Author’s response to reviews

Title: Differential efficacy of cisplatin plus pemetrexed between L858R and Del-19 in advanced EGFR-mutant non-squamous non-small cell lung cancer

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Response to Editor::

Before addressing reviewer concerns, we made the following correction ourselves, italicizing “EGFR” to “EGFR”:

On Results section, line 6, page 13.
On Discussion section, line 2, page 15.
On Discussion section, line 3, page 15.
On Discussion section, line 4, page 15.
On Discussion section, line 9, page 15.
Response to Reviewer:

Major point:

It is interesting that ORR was not different between L858R and exon 19 deletion, while PFS was. Along these lines, the authors discuss the possibility of different responses to PEM based on mutation rate. For me, particularly in light of the ORR non-difference, there is at least two explanations as plausible as the one the authors discuss, for the difference in PFS b/w the mutants:

1) the biology of the two EGFR mutant proteins are different causing quicker regrowth sometime after the initial cycles of induction therapy.

R: Thank you so much for your thoughtful comments. We fully agree.
In this study, ORR is similar, but PFS contains a significant difference. Carey et al. compared the proliferation abilities of induced wild type, Del-19, and L858R NR6 fibroblasts. According to this report, there are differences in cell proliferation ability among wild type, Del-19 and L858R. Especially in Del-19, high cell proliferation ability has been confirmed. Therefore, Del-19 may be faster in progression speed than L858R, and this point may have been involved in prolonging PFS of L858R.

According to your comment, we added the following sentences in Discussion section, line 2, page 16; Carey et al. compared the proliferation abilities of induced wild type, Del-19, and L858R NR6 fibroblasts. According to this report, there are differences in cell proliferation ability among wild type, Del-19 and L858R. Especially in Del-19, high cell proliferation ability has been confirmed. Therefore, Del-19 may be faster in progression speed than L858R, and this point may have been involved in prolonging PFS of L858R.

2) because of the different potencies of the mutants reported (as the authors discuss), other events necessary for cancer formation, like EGFR amplification or other RTK co-amplification, is causing differences in regrowth sometime after the initial cycles of induction therapy. This becomes even more relevant (i.e. ErBB family receptor amplification), when Afatinib enters the picture (as an inhibitor of both EGFR and HER2). These points should at least in part be raised in the discussion.

R: Thank you very much for your comment.

As you pointed out, EGFR-TKI treatments encounter various resistance mechanisms; for instance, EGFR amplification or T790M mutation. You presented examples such as ErBB family receptor amplification or other RTK co-amplification. However, the main subject in this study was not EGFR-TKI therapy, but also cytotoxic chemotherapy; cisplatin and pemetrexed therapy. Although we searched for reported resistance mechanisms of ErBB family receptor amplification or other RTK co-amplification in cytotoxic chemotherapy, there was no report. The resistance mechanism induced by CDDP+PEM therapy may differ between Del-19 and L858R.

According to your comment, we revised the following sentences in Discussion section, line 8, page 16; Accordingly, L858R and Del-19 may respond differently to pemetrexed. Furthermore, unknown resistance mechanism induced by cisplatin and pemetrexed therapy may differ between Del-19 and L858R, which require further research. The possible differences between Del-19 and L858R require further research.
Minor point:

On page 7, line 7, it is unclear what is the PFS for gem for L858R and what is it for exon 19 deletion.

R: Thank you very much for your comment.

In LUX-Lung 6, Del-19 patients’ PFS was 5.6 months, similar to L858R. Therefore, we revised the following sentences in Background section, line 7, page 7; longer PFS than in L858R and Del-19 patients treated with gemcitabine in LUX-Lung 6 (5.6 months, both