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Peer Review File

PD-1/ PD-L1 Bispecific Antibody IBI318 Combined with Lenvatinib in Advanced Non-Small Cell Lung Cancer with Acquired Resistance to Immune Checkpoint Inhibitors: A Phase II Trial

Corresponding Author: Professor Yongchang Zhang

This manuscript has been previously reviewed at another journal. This document only contains information relating to versions considered at Nature Communications.

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for consideration of my comments and suggestions.
I have no further concerns.

Reviewer #3

(Remarks to the Author)
The manuscript has been largely improved, I have no further questions.

Reviewer #5

(Remarks to the Author)
This phase II single-arm trial evaluated the bispecific PD-1/PD-L1 antibody IBI318 combined with lenvatinib in patients with advanced, ICI-refractory NSCLC.
The regimen achieved an objective response rate of 40%, a median PFS of 6.9 months, and OS of 18.2 months, with manageable toxicity.
Single-cell RNA-seq and multiplex immunofluorescence revealed enriched $CD4^+$, $CD8^+$ T-cell, and macrophage populations in responders, supporting a VEGF-related immune-modulatory mechanism.
The authors have provided comprehensive and well-structured replies to the previous reviewers' comments.
For Reviewer #2, all major points were addressed appropriately. The introduction was streamlined and expanded to include the VEGF-related resistance mechanisms and recent phase III data. Early clinical data and the rationale for IBI318 were added. Molecular testing (NGS), PD-L1 distribution, and safety monitoring procedures were clarified in detail. The requested multivariate Cox analysis was conducted and incorporated, I suggest to report the results using a logorhithmic scale. Translational aspects, including T-cell exhaustion and comparison of pre- vs. post-ICI samples, were newly analyzed and clearly reported. The limitations of the single-arm design are now explicitly acknowledged. Overall, the responses are complete and scientifically sound.
For Reviewer #4, the authors also provided detailed revisions. They added full information on first-line regimens, included discussion of the HARMONi-2 (ivonescimab) study, and reported relevant mutations (STK11, TP53, etc.). Translational findings were expanded with new Kaplan-Meier analyses of TNFRSF9-positive subsets and a pathway-level analysis of the dsRNA response. The discussion and limitation sections now appropriately reflect these additions.
The authors have adequately and convincingly addressed all major issues raised by reviewers #2 and #4. The revised manuscript is substantially improved in clarity, methodological transparency, and depth of translational interpretation. No major points remain unresolved.

Point-by-point response to the reviewers' comments

Reviewer-Specific Responses:

Reviewer #1 (Remarks to the Author):

Thank you for consideration of my comments and suggestions.

I have no further concerns.

Response: Thank you for your constructive feedback and for carefully reviewing our revised manuscript. We appreciate your time and valuable input.

Reviewer #3 (Remarks to the Author):

The manuscript has been largely improved, I have no further questions.

Response: Thank you for your valuable feedback and for recognizing the improvements made to our manuscript. We appreciate your thorough review.

Reviewer #5 (Remarks to the Author):

This phase II single-arm trial evaluated the bispecific PD-1/PD-L1 antibody IBI318 combined with lenvatinib in patients with advanced, ICI-refractory NSCLC.

The regimen achieved an objective response rate of 40%, a median PFS of 6.9 months, and OS of 18.2 months, with manageable toxicity.

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relevant mutations (STK11, TP53, etc.). Translational findings were expanded with new Kaplan-Meier analyses of TNFRSF9-positive subsets and a pathway-level analysis of the dsRNA response. The discussion and limitation sections now appropriately reflect these additions.

The authors have adequately and convincingly addressed all major issues raised by reviewers #2 and #4. The revised manuscript is substantially improved in clarity, methodological transparency, and depth of translational interpretation. No major points remain unresolved.

Response: Thank you for your review and positive feedback. We appreciate your time.