Peer Review File

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Reviewer A

The authors commented on the article of "Pharmacokinetic/Pharmacodynamic Analysis of Savolitinib plus Osimertinib in an EGFR Mutation-Positive, MET-Amplified Non-Small Cell Lung Cancer Model". This is well-described comment, however there are some points to be improved.

Comments:
The authors should consider adding that the amivantamab has been approved by FDA for the NSCLC patients with EGFR exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy in the paragraph of amivantamab.

REPLY: We have added the sentence: Amivantamab has been approved by FDA for the NSCLC patients with EGFR exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy.

In the last sentence should be inappropriate because the authors described optimal combinations of EGFR and MET inhibitors for NSCLC patients with EGFR mutations in this manuscript and would be unrelated to European union, China, and single use of MET inhibitor.

REPLY: We have deleted: "In the European Union, to date, no drug has been registered for clinical practice in the treatment of NSCLC with *EGFR* mutation and *MET* gene disorders. Savolitinib has received conditional approval in China for the treatment of NSCLC patients with *MET* mutations in exon 14 whose disease has progressed after prior systemic therapy or who were unable to receive chemotherapy".

Reviewer B

The manuscript focuses on a commentary on the How to optimally treat with an EGFR and MET receptor inhibitor? represents a technically correct and timely relevant manuscript able to be accepted for the publication on this journal after minor suggestions

- in the manuscript, please, could the authors underline the clinical need of simultaneous molecular profiling of all druggable genes in lung cancer patients?

REPLY: We have added as conclusions:

In conclusions an absolute condition for starting lung cancer treatment is to establish a pathological diagnosis based on the examination of tissue or cellular material, which should be supplemented by the results of immunohistochemical and genetic tests. In patients with advanced lung cancer, it is recommended to perform multigene profiling based on next generation sequencing due to possible available treatment with new targeted therapies. not only EGFR, ALK and ROS1 but also many others (like BRAF, MET, RET, NTRK, HER2, KRAS etc.).

- In the manuscript, please, could the authors evaluate how this approach may impact on pre clinical and clinical models?

REPLY: We have added at the end of the manuscript:

Identification of genes with predictive significance determines the choice of targeted therapy and redefines both the first and also subsequent line of cancer therapy. Combining targeted therapies is important in overcoming primary resistance and preventing secondary resistance to therapies, which translates into improved patients' survival. It is difficult to simultaneous use of targeted therapies due to the high risk of interactions and cumulative toxicity. Preclinical models help to select an appropriate dose that guarantees optimal control of cancer disease while minimizing a risk of side effects.

- Please, could the authors report in italics gene signature?

Reply: We reported each gene signature in italics