Peer Review File

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Reviewer A

This is a well-written editorial. At times it is a bit dry, more or less restating the information from the original article on which it is based. It would be better if the authors took some time to discuss the implications of these new data from the Vision trial.

Response: We agree that some parts of the manuscript may be a bit try. However, we think it is important to describe both cohort A data by Paik et al. and long-term cohort C data by Mazieres et al. to ease the readers' understanding in relation to study design and outcome data. The design of the VISION trial was complex, and two different companion diagnostic assays were used for patient selection, necessitating further clarification. However, according to the recommendation of Reviewer A, a section on page 6 has been added to discuss the implications of the VISION trial data.

How does efficacy compare to long-term outcomes for the best targeted therapies for other targetable driver mutant lung cancer- EGFR, ALK, ROS1, RET, etc?

Response: We have added a brief discussion on the subject on page 5 as well as references to several papers on targeted therapies related to EFGR, ALK, ROS1, and RET. The following text has been added: "The efficacy of tepotinib observed in the VISION study is comparable to that of other oncogene-defined NSCLC patients treated with targeted therapies (23-28). Both the ORR and DOR reported in the VISION trial are clinically meaningful and constitute a good basis for the use of targeted therapy with tepotinib in NSCLC patients with METex14, both as first and further lines."

What about CNS penetration compared to other targeted therapies including capmatinib? Are there any data in this study that differentiate tepotinib from other met this like savolitinib and capmatinib?

Response: We have added a brief discussion on this subject and on page 5 and the following sentence has been added: "Similar outcomes have been obtained using capmatinib and savolitinib, as both drugs are capable of crossing the blood-brain barrier (9, 13, 16, 22).

Clinically, what does the lack of companion diagnostic mean? I am not sure this has any real implications.

Response: We have added a discussion of the importance of companion diagnostic assays for targeted therapy on page 5. The following text has been added: "Patients enrolled in the VISION trial, based on tissue biopsy results, demonstrated extended time-dependent endpoints compared to patients enrolled via liquid biopsies (19). This observation suggests variation in sensitivity between the methods used for enrollment. To enable safe and effective treatment decisions, sampling methods and assays should represent highest possible sensitivity and specificity. Therefore, it is imperative to develop companion diagnostics that guarantee high precision, repeatability, overall robustness, and sensitivity to ensure correct clinical and therapeutic decisions for every patient.2

How should these data affect the treatment algorithm for met exon 14 skip positive lung cancer? Should we be

using tepotinib (or capmatinib) first line in regions where these drugs are approved first line? If not approved, what should be used first line? Should tepotinib then be used second line based on cohort A and C from this study?

Response: We have included a discussion of the above questions and on page 6 and the following text has been added:" The efficacy and safety data from the VISION trial support the use of tepotinib as first or subsequent line of treatment, as it has recently been recommended by the NCCN (34). In regions where tepotinib or capmatinib are available, these MET-TKIs should be used because of their efficacy in terms of high ORR and median PFS (35). No head-to-head comparison has been performed with different MET inhibitors, but using the matching-adjusted indirect comparison methodology, a potential difference was identified in the efficacy endpoints with prolonged PFS and OS with tepotinib compared to capmatinib and crizotinib (36). If the MET-TKIs are not approved or available, patients may be offered standard of care or be screened to clinical studies with tepotinib or capmatinib or other MET-TKIs. No direct comparison of MET-TKIs with the current first line standard treatment is available in NSCLC-patients with METex14. However, the recently published retrospective review collected data of 1401 NSCLC-patients with METex14 showed higher ORR and longer median PFS in patients treated with MET-TKIs comparing to patients treated with chemotherapy +/- immunotherapy or immunotherapy alone (2)."

Moreover, on page 6, we have added the following text: "Based on data from the VISION trial in previously treated patients in cohorts A and C, the efficacy of second-line treatment in terms of an ORR of 45% and a DOR of 12.6 months represents a good therapeutic option as there is no other second-line treatment with such efficacy for these patients (19).

Reviewer B

This editorial comment is mainly focused on the VISION trial and tepotinib. It appears mainly incomplete. The authors describe that trial without a widely discussed personal view. Many recent review articles addressed and discussed this topic, so that it seems that this paper does not add further information or points of view. The paper should be deeply rewritten to be useful and attractive.

Response: The assignment given to us by Translational Lung Cancer Research was to write an Editorial Commentary on the long-term follow-up of the VISION Phase 2 clinical trial, which is why it has been discussed thoroughly. This may not have been sufficiently clear in the first version of our manuscript, why we on page 2 has added the following text:" The main objective of this Editorial Commentary was to present and discuss long-term follow-up data for tepotinib, a selective MET inhibitor, in NSCLC patients with METex14 mutations from the VISION Phase II clinical trial."

Moreover, on pages 5 and 6, we have included more personal views in the various sections of the manuscript.

Reviewer C

The authors did a good job summarizing the available evidence highlighting clinical findings.
However, it is a little confusing to understand the scope of the paper (Is it just about clinical efficacy for a single trial data?). Since there are 3-4 approved therapies, I was not clear why results related to only one

therapy were presented. Can the scope be explained in the beginning?

Response: The assignment given to us by Translational Lung Cancer Research was to write an Editorial Commentary on the long-term follow-up of the VISION Phase 2 clinical trial, which is why it has been discussed thoroughly. This may not have been sufficiently clear in the first version of our manuscript, why we on page 2 has added the following text:" The main objective of this Editorial Commentary was to present and discuss long-term follow-up data for tepotinib, a selective MET inhibitor, in NSCLC patients with METex14 mutations from the VISION Phase II clinical trial."

Overall, it would also be good to mention what was not captured from the trial (secondary end points etc.)

Response: We have added a brief discussion of the secondary endpoint that was not captured in the VISION trial. On page 6, the following text has been added: "With regard to the secondary endpoints of PFS and OS, the follow-up time is still relatively short, and more mature data may help specify these endpoints in the future. Furthermore, the use of different NGS assays to identify patients with METex14 in the VISION trial identified different patient populations with different disease dynamics, which may also have affected PFS and OS."

Reviewer D

The Editorial Commentary was well written with minor comments to be added. Could you please add some more recent refs to it and also revise grammar in the whole text?

Response: We have included more recent references in the revised version of our manuscript. Please refer to references 22, 23, 24, 25, 26, 27, 28, 35, and 36. The original manuscript contained 28 references, of which 24 were published between 2020 and 2024. Therefore, we have ensured that the latest research has been incorporated. Furthermore, the manuscript has been thoroughly proofread and some corrections have been made.