

Peer Review File

Article Information: <http://dx.doi.org/10.21037/apm-21-213>

Comments:

Reviewer A comments

Comment 1: Ref 6 is not complete for the title.

Reply 1: Thank you for your kind comment. We have revised and completed the Ref 6 and the rest of the references were rechecked.

Changes in the text: we have modified our text as advised (see Page 6, line 27 to 29)".

Comment 2: Table S1 is not really useful.

Reply 2: Thank you for your kind comment. The Table S1 has been deleted.

Changes in the text: we have modified our text as advised (see Page 4, line 7 to 9)".

Reviewer B comments

Comment 1: In the introduction section, the authors shed too much light on LM. LM is a relatively rare status with poor prognosis. However, EGFR exon 20 mutation is quite uncommon without established molecular targeting therapy. I think both points should be delivered in the introduction section.

Reply 1: Thank you for your kind comment. We have deleted some descriptions of LM and added some descriptions of EGFR exon 20 mutation in the section of "Introduction".

Changes in the text: we have modified our text as advised (see Page 2, line 26 to Page 3, line 4)".

Comment 2: Although the authors mentioned that EGFR mutation was not detected in the original sample, and next-generation sequencing (NGS) of the original sample, cerebrospinal fluid (CSF), and plasma exhibited EGFR exon 20 insertion. I think the PCR-invader or Cobas could have detected this uncommon mutation. Did this uncommon mutation emerge as a consequence of intratumor heterogeneity? Then,

the authors should refer to the reason why they failed to detect this uncommon mutation at the time of diagnosis.

Reply 2: Thank you for your professional comment. We are not sure whether there is an insertion mutation in exon 20 of HER-2 in the original lung tissue, because only two genes, EGFR and ROS-1, were detected for the original sample. In addition, we also added to the reasons for failure to detect this rare mutation in the section of “Case Presentation”.

Changes in the text: we have modified our text as advised (see Page 3, line 16 to 17)".

Comment 3: Poziotinib is a small molecule, however, the rates of central nervous system (CNS) penetration of EGFR-TKIs are different. For instance, higher CSF concentration is reported in erlotinib compared to gefitinib, though they are the same 1st generation EGFR-TKIs. And the pronounce CSF concentration in osimertinib is well known. The authors should refer to the CNS penetration rate of poziotinib.

Reply 3: Thank you for your professional comment. We added the conjecture about the CNS penetration rate of poziotinib in the section of “Discussion”.

Changes in the text: we have modified our text as advised (see Page 5, line 21 to 30)".

Comment 4: The English terminology and grammar should be checked by a native speaker.

Reply 4: Thank you for your kind comment. The English language of the whole manuscript has been improved (‘manuscript with tracked changes’) by native speaker and “the certificate of English editing” has been uploaded as the supplementary files.

Comment 5: There are some recent references on poziotinib. The references in the manuscript should be updated.

Reply 5: Thank you for your kind comment. We have updated the references concerning poziotinib in the manuscript.

Changes in the text: we have modified our text as advised (see Page 6, line 12 to Page 8, line 27)".

Comment 6: Pemetrexed (PEM) plus carboplatin combined with bevacizumab (BEV) as an induction therapy is usually followed by continuation maintenance therapy (CMT) with PEM plus BEV. In the current report, BEV-CMT was adopted. Was there any event which hampered the usage of PEM?

Reply 6: Thank you for your kind comment. The patient could not tolerate the adverse reactions to chemotherapy due to the poor physical condition at that time. Therefore, only 4 cycles of pemetrexed combined with carboplatin (AC regimen) combined with bevacizumab was accepted followed by 12 cycles of bevacizumab alone for continuation maintenance therapy (CMT). In addition, we have added to the reasons of hampered the usage of PEM in the section of "Case Presentation".

Changes in the text: we have modified our text as advised (see Page 3, line 23-26)".