Peer Review File

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Reviewer A

Comment 1: The main EGFR gene mutations are exon 19 deletion and the L858R point mutation. Both PC-9 and HCC827 cell lines used by the authors have exon 19 deletion mutations. The experiments should also be conducted on cell lines with the L858R mutation.
Reply 1: The majority of EGFR-activating mutations (~ 90%) primarily present as an exon 19 deletion (Del19; ~ 60%) or exon 21point mutation L858R (~ 30%) [15]. PC-9 and HCC827 cells were studied in most reports related to acquired resistant cells to EGFR-TKI. Therefore, we used these highly available EGFR mutated cell lines (PC-9, HCC827). I would consider to conduct on other cell line (NCI-H3255).

Comment 2: When comparing CB538 with capmatinib using the authors' data, the effects are almost the same. According to the data from the FLAURA trial, MET amplification is the primary resistance mechanism that arises from osimertinib resistance. From this, one would expect that CB538, which is said to be effective against MET itself without specific mutations, would have a higher efficacy than capmatinib, which is specific to MET exon 14 skipping mutations. However, the data show that the efficacy is nearly equivalent to that of capmatinib. In some aspects of signal inhibition, capmatinib outperforms CB538. Thus, the second sentence in the "Key Findings" section is difficult to accept.

Reply 2: I agree that CB538 had the similar efficacy overall with that of capmatinib, but CB538 showed better effects on inhibiting the colony formation and migration of PC9/ER cells (Fig, 2B and C). Capmatinib also, inhibited both MET wild type and exon14 skipping mutation on my data (Table S2) and reference data (Clin Cancer Res 2019; 25(10):3164-75). I deleted ‘or superior’ in second sentence of “key findings”.

Comment 3: Additionally, in the second sentence of the "What is known and what is new?" section, there is an impression that only Type II inhibitors inhibit AXL, but according to the data, capmatinib also inhibits AXL. It is necessary to rewrite this to avoid misleading the readers.

Reply 3: I amended the sentence.

Key findings
• CB538 inhibited the colony formation and migration in MET activated, EGFR TKI-resistant NSCLC cells.
• CB538 exhibited a similar inhibition efficacy than clinically available MET inhibitor, capmatinib on migration and invasion of MET activated, .EGFR TKI-resistant cell lines.
What is known and what is new?
• Concomitant treatment of MET inhibitor with osimertinib has potentials to overcome a drug resistance in EGFR TKI-resistant, *EGFR* mutant NSCLC cells with *MET* gene amplification.
• MET knockdown inhibited the expression of Axl as well as MET in EGFR mutant NSCLC cells.
• Single treatment of CB538 was as effective as combination treatment in MET-activated, EGFR TKI-resistant NSCLCs by inhibiting multiple oncogenic signaling networks, including MET, Axl and EMT.
What is the implication and should change now?
• More selective and potential MET inhibitor, including CB538 could be the treatment option to overcome EGFR-TKI resistant NSCLC.

Reviewer B

Comment: Please describe not only the background but also the aim/objective of this study in the Background section.

Reply: I added the aim of this study.

Comment: Please indicate the source of the mice in the methods section.

Comment: Please indicate the URL in your text for the pdf. file.

Reply: I added.

analyzed using the imageJ software (n=3). We performed as follows; CBA-100-C-cell-migration-invasion-assay.pdf (cellbiolabs.com)

Comment: Figure 1: Please unify the case of the words.

The legends of Figure 2D doesn't match the figure. Please check and revise.

Figure 3: Please unify "AXL" to "Axl".

Reply: I checked above comments and amended that.