Peer Review File

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Reviewer A

The manuscript entitled 'To be or low TMB' shows an interesting Editorial Commentary on the article by van de Haar et al that reflects on the role of TMB in NSCLC with mutations predictive of resistance to immunotherapy. Undoubtedly, the original article already shows a study of great clinical relevance and the current reflection in Editorial Commentary I think is very accurate because the role of TMB is not yet well established in clinical practice in contrast to PD-L1. Therefore, analysing the most important conclusions of the original article is essential.

The authors' manuscript is well written in plain and easily understood English. It is also well structured and does not need major changes apart from some annotations that I think could improve its quality.

In my view, it is publishable, although the following changes could be made first:
- Human genes should be in italics.
Reply: The manuscript was adjusted accordingly.

- Lines 49-51: it would be correct to add the bibliographic citation.
Reply: Two references were added (Ref 4,5).

- More specific data from the original article could be added in the penultimate paragraph to give the reader a clearer idea of the conclusions being discussed.
Reply: An additional paragraph was included in the penultimate paragraph to highlight key findings and conclusions of the original article.

Reviewer B

This editorial is interesting and well-written.

However, response to immunotherapy is not solely dependent on somatic mutations (e.g., binding of rs822336 to C/EBPβ and NFIC modulates induction of PD-L1 expression and predicts anti-PD-1/PD-L1 therapy in advanced NSCLC. Mol Cancer. 2024 Mar 25;23(1):63. doi: 10.1186/s12943-024-01976-2.). Germline genetic variations also influence patient outcomes and therapeutic response. This aspect should be discussed.

Reply: We included this valid point at the end of the penultimate paragraph and added reference 6 to the literature list.

Reviewer C

The editorial is well-written, delivering its message clearly and concisely.

It effectively highlights the potential of combining biomarkers to better predict which NSCLC patients will benefit from immunotherapy.

The editorial thoughtfully addresses the contributions of the van de Haar study and its limitations.

The comment on recent findings about multi-drug combinations adds relevance for clinical application.

Including a simple flowchart could further clarify the steps for applying this combined biomarker approach in clinical practice.
Reply: We thank the reviewer for this idea, however considering the format requirements we would prefer to exclude figures from the manuscript.

Minor points:
Page 3, line 67: "reveice" – change to "receive"
Reply: Text was adjusted accordingly.

Page 2, line 59: "...with low allelic frequencies thus, routine use..." – change to "...with low allelic frequencies. Thus, routine use...".
Reply: Text was adjusted accordingly.