Peer Review File
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Reviewer Comments

This commentary provides a timely overview of the role of TROP2 in advanced NSCLC, focusing on its potential as a predictive biomarker for immunotherapy resistance. The authors effectively summarize recent research, notably the study by Bessede et al., highlighting the association between TROP2 expression and primary resistance to PD-L1 blockade. The commentary also discusses ongoing clinical trials investigating TROP2-targeted therapies, particularly ADCs, in combination with ICIs. While the commentary mentions the use of TROP2 ADCs with ICIs, it could benefit from a broader discussion of other combination strategies under investigation. Moreover, exploring potential differences in TROP2 expression and its impact on ICI resistance across various subtypes would be informative. The Rise of the TROP2-Targeting Agents in NSCLC: New Options on the Horizon and TROP2-Directed Antibody-Drug Conjugates in Advanced Non-Small Cell Lung Cancer: A Fading Hope? offer valuable insights into the potential of TROP2-targeted therapies, specifically ADCs, in combination with ICIs for treating advanced NSCLC. Including these two articles would support your discussion on the emerging role of TROP2 and its potential as a predictive biomarker.

Responses:

We sincerely appreciate the positive feedback from the reviewers and the editorial board. In the revised manuscript, we have thoroughly addressed all the concerns and suggestions put forth by the reviewers. Below, we outline specific issue raised by the reviewers. Additionally, we have uploaded a revised and cleaned version of the manuscript for your consideration. We have highlighted/ amended/ modified the following changes.

1. The current literature is also consistent with the clinical use of emerging TROP2 ADC in advanced NSCLC (20). Pérol M also summarized the exponential role of SG, as per the EVOKE phase III trial results, in the subsequent-line treatment for advanced NSCLC. The study showed an overall survival benefit of 11.8 months with SG compared to 8.3 months with docetaxel chemotherapy in patients who had previously received immune checkpoint inhibitors and were non-responders. This also explains the potential benefit of TROP2 ADC in post-ICI-resistant patients (21). (Page # 3, Paragraph # 1, Line # 11-17).

2. Added the following references as per the suggestions (Page #9, ref. 20 & 21).

20. Ahmed Y, Berenguer-Pina JJ, Mahgoub T. The Rise of the TROP2-Targeting Agents in NSCLC: New Options on the Horizon. Oncology. 2021; 99(10):673-80.
21. Pérol M. TROP2-Directed Antibody-Drug Conjugates in Advanced Non–Small Cell Lung Cancer: A Fading Hope? Journal of Clinical Oncology. 2024; 42(24):2839-42.

3. Understanding how TROP2 expression varies across different NSCLC subtypes, such as adenocarcinoma, squamous cell carcinoma, adenosquamous, and large cell carcinoma, is also vital. Given these complexities, validating and implementing TROP2 as a biomarker in the current therapeutic landscape requires large-scale, prospective RCTs. Such trials must consider not only the biomarker's predictive value but also its interaction with various treatment combinations and cancer subtypes. (Page # 4, Paragraph #2, line # 11-14).