Peer Review File

Article information: https://dx.doi.org/10.21037/atm-2022-56

To Reviewer A

Thank you for your many informative comments. Our point-by-point reply is below. We hope that you will find our changes acceptable.

Responses to your comments

Comment 1: Page 3 line 9. Check references 11 and 12.

Reply 1: Thank you for your comment. We have checked references 11 and 12 again. Then, we have revised the style in the references section. Additionally, we have cited an another reference (number 13).

Comment 2: Page 5 line 11-13. ORR and PFS towards what? You probably meant TKIs based on the fact that you are citing Table 1 but the readers should not have to guess. Please clarify.

Reply 2: Thank you for your valuable suggestion. According to your suggestion, we have revised as follows.

Changes in the text: (page5 L11); Previous reports indicated unfavorable outcomes of EGFR-TKIs

Comment 3: Page 5 line 15 references 2-6 and line 17 references 2-4 are regarding common EGFR mutations. The data on response to chemotherapy is of particular importance. Please cite the references cited in Table 2 here.

Reply 3: Thank you for your valuable suggestion. According to your suggestion, we have cited the references (page5 L15 and L17).

Comment 4: Page 6 line 15. In the US, the approved dose is 1400mg in patients >80kg. It is possible that 1450 was still the RP2D but please double check.

Reply 4: Thank you for your pointing out our mistake. We have corrected to 1400mg (page6 L17).

Comment 5-1: Page 7 line 8-17. Reference 49 and the content is true as preclinical data but please note that the SWOG study utilizing afatinib and cetuximab was negative (Goldberg et al, J Clin Oncol. 2020 Dec 1;38(34):4076-4085. doi: 10.1200/ JCO.20.01149).

Reply 5-1: Thank you for your valuable comment. According to your comment, we have added a sentence and cited a reference as follows.

Changes in the text: (page7 L16-L19): Although first-line afatinib plus cetuximab did not improve clinical outcomes compared with afatinib alone for advanced EGFR-mutant NSCLC in the randomized phase II SWOG S1403 trial, the potential for concomitant use of these kind of drugs still remains an area of interest (50).

Comment 5-2: Amivantamab is likely more than just an antibody given its immuno-modulatory effects such as trogocytosis. Please elaborate more.

Reply 5-2: Thank you for your valuable suggestion. According to your suggestion, we have added a sentence as follows.

Changes in the text: (page6 L10-L11); This increases immune-mediated antitumor activities such as antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and trogocytosis (47, 48).

Comment 6: Page 8 line 17. The FDA approval was based on pre-platinum treated

patients N=114. I do not know if you need to talk about another cohort from the EXCLAIM study (N=96) but if you are, please specify what this cohort was.

Reply 6: Thank you for your valuable suggestion. According to your suggestion, we have deleted a sentence regarding EXCLAIM cohort.

Comment 7: Page 10. Both CLN-081 as well as DZD9008 have been given FDA breakthrough therapy designation in January 2022. Please update the paper to include this information.

Reply 7: Thank you for your valuable suggestion. According to your suggestion, we have added sentences as follows.

Changes in the text: (page10 L13-L14); The FDA has granted a breakthrough therapy designation for CLN-081 in January 2022.

(page11 L4-L5): The FDA has granted a breakthrough therapy designation for DZD9008 in January 2022.

Comment 8: Page 11 Line 18. Grammar. change have been developed to had been developed.

Reply 8: Thank you for your comment. We have revised as you pointed out (page 12 L4).

Comment 9: Page 12 Line 1-2. Please mention here again that both amivantamab and mobocertinib have been given FDA accelerated approval.

Reply 9: Thank you for your valuable suggestion. According to your suggestion, we have added sentences as follows.

Changes in the text: (page12 L8); Based on the results, FDA has accelerated the

approval of amivantamab and mobocertinib.

Comment 10: Page 12 line 4. "are not comparable" may replace with a better wording

Reply 10: Thank you for your comment. We have revised as follows.

Changes in the text: (page12 L10); However, the efficacy data observed with these novel EGFR inhibitors do not come up to those of highly effective molecular targeted therapies (e.g., osimertinib in common EGFR mutations).

Comment 11: Page 12 line 16. Grammar. Omit "the". their efficacy might be limited by CNS progression.

Reply 11: Thank you for your comment. We have omitted as you pointed out (page 13 L3).

Comment 12: Page 13. Not only was IO not effective for EGFR mutated patients but was harmful with increased rates or irAEs such as pneumonitis. Please also note that Pasi Janne presented the pre-IO treated patient cohort from the mobocertinib study at World Lung 2021 and there was increase in adverse events.

Reply 12: Thank you for your valuable suggestion. According to your suggestion, we have added sentences and cited a reference as follows.

Changes in the text: (page14 L3-L7); Furthermore, it might be necessary to consider the order in which ICI and these novel targeted therapies are used in terms of safety concern. In an aforementioned phase I/II clinical trial of mobocertinib, grade 3 or higher treatment-related adverse events occurred in 58% of the previously platinum-treated patients subset who received prior ICI and 39% of patients who did not receive prior ICI, respectively (33, 74).

To Reviewer B

(Reviewer B provided a summary of our manuscript and future direction of this field. No specific points to be corrected were attached)

Thank you for reviewing our manuscript. We have updated our previous manuscript according to the comments of the other reviewer. We hope you find the changes acceptable.