Author’s response to reviews

Title: EGFR Exon 20 Insertion Mutations and Response to Osimertinib in Non-small-cell Lung Cancer

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Author’s response to reviews:

Dear BMC Cancer Editorial Office

Thank you very much for your letter and advice. We have revised the manuscript “EGFR Exon 20 Insertion Mutations and Response to Osimertinib in Non-small-cell Lung Cancer” (BCAN-D-19-00223R1), and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers. Point by point responses to the reviewers’ comments are listed below this letter.

In addition to the revisions requested, we would like to make some amendments in the manuscript. Firstly, the e-mail address of Dr. Wenfeng Fang has changed, which is fangwf@sysucc.org.cn (line7,11, page1) in the revised version. Secondly, there was a spelling mistake in “Origimed”, which was corrected as “OrigiMed” in the author affiliations (line 27, 29, 31, page 2) and Method Section. Thirdly, we deleted one reference and added reference 8 (Background section, line 89, page 5) which is more suitable for the opinions. Fourthly, we added one more funding number, 81702283 of Chinese National
Natural Science Foundation in the funding section.

We confirmed that all author details on the revised version are correct, that all authors have agreed to authorship and order of authorship for this manuscript and that all authors have the appropriate permissions and rights to the reported data.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

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We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

Replies to Editor Comment:
1. some of the patients appear to be minors (under the age of 16)
   Answer: The study was approved by the Institutional Review Board of SYSUCC and written informed consent was obtained for each patient prior to sample collection. For patients under the age of 16, the legal representatives(patients) of patients consented on their behalf. We also add the statement in Method section, line 113, page 7.

Replies to Reviewer 2:
1. The male/female frequency of Exon 20 insertions lacks the female predominance noted in other series.
   Answer: Although the M/F of EGFRex20ins mutations lacks the female predominance in our study, it was significantly different from that of EGFR-WT patients. We could still consider that EGFRex20ins mutations appeared more in females than males compared with EGFR WT (47% vs 28%, p=0.003). The unobvious M/F frequency might due to the small number of EGFRex20ins patients.
2. The M/F in Tables 1 and 2 are slightly different 26/23 and 28/25.
   Answer: The M/F in Tables 1 is 26/23 in adenocarcinoma and 28/25 in total NSCLC patients. The M/F in table 1 is consistent with table 2.
3. the response to osimertinib in reference #33 was at 160 mg/d dose double the standard dose used in their trial.
Answer: Dose is a significant difference between reference #33 and our study. We have emphasized this point in the revised version (Discussion section, line 282, page 13).

4. The authors need to complete references 17 and 29.
Answer: Correction has been made in references 17 and 29.

Replies to Reviewer 3:

Use of the foundation medicine cohort, may not give an accurate representation of the frequency of EGFRex20 ins in Caucasians patients as this only ordered in a small subset of patients. The use of a larger nationwide NGS effort would provide a more accurate picture of this disease. The IFCT cohort data is available and published and would serve as a better comparator. Leduc et al. Annals of Oncology 28: 2715-2724. 2017.

Answer: Although the IFCT cohort data is a larger nationwide cohort, foundation medicine cohort covers more EGFRex20ins mutant patients (263 EGFRex20ins mutant patients in FM cohort vs 102 EGFR exon20 mutated patients in IFCT cohort). Therefore, the foundation medicine cohort might serve as a better comparator in this article.

2. Supplementary Figure 1 and 2: Were any co-alterations significantly more or less common in EGFRex20 ins tumors? It looks like APC mutations maybe less common. Are the ERBB2, KRAS and BRAF mutations listed classic driver mutations or substitutions at other less common sites?
Answer: Although there is a tendency that APC and CDKN2A genes are less common in EGFRex20ins tumors, it is not statistical significance. This may due to relatively small number group in each EGFR subtype.
We included all mutation types and sites in co-alterations analysis. Specifically, for co-alterations in EGFR20ins subgroup, driver mutations included ERBB2 amp, ERBB2 E115K, BRAF G469A, KRAS G12D, ALK V349D and RET K666N. It seems that driver mutations are not classic types and sites.

3. It would be helpful if the presence or absence of CNS disease was document for all patients? Was bone or liver disease present in these patients (already stated for patient 5)? What was the M1 stage of these patients?
Answer: the metastasis stage of all patients before osimertinib has been added to the revised version. Patient 5 had brain metastasis before osimertinib treatment. Patient 6 was diagnosed with bone metastasis before osimertinib and confirmed brain metastasis after disease progression. None of the other patients developed brain metastasis after progression. The metastasis status has been added in the revised version (Results section, line 200, 230, page 10)

4. Table 2 could be clearer. For example, for sex, patient number is listed but not percentage is probably more relevant.
Answer: we have updated Table 2 in the revised version.

5. The second published case of osimertinib response in an EGFRex20 mutation patient should be cited as well. Yang et al. Lung Cancer. 2018 Jul; 121:1-4
Answer: We have cited the reference in Discussion section, line 286, page 13.

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Editorial Policies
For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found.

Answer: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Correction has been made in this section.