Peer Review File

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Reviewer A

This editorial commentary entitled "What the future holds: BBT-176, beyond third-generation EGFR tyrosine kinase inhibitors" by Dr. Laface reviewed focusing on new generation EGFR TKI, BBT-176 with regard to the resistance of osimertinb. This comment is comprehensive enough as they mentioned the structure and activity of EGFR pathway.

Line 58-59: "and monoclonal antibodies (e.g., lazertinib with amivantamab) [12], antibody-drug conjugates targeting the extracellular domain of receptor tyrosine kinase (e.g., patritumab deruxtecan) [13]".

I think laz-ami is related to overcome MET targeted resistance. I recommend the authors to delete or add here.

Reply A: we heartly thank you for the favorable comment and for providing suggestions that allow us to improve the quality of our manuscript. As recommended by the Reviewer, we deleted line 58-59.

Changes in the text: deletion of the following sentence at line 58-59: "and monoclonal antibodies (e.g., lazertinib with amivantamab) [12], antibody-drug conjugates targeting the extracellular domain of receptor tyrosine kinase (e.g., patritumab deruxtecan) [13]".

Reviewer B

This clinical cancer research article on BBT-176 is an important article for future treatment of EGFR-mutated lung cancer with tertiary resistant mutations.

This commentary is timely in announcing it to the readers of this journal.

Reply B: we heartly thank you for the favorable comment.

Reviewer C

Resistance to the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib poses a challenge to the treatment of non-small cell lung cancer (NSCLC), as there are no targeted treatment options for such patients. In a recent exciting publication, Lim and colleagues have assessed BBT-176, a novel fourth-generation TKI that targets the EGFR L858R/C797Smutation that is responsible for resistance. Their data support the further clinical development of BBT-176 as a treatment for osimertinib-resistant EGFR-mutant NSCLC. The submitted commentary by Laface and Fedele highlighted the potential role of this drug in the treatment of patients with triple-mutant EGFR L858R/T790M/C797S and 19Del/T790M/C797S. This commentary is suitable for publication in the TLCR.

Reply C: we heartly thank you for the favorable comment.