Peer Review File

Article Information: https://dx.doi.org/10.21037/jtd-2025-1882

Reviewer A

The manuscript provides a clear and comprehensive summary of clinical trials evaluating the combination of PD-1 antibodies and VEGF inhibitors in the context of PD-1 antibody resistance. As "overall survival (OS)" is already abbreviated at line 60, the same abbreviation should be used consistently in lines 94, 97, 114, and 142.

Likewise, please correct "antibody–drug conjugate" to "ADC" in lines 101 and 113 for consistency.

Comment A1: consistency of OS abbreviation

Response: I thank the reviewer for this correction. OS is now used consistently in all corresponding lines.

Comment A2: "antibody–drug conjugate" → "ADC"

Response: Corrected as recommended.

Reviewer B

Thank you for the opportunity to review this thoughtful and clearly written editorial.

It presents an excellent overview of ICI resistance mechanisms in NSCLC, particularly the restricted effectiveness of VEGF blockade in the post-immunotherapy context.

While the commentary is concise and informative, several aspects could be expanded to further enrich its scientific and clinical impact.

1. Tumor-type differences (RCC/HCC vs NSCLC)

The manuscript could benefit from a clearer explanation of why VEGF–ICI combinations succeed in renal cell carcinoma and hepatocellular carcinoma but have failed to replicate this efficacy in NSCLC.

A brief mechanistic comparison emphasizing the angiogenesis-driven biology of RCC/HCC versus the molecular heterogeneity, stromal fibrosis, and immune exclusion typical of NSCLC would help contextualize the inconsistent results across tumor types.

Response: I agree that this comparison strengthens the context. Accordingly, a brief mechanistic contrast has now been added to the *Introduction* section, at line 25 — i.e., immediately following the sentence "in renal cell (13) and hepatocellular carcinoma (14)."

Insertion sentence:

RCC and HCC are biologically more angiogenesis-driven, whereas NSCLC is characterized by molecular heterogeneity, stromal fibrosis, and immune exclusion, which may partly explain the inconsistent efficacy of VEGF–ICI combinations.

2. Myeloid-mediated immunosuppression

Recent literature (e.g., Targeting Myeloid Cells for Cancer Immunotherapy, 2025) underscores

that tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) remain key mediators of immune evasion, even after VEGF pathway inhibition.
A short discussion on the therapeutic potential of targeting this myeloid axis—through agents such as CSF1R, AXL, or PI3Kγ inhibitors—would expand the future perspectives section and align it with current translational directions.

Response: I agree. A concise statement has now been incorporated at the end of the *Introduction* section, at line 39. In addition, this paper (Targeting Myeloid Cells for Cancer Immunotherapy, 2025) has now been added to the reference list.
Insertion sentence:
Notably, tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells continue to drive immune evasion after VEGF blockade, and targeting this myeloid axis (for example via CSF1R, AXL, or PI3Kγ inhibition) is an emerging therapeutic direction.

Ref. 19 Blanchard L, Mijacika A, Osorio JC. Targeting Myeloid Cells for Cancer Immunotherapy. Cancer Immunol Res. 2025 Nov 3;13(11):1700-1715.

3. Epigenetic regulation of resistance
Increasing evidence suggests that chromatin remodeling and aberrant DNA methylation can downregulate antigen-presentation machinery (B2M, HLA) and limit cytotoxic T-cell infiltration, fostering immune ignorance independent of angiogenesis.
Moreover, adaptive epigenetic reprogramming during prolonged ICI exposure can lead to interferon-γ signaling loss and T-cell exhaustion, driving secondary resistance.
Because these processes are potentially reversible, mentioning them could highlight the rationale for combining ICIs with epigenetic therapies (e.g., DNMT, HDAC, or BET inhibitors) to restore immunogenicity in resistant tumors.

Response: I appreciate this suggestion. To address this point, I have now added a more explicit statement highlighting that epigenetically driven loss of antigen-presentation and interferon-γ signaling provides a mechanistic basis for acquired/secondary resistance to ICIs, and thus supports the rationale for epigenetic combination strategies. This sentence has been inserted at line 100 (i.e., following the sentence "…multiple ADCs (27,28) have not demonstrated consistent improvements in OS."). In addition, the paper by Wenjun Huang et al., Cell Death Discov. 2024 (Dual inhibitors of DNMT and HDAC induce viral mimicry to induce antitumour immunity in breast cancer) has now been added to the reference list to support this point.
Insertion sentence:
Reversible epigenetic alterations—including chromatin remodeling and aberrant DNA methylation—can silence antigen-presentation machinery (e.g., beta2-Microglobulin, HLA) and attenuate interferon-γ signaling, thereby fostering immune ignorance and driving secondary resistance; consequently, evaluating DNA methyltransferase, histone deacetylase, or bromodomain and extra-terminal domain inhibitors in combination with ICIs represents a rational approach to restore tumor immunogenicity.

Ref. 30 Huang W, Zhu Q, Shi Z, et al. Dual inhibitors of DNMT and HDAC induce viral

mimicry to induce antitumour immunity in breast cancer. Cell Death Discov. 2024 Mar 15;10(1):143.

4. Host and microbiome influences
Emerging data demonstrate that gut microbiota composition and systemic inflammatory status can profoundly affect ICI responsiveness.
Briefly acknowledging these host-derived modulators in the conclusion would emphasize that therapeutic resistance extends beyond tumor-intrinsic or angiogenic pathways.

Response: Thank you for this helpful comment. As suggested, I have now added a concise statement acknowledging host-derived modulators of ICI responsiveness. This sentence has been inserted in the *Conclusion* section at line 136 (i.e., following the sentence "…no VEGF plus ICI regimen has demonstrated efficacy…" on line 136).
Insertion sentence:
Host-derived factors such as gut microbial composition and systemic inflammatory state also modulate ICI responsiveness and contribute to resistance beyond tumor-intrinsic mechanisms.

5. Dynamic evolution of immune resistance
The manuscript could elaborate on the dynamic nature of immune resistance.
Discussing how tumors transition over time from an immune-inflamed to an immune-exhausted phenotype would support the importance of longitudinal immune profiling and biomarker-based stratification in clinical trial design.

Response: I thank the reviewer for this valuable suggestion. I agree that immune resistance is not a static phenomenon, but evolves under treatment selection pressure. Initially immune-inflamed phenotypes can shift towards exhausted states through adaptive T-cell dysfunction and progressive remodeling of the tumour microenvironment. To reflect this dynamic transition more explicitly, I have added a short sentence emphasising that longitudinal immune profiling and resistance-type stratification are therefore essential for clinical trial design. This sentence has been inserted immediately after line 118.

Insertion sentence
Over time, initially immune-inflamed tumors can transition towards immune-exhausted phenotypes through treatment-induced adaptive changes in the TME, highlighting the importance of longitudinal immune profiling and biomarker-based stratification in clinical trials to capture, and respond to, this dynamic evolution of resistance.