been added. The response-rate statement has been corrected to indicate that objective responses occur in approximately 20% of broadly selected patients in historical monotherapy settings, rather than suggesting that only 20% have unsatisfactory responses. In addition, the abstract now concludes with the clinical implication that integrated, dynamic, and context-specific biomarker assessment is more informative than reliance on any single factor. (Page 4, lines 42–62).

Comment 2: The introduction provides adequate clinical context but lacks a clear explanation of how the review was conducted. For a contemporary review article, readers should be informed whether literature selection was systematic or narrative. Databases searched, time periods covered, language restrictions, and article selection criteria should be described.
The authors should also better define the scope of the review. While they appropriately justify focusing on PD-(L)1 inhibitors, the review intermittently expands into broader immunotherapy discussions. A more explicit statement of scope would improve coherence.
The claim that objective response rates are approximately 20% in broader NSCLC populations should be updated with more nuanced discussion according to treatment line, PD-L1 expression level, and treatment regimen. Response rates vary substantially across clinical settings.
Response: We appreciate this recommendation. The Introduction now states that the article is a narrative review and briefly describes the literature-selection framework, including the databases and sources consulted, the period covered, language considerations, and the prioritization of major clinical trials, translational studies, guidelines, and recent high-quality reviews. The scope has also been clarified as factors influencing the efficacy of PD-1/PD-L1-directed therapy in NSCLC; broader immunotherapy concepts are retained only when they directly inform this focus. We also revised the discussion of the approximately 20% response rate to explain that response varies substantially according to treatment line, PD-L1 expression, monotherapy versus combination treatment, molecular subtype, and patient selection. (Pages 5–6, lines 72–98)

Comment 3 This section is generally strong and scientifically current. However, the discussion remains largely descriptive. The authors should incorporate a more critical discussion regarding the clinical utility of TME biomarkers. While CD8+ infiltration, Tpex cells, Tregs, MDSCs, and TANs are extensively described, the manuscript does not adequately address whether these biomarkers are reproducibly measurable, standardized, or clinically actionable.
For example, the section on Tpex cells presents them as promising predictive biomarkers but does not discuss the practical limitations of measuring Tpex populations in routine clinical settings.

The review would be strengthened by discussing why many TME biomarkers remain investigational despite strong biological rationale.
The authors should also consider discussing tertiary lymphoid structures (TLSs), which have emerged as important predictors of immunotherapy response and are only briefly mentioned later in the glucocorticoid section.
Response: Thank you for highlighting the distinction between biological relevance and clinical utility. The TME section has been revised to discuss assay reproducibility, spatial and temporal heterogeneity, tissue-sampling limitations, pre-analytical variability, absence of standardized thresholds, and the limited prospective validation of many proposed biomarkers. The text on progenitor exhausted T cells now notes that their identification generally requires multiparametric flow cytometry, immunophenotyping, or high-dimensional transcriptomic methods that are not routinely available or standardized. We also added a focused discussion of tertiary lymphoid structures, including their association with immunotherapy benefit and the current limitations in pathological definition, quantification, and prospective clinical implementation. (Pages 7–9, lines 100–154)

Comment 4: The discussion appropriately acknowledges limitations of PD-L1 as a biomarker. However, the review should more comprehensively discuss the variability among PD-L1 assays and the consequences for clinical decision-making.
The manuscript would benefit from a dedicated summary comparing:22C3,SP263, SP142, Combined Positive Score (CPS), Tumor Proportion Score (TPS). The current discussion is too brief for such a clinically important biomarker.
The authors should also emphasize that PD-L1 remains the only widely adopted biomarker in routine clinical practice despite its imperfections.
Response: We thank the reviewer for emphasizing this clinically important issue. The PD-L1 section has been expanded to compare the principal assay platforms, including 22C3, 28-8, SP263, and SP142, and to clarify the distinction between Tumor Proportion Score and Combined Positive Score. The revised text also explains differences in tumor-cell staining, scoring methods, inter-assay concordance, specimen-related limitations, and the need to match the assay and cutoff to the relevant treatment indication. We respectfully did not add a separate assay table because these relationships can be presented more accurately in the text, whereas a condensed table could imply that assays, scoring systems, and thresholds are directly interchangeable across indications. The manuscript now explicitly identifies PD-L1 immunohistochemistry as the most widely implemented biomarker in routine NSCLC practice despite its limitations. (Page 11, lines 199–224)

Comment 5: The TMB section is one of the manuscript's strongest components. The discussion of standardization challenges is particularly valuable. However, several improvements are recommended.
First, the authors should discuss more explicitly why enthusiasm for TMB has decreased in some clinical settings despite early positive trial results. Regulatory and clinical adoption of TMB has become increasingly controversial, and this should be reflected.
Second, the review should provide a balanced discussion of negative studies and limitations. Most evidence presented supports TMB, while less attention is devoted to studies demonstrating weak predictive value.
Third, the manuscript would benefit from discussing composite biomarkers integrating TMB, PD-L1, gene expression signatures, and immune infiltration rather than treating TMB largely as a standalone marker.
Response: We appreciate this balanced assessment. The TMB section has been expanded to explain why initial enthusiasm has diminished in some settings, including variable assay platforms and cutoffs, tissue-versus-blood discordance, tumor-type dependence, uncertain predictive independence from PD-L1, and inconsistent validation across randomized studies. Negative and equivocal findings are now discussed alongside supportive evidence. We have also reframed TMB as one component of a broader predictive framework and added discussion of composite approaches integrating TMB with PD-L1 expression, immune gene-expression signatures, genomic alterations, immune-cell infiltration, and circulating biomarkers. (Pages 12–14, lines 233–290)

Comment 6. This is another strong section and appropriately highlights molecular heterogeneity.
However, the review currently devotes disproportionate attention to EGFR and KRAS while providing limited discussion of other clinically relevant driver alterations such as ALK, ROS1, RET, MET exon 14 skipping, HER2, BRAF. Given the title of the manuscript, a broader overview of oncogenic drivers affecting immunotherapy efficacy would be appropriate.
The discussion of EGFR subtypes is valuable but some conclusions appear stronger than the available evidence supports. For example, statements regarding differential immunogenicity between L858R and exon 19 deletion should be presented more cautiously because evidence remains somewhat inconsistent.
Similarly, the discussion of STK11 and KEAP1 mechanisms is detailed and informative, but the review should distinguish more clearly between preclinical mechanistic evidence and clinically validated predictive biomarkers.
Response: Thank you for this thoughtful suggestion. The molecular section has been broadened to include ALK, ROS1, RET, MET exon 14 skipping, HER2, and BRAF alterations, while maintaining greater detail for EGFR and KRAS because these alterations have the largest and most mature NSCLC immunotherapy evidence base. Statements comparing EGFR L858R and exon 19 deletion have been softened and now explicitly acknowledge inconsistent findings and the influence of co-mutations, smoking history, and treatment context. The STK11 and KEAP1 discussion has also been revised to distinguish mechanistic and preclinical evidence from retrospective clinical associations and prospectively validated predictive biomarkers. These alterations are therefore presented as clinically relevant resistance-associated factors rather than fully established standalone treatment-selection biomarkers. (Pages 14–18, lines 292–374)

Comment 7: The section comprehensively reviews chemotherapy, radiotherapy, antiangiogenic therapy,

and dual checkpoint blockade.
However, the manuscript often presents positive findings without equivalent discussion of negative studies, failed trials, toxicity concerns, cost considerations, or patient-selection challenges. For example, the discussion of chemoimmunotherapy should more thoroughly address: Increased toxicity, Treatment discontinuation rates, Quality-of-life considerations, Economic burden
Similarly, radiotherapy combinations are discussed primarily through positive studies. More discussion is needed regarding unresolved questions surrounding radiation dose, sequencing, timing, and patient selection.
The authors should also consider including a dedicated subsection summarizing ongoing phase III trials likely to influence future practice.
Response: We appreciate the reviewer's request for a more balanced assessment. The combination-therapy section has been revised to discuss treatment-related toxicity, discontinuation, patient-reported quality of life, financial burden, and the need for clinical and biomarker-based patient selection. The radiotherapy discussion now clarifies that the available phase II signals do not constitute definitive phase III evidence of a universal abscopal effect and addresses unresolved questions regarding dose, fractionation, irradiated site and volume, sequence, timing, and pulmonary or immune-mediated toxicity. Rather than provide an exhaustive catalogue of negative and ongoing studies, which would rapidly become outdated and exceed the scope of this narrative review, we incorporated selected clinically informative examples and added a concise forward-looking paragraph on phase III programs and their principal design questions. (Pages 19–22, lines 376–468)

Comment 8
This section covers many clinically relevant variables but would benefit from greater critical evaluation.
Age
The authors appropriately acknowledge conflicting evidence. However, the speculation that poorer outcomes in elderly patients are attributable to performance status should be explicitly identified as a hypothesis rather than an evidence-based conclusion.
Obesity
The discussion of the obesity paradox is balanced, but the section should place greater emphasis on body composition measures such as sarcopenia, visceral adiposity, and muscle mass, which may be more informative than BMI alone.
Sex Differences
The manuscript discusses biological mechanisms but ultimately acknowledges inconsistent clinical evidence. The conclusion that women generally demonstrate poorer responses to PD-(L)1 inhibitors may be overly definitive given the conflicting literature cited in the same section. The language should be softened.
Smoking
The discussion appropriately addresses smoking-associated immunogenicity but should more strongly emphasize that smoking is not clinically desirable despite its association with increased immunotherapy responsiveness. Some readers could misinterpret this section without appropriate contextualization.
Gut Microbiota
This section is timely and comprehensive. However, the review should more clearly distinguish between association and causation. Many microbiome findings remain exploratory and have not yet been translated into standard clinical practice.
The authors should also discuss challenges in microbiome standardization, reproducibility, geographic variation, dietary influences, and sequencing methodologies.
Glucocorticoids
This is a well-developed section. Nonetheless, it would benefit from discussion of indication bias. Patients receiving corticosteroids often have more advanced disease or worse clinical status, which may partially explain poorer outcomes observed in retrospective studies.
Response: Thank you for these detailed recommendations. The section has been revised as follows:
Age: The proposed contribution of performance status and comorbidity to poorer outcomes in some older cohorts is now explicitly described as a hypothesis and a potential source of confounding rather than an established causal explanation. Pages 23–24, lines 477–491.
Obesity: The revised text places greater emphasis on sarcopenia, skeletal-muscle mass, visceral adiposity, and body-composition phenotypes, while noting that BMI alone may inadequately characterize metabolic and nutritional status. Page 24, lines 502–512.
Sex differences: The conclusion has been softened. The manuscript now states that sex-related differences remain inconsistent across studies and cannot presently support sex-specific treatment selection. Pages 24–25, lines 513–523.
Smoking: We now explicitly state that smoking should never be interpreted as clinically desirable or recommended. The association with immunotherapy responsiveness is presented as a marker of smoking-related mutational exposure and tumor immunogenicity, not a beneficial effect of smoking. Page 25, lines 524–532.
Gut microbiota: The revised section distinguishes association from causation and emphasizes that microbiome-based prediction or intervention remains investigational. Standardization, reproducibility, geographic and dietary variation, antibiotic exposure, sample handling, sequencing platforms, and bioinformatic pipelines are now discussed. Pages 25–26, lines 533–558.
Glucocorticoids: Indication bias and residual confounding have been added as major interpretive limitations because corticosteroid use frequently reflects symptomatic brain metastases, respiratory compromise, poor performance status, or advanced disease burden. Pages 26–27, lines 559–575.

Comment 9
The conclusion effectively synthesizes the major findings.
However, the manuscript should move beyond simply listing positive and negative factors. A stronger

conceptual framework is needed. Specifically, the authors should emphasize: Integration of biomarkers rather than reliance on single biomarkers. Multi-parameter predictive models. AI-assisted prediction tools.Spatial transcriptomics. Single-cell sequencing.Circulating tumor DNA biomarkers. Dynamic biomarkers measured during treatment. These topics are likely to represent the future direction of precision immuno-oncology.
Response: We appreciate this forward-looking recommendation. The Conclusion has been reorganized around a conceptual framework in which treatment response reflects the interaction of tumor genomics, immune contexture, host factors, treatment exposure, and time. The revised manuscript emphasizes integrated multiparameter models rather than isolated biomarkers and discusses artificial-intelligence-assisted prediction, spatial transcriptomics, single-cell sequencing, circulating tumor DNA, and on-treatment dynamic biomarkers. These approaches are presented as promising research directions that require analytical standardization, prospective validation, clinical utility assessment, and demonstration of added value over established clinical variables. Pages 28–30, lines 577–626

Comment 10
The manuscript requires moderate language editing by a fluent scientific English editor.
Examples include: Inconsistent article usage. Occasional awkward phrasing. Repetitive sentence structures. Overly long sentences. Frequent use of speculative language without qualification. Examples include phrases such as "we speculate" and several instances where causation is implied despite observational evidence.
The manuscript should also undergo a careful terminology review to ensure consistent use of: PD-1, PD-L1, PD-(L), ICI, Immunotherapy throughout the text.
Response: Thank you for identifying these language and terminology issues. The manuscript has undergone substantial scientific English editing to improve article usage, awkward constructions, repetitive syntax, and overly long sentences. Causal wording has been revised where the supporting evidence is observational, and speculative statements are now more explicitly qualified. Terminology has also been harmonized according to context: “PD-1” and “PD-L1” are used when the individual targets are specified, whereas “PD-(L)1” is used when a statement applies to either pathway. “Immune checkpoint inhibitor” or “ICI” is used after definition, and the broader term “immunotherapy” is retained only when the statement extends beyond checkpoint inhibition. (Pages 4–6, lines 42–98, and Pages 28–30, lines 577–626.)

Comment 11
The manuscript references multiple figures (Figures 1–6), but based on the text alone it is unclear whether they adequately synthesize information or merely illustrate concepts. The figures should be evaluated to ensure that they: Add value beyond the text. Are sufficiently detailed. Include clear legends. Clearly distinguish established evidence from emerging hypotheses. Provide integrated models rather than isolated mechanisms.
Response: We appreciate this recommendation. All six figures and their legends were reassessed against the revised manuscript. The existing figure designs were retained because each provides a focused mechanistic or conceptual overview that adds visual value beyond the corresponding text. We did not introduce visual labels that classify relationships as “established” or “emerging,” because this narrative review did not apply a formal evidence-grading framework; such labels could imply a level of certainty that was not determined by a prespecified grading process and would substantially increase visual complexity. Instead, the revised main text now states the evidentiary status, limitations, and clinical actionability of the relationships depicted. The legends were reviewed and retained to preserve concise definitions of the illustrated mechanisms and abbreviations.
(Figures 1–6 appear on Pages 7, 14, 16, 17, 19, and 23; figure legends appear on Pages 43–45, lines 1077–1162.)

Reviewer: 2
We sincerely thank Reviewer 2 for the positive assessment of the manuscript’s structure and figures and for identifying areas requiring stronger citation support, clearer synthesis, and greater mechanistic depth. The manuscript has been revised accordingly, with particular attention to citation support, multi-omics evidence, emerging combination strategies, and specific future trial concepts. As explained below, after considering the proposed summary table, we addressed the underlying need for synthesis through the revised Clinical Question Box, expanded critical appraisal, and integrated conclusion rather than adding a table that could oversimplify context-dependent evidence.

Comment 1 Lack of references for key statements: Several crucial mechanistic and clinical statements lack citations, undermining the manuscript's academic rigor. The authors should thoroughly review the entire manuscript and provide appropriate references. Examples include, but are not limited to, the following statements in Section 3.3:
"While classical drivers like EGFR are typically linked to an immunosuppressive TME, rationally designed combination regimens are showing potential to overcome this resistance."
"Conversely, the immunogenicity of KRAS-mutant tumors is predominantly defined by co-mutational status, with STK11 or KEAP1 co-mutations driving profound resistance and TP53 co-mutations often enhancing sensitivity."
"Previous views held that EGFR-mutant NSCLC is typically characterized by a 'cold' TME featuring low TMB and low CD8+ T-cell infiltration, which is associated with poor response to ICI monotherapy."
Response: Thank you for identifying this important deficiency. We reviewed the manuscript comprehensively and added references for mechanistic and clinical statements that were previously unsupported or insufficiently supported. In particular, citations have been added to the statements concerning EGFR-associated immunosuppressive tumor microenvironments and combination strategies, the modifying effects of STK11, KEAP1, and TP53 co-mutations in KRAS-mutant disease, and the low-

TMB/low-CD8 phenotype and limited ICI-monotherapy activity historically reported in EGFR-mutant NSCLC. Where evidence is heterogeneous or mainly retrospective, the wording has also been qualified to avoid presenting these associations as universal or definitively causal. (Pages 14–18, lines 292–374, particularly lines 302–324 and 337–374.)
Comment 2 Addition of a comprehensive summary table: Although various factors are discussed in the text, an intuitive summary is missing. It is highly recommended to add a comprehensive table summarizing the biomarkers and clinical features discussed. Suggested columns include, but are not limited to: Biomarker/Factor, Clinical Role (Positive vs. Negative predictor), Brief Mechanism, Evidence/Specimen Data Support.
Response: We appreciate this practical suggestion. After considering a comprehensive summary table, we respectfully chose not to add one. The factors discussed in this review are highly context dependent, and many represent prognostic associations rather than validated treatment-specific predictors. Organizing them in a simple positive-versus-negative table could therefore overstate clinical actionability and obscure important differences in treatment setting, specimen type, assay method, and level of evidence. A table covering all tumor, microenvironmental, molecular, host, microbiome, medication, and treatment-related factors would also be extensive and would substantially duplicate the six figures and the expanded narrative sections. To address the reviewer's underlying request for clearer synthesis, we revised the Clinical Question Box, added explicit statements regarding clinical implementation and evidentiary limitations throughout the manuscript, and reorganized the conclusion around an integrated, dynamic, multiparameter framework. (Page 3, lines 27–39 and Pages 28–30, lines 577–626)
Comment 3. Integration of high-resolution multi-omics perspectives: The current discussion on TME heterogeneity is somewhat macroscopic. In Section 2 (TME factors), it is advised to incorporate recent insights from single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics. For instance, discuss the formation of Tertiary Lymphoid Structures (TLS) and the critical role of specific cell-cell communication networks in predicting immunotherapy benefits.
Response: Thank you for this valuable recommendation. Section 2 now incorporates evidence from single-cell RNA sequencing and spatial transcriptomics to illustrate intratumoral immune heterogeneity, cellular states, spatial organization, and treatment-induced evolution. The revised discussion includes tertiary lymphoid structures and selected cell-cell communication networks involving tumor cells, T-cell subsets, myeloid populations, stromal cells, and endothelial compartments. We also emphasize that these technologies currently have limited standardization, accessibility, and prospective clinical validation and should therefore be viewed as high-resolution discovery and stratification tools rather than routine biomarkers. (Pages 8–9, lines 133–154, and Page 28, lines 585–592.)
Comment 4. Update on novel combination strategies: In Section 4 (Combination therapy), alongside traditional anti-angiogenic and bispecific agents, please briefly introduce the strategy of combining Antibody-Drug Conjugates (ADCs) with PD-(L)1 inhibitors. This emerging approach is currently demonstrating significant potential in remodeling the TME in NSCLC.
Response: We appreciate this timely suggestion. The combination-therapy section now includes a concise discussion of antibody-drug conjugates combined with PD-(L)1 inhibitors, including the potential contributions of immunogenic cell death, enhanced antigen release, Fc-mediated immune effects, and remodeling of the tumor microenvironment. We have deliberately used cautious language because efficacy and toxicity vary by target, payload, disease setting, and treatment sequence, and the optimal role of these combinations in NSCLC remains under active investigation. (Pages 21–22, lines 448–468)

Comment 5. Enhance the specificity of future directions: In Section 6.2 "Controversies and Directions", it is recommended that the authors propose 1-2 specific, novel trial design concepts to serve as potential breakthroughs for future research in this field.
Response: Thank you for encouraging greater specificity. The future-directions section now proposes two illustrative trial concepts. First, a biomarker-adaptive platform trial could assign or reassign patients according to integrated baseline genomic, spatial immune, and circulating biomarker profiles rather than a single marker. Second, a longitudinal co-clinical trial could incorporate serial circulating tumor DNA, blood immune profiling, and paired tissue or spatial analyses to identify early response and resistance states and adapt therapy before radiographic progression. The manuscript also notes that such designs require prespecified algorithms, assay harmonization, independent validation, and clinically meaningful decision rules. (Page 29, lines 608–623)

Best Regards
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