Peer Review File

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Reviewer A

Comment 1. The Editorial Commentary is well summarized concerning MET. Line 80: del 18 -> del 19?

Reply 1: Corrected, thank you.
Changes in the text: Line 104: del 18 -> del 19.

Reviewer B

Comment 1. The author should go through the entire text carefully for errors, e.g. row 80 (del 18 versus L858R), should be exon 19 deletion.

Reply 1: Corrected, thank you.
Changes in the text: Line 104: del 18 -> del 19.

Reviewer C

Comment 1. L67-69. The addition of erlotinib to Teliso-V improved efficacy in the c-MET high EGFRm population compared to prior studies with single-agent Teliso-V, where ORR was only 11.6%. Compared to prior studies with single-agent Teliso-Vin the c-MET high EGFRm population,where ORR was only 11.6%.
It would be better to clearly state that this is a prior study in the c-MET high EGFRm population.

Reply 1: Clarification added, thank you.
Changes in the text: Lines 87-88: Added "…in the c-MET high EGFRm population".

Reviewer D

Comment 1. Introductory part, line 8-18: to be complete it should be mentioned that capmatinib and tepotinib are FDA-approved for treating MET ex14-positive NSCLC, while these drugs are EMA-approved for second-line therapy of this molecular subtype of NSCLC. Furthermore, there is savolitinib, which is only approved in China so far, but is being tested. The authors rightfully cite reference 5 for MET-TKI treatment of MET-amplified NSCLC but the other mentioned MET-TKIs (and others) as well as the bispecific mAb amivantamab, some recombinant mAbs and Ab-drug-conjugates are also being tested in different trials for de novo MET-amplified NSCLC and for acquired MET-amplification in EGFR-mutated NSCLC. See the article by Remon J. et al in JTO 2023 (doi: 10.1016/j.jtho.2022.10.015) for an updated review on this issue that might be cited by the authors to provide a more complete introductive overview.

Reply 1: Thank you, we have provided more detail on the different TKIs and mAbs that target MET. We have added the recommended reference to this section.

Changes in the text: Lines 22-35: “The MET TKIs capmatinib and tepotinib are FDA-approved in the United States for patients with METex14 mutation-positive non-small cell lung cancer (NSCLC), and approved by the EMA in Europe as a second-line treatment option. Savolitinib is approved in the second-line setting in China. Apart from MET TKIs, amivantamab (a bispecific antibody targeting epidermal growth factor receptor (EGFR) and MET) and Sym015 (a mixture of two humanized monoclonal antibodies that degrade MET receptor by binding to its extracellular domain), have shown activity against METex14 positive NSCLC.(5,6) (Figure 1). These MET TKIs and antibodies have shown activity against both de-novo and acquired MET-amplification in NSCLC but further studies are needed to delineate the role of these agents in treating patients with MET-amplified NSCLC (Reviewed in Remon et al, 2023.)(7)”.

Comment 2. Line 20-21, “However, c-Met overexpression is far more common in patients with NSCLC at 30%-70%”: It would be more correct to state that it is more common (frequency 30%-70%) than MET ex14 mutations and MET-amplification, suggesting that additional mechanisms of MET protein upregulation exist in NSCLC.

Reply 2: Clarification added, thank you.
Changes in the text: Line 38: Added “…than METex14 and MET amplification”.

Comment 3. Line 26-27, “antibody drug conjugates’”: it should be “antibody-drug conjugates”.

Reply 3: Corrected.
Changes in the text: Line 44: Hyphen added.

Comment 4. Line 44-45, “Archival tissue was required to confirm c-Met overexpression”: for clarification to readers unaware of the phase 1b study by Camidge et al. in reference 14, it may be worth specifying that MET-expression in that study was considered positive when it showed a histology [H]-score of at least 150.

Reply 4: Additional information added.
Changes in the text: Lines 63-74: Added “c-Met-overexpression in this study was defined as histology (H) - score of 150 or greater.”

Comment 5. Line 48, off target should be off-target.

Reply 5: Corrected.
Changes in the text: Line 67: Hyphen added.

Comment 6. Line 60, “had an ORR of 52.8% including one CR”: in reference 14 they wrote 52.6%.

Reply 6: Corrected, thank you.
Changes in the text: Line 80: 52.8% changed to 52.6%.

Comment 7. Line 71-73, “The median PFS was only 3.7 months in the T790M patients (46%), compared to 6.8 months in the patients without T790M”: this sentence is a repetition, as the same comment is written on line 57-59. One of the two sentences should be eliminated or reformulated. The main point is, in any case, that the presence of T790M impairs the effect of erlotinib in the Teliso-V + erlotinib combination treatment.

Reply 7: Second sentence deleted.
Changes in the text: Lines 94-96: Deleted “The median PFS was only 3.7 months in the T790M patients (46%), compared to 6.8 months in the patients without T790M”.

Comment 8. Line 73-74, “A phase I/Ib study combining Teliso-V with the 3rd generation EGFR TKI osimertinib in patients who previously failed osimertinib, reported an ORR of 58%”: true but is should be specified that this was only observed in MET-overexpressing cases (3+ intensity of immunostaining in over 25% of tumor cells in the study of reference 17)

Reply 8: Clarification added.
Changes in the text: Lines 97-98: Added “…with c-Met-overexpression, defined as 3+ intensity of immunostaining in over 25% of tumor cells…”

Comment 9. Line 80, “(del 18 versus L858R)” should be “(ex19del vs. L858R)”.

Reply 9: Corrected, thank you.
Changes in the text: Line 104: del 18 -> del 19

Comment 10. Line 91, “for c-Met overexpressing” should be “for c-Met-overexpressing”.

Reply 10: Hyphen added.
Changes in the text: Line 116: Hyphen added.

Reviewer E
Comment 1. I think there is a minor typo in line 60 “Patients with high c-Met scores (H score > 225) had an ORR of 52.8% including one CR”. Can you check the 52.8% figure

as per my reading it is 52.6%?

Reply 1: Corrected, thank you.
Changes in the text: Line 80: 52.8% changed to 52.6%.