Peer Review File

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Reviewer A

This case describes the benefit of aumolertinib in treating a patient with EGFR ex19del -mutated disease with concurrent mutation in TP53 and EGFR amplification. Patient was initially on a first generation TKI with eventual progression and then clinical and radiographic diagnosis of LMD (cytology negative at that time) who benefited from 110 mg daily doing of aumolertinib. After 11 months of this, clinical symptoms worsened and repeat CSF examination revealed tumor cells. Dose of aumolertinib was increased to 165 mg daily and bevacizumab added with clinical benefit. At the time of the writing of this case, the patient was still alive and reportedly doing well.

This is an interesting case, however there are several other prior published reports on the activity of aumolertinib in treated LMD. I referenced some of these below. Huang et al. also describes differences in outcomes in patients with LMD and concurrent mutations in TP53. At the very least, I think these other published reports need to be acknowledged by the authors and they should discuss their particular case in the context of these other published experiences and data.

I would also recommend going into further detail about (lines 210 -) their experience with the patient when aumolertinib dose was increased and anti-VEGF was added. Their reported clinical benefit with this is impressive. Again, they are not the first to report such an approach (see Zhang Y 2022 cite). This other report should be acknowledged. In addition, they should discuss the ongoing research/trials in this space using aumolertinib +/- bevacizumab to treat EGFR-mutated LMD. Also, the iMDT Corner section discusses the BLOOM study and osimertinib, however some discussion regarding data with aumolertinib and LMD in this section would be appropriate given the focus of this case is on this specific TKI.

While the case the authors describe is of interest, the manuscript suffers from poor clarity and many sections are not well written. It would benefit from significant edits to improve its readability.

X. Zhang, Y. Wu, Y. Hu, S. Zhang,EP08.02-039 An Effective Treatment for EGFR-mutated Lung Adenocarcinoma with Symptomatic Leptomeningeal Metastases Using Aumolertinib, Journal of Thoracic Oncology, Volume 17, Issue 9, Supplement, 2022,

Huang et al., A Retrospective Study of Aumolertinib Monotherapy or Combination Therapy Treated EGFR-mutated NSCLC Patients with Leptomeningeal Metastases

Zhang Y, Zhang M, Cheng W, Fang S. Case report: Almonertinib in combination with

bevacizumab for leptomeningeal metastases from epidermal growth factor receptor-mutation non-small cell lung cancer: Case series. Front Oncol. 2022 Nov 10;12:1040450. doi: 10.3389/fonc.2022.1040450. PMID: 36439478; PMCID: PMC9685536.

Reply: Since the research of "Zhang Y 2022 cite" (reference 3 above) is part of the study of "Huang et al 2022 cite" (reference 2 above) so "In previous reports, high-dose aumolertinib was treated for patients with catastrophic symptoms of LMs and poor performance status (19). Another study suggested that aumolertinib monotherapy or combination therapy demonstrated superior activity for LMs of advanced EGFRmutated NSCLC, ORR was 54.5%, DCR was 81.8 % and median PFS was 8.1 months (20). " was added in the background. High-dose aumolertinib and anti-VEGF was added as maintenance treatment since the decease had not been controlled by regular dose.

Reviewer B

This is an interesting case to share general audience of JTD.

Reviewer C

1) First, in the title the authors described this study as a case report and a literature review. However, the main text had no a separated section of literature review and the abstract had no summary of findings from the literature. So the authors need to reconsider whether it is appropriate to describe this study as a review.
2) Second, the abstract needs some revisions. The background did not explain why the current case deserved to be reported and what the unique clinical contribution of this case report is. In the methods, please provide more data on the clinical and pathological characteristics of this case and adverse events associated with the treatment. The conclusion is overstated since the findings are from a case report only. Please tone down it and have comments for the clinical implications of the findings.
3) Third, in the introduction of the main text, one rationale for this study was described as "few reports have discussed the efficacy and safety of aumolertinib treating concurrent mutated LM NSCLC". However, case report cannot answer the research question of efficacy and safety. The authors need to clearly describe the rarity and unique clinical contribution of this case.
4) Fourth, in the case presentation, the timeline figure is not informative, which should not be treatments only. Please add the treatment response and adverse events after the treatments. In the discussion, please tone down the current conclusion and provide the take-home messages and lessons for the clinical implications of the findings.

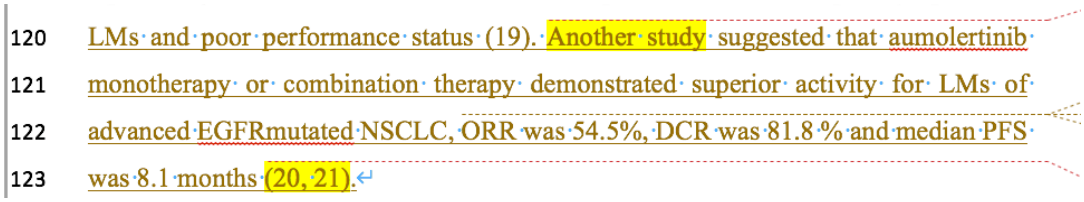
Reply:

1) We have deleted the “literature review” in the title.
2) We provided a case of aumolertinib treatment in EGFR concurrent mutated leptomeningeal metastasis NSCLC, this remain unknown before. In consideration of the length of an article, we chose to describe “Before the 1st-line treatment, the patient underwent a lung biopsy to examine the 520 genes of all cancers using illumia high-throughput sequencing. The sequencing results showed that the patient had the EGFR 19del (p.Leu747_Thr751del)/TP53 (p.lys120fs)/EGFR amplified multiple mutation with a low tumor mutational burden.” and “grade 2 rash” on the clinical and pathological characteristics of this case and adverse events associated with the treatment. We changed the words as “The findings suggested that almonertinib may result in long-period clinical improvement and tolerable safety in concurrent mutated LM NSCLC.”
3) We deleted the sentence and in this case, we discussed the efficacy and safety of aumolertinib treating concurrent mutated LM NSCLC.
4) “PR, partial response; SD, stable disease; rash” were added as treatment response and adverse events after the treatments. In discussion, we added “In this case, aumolertinib has been shown to have efficacy in treating leptomeningeal metastatic NSCLC patients with EGFR 19Del, TP53 and EGFR amplification multi-mutations. The patient in this case achieved PFS for 12 months and is still alive. The patient’s overall survival is significantly longer than that reported in previous research.” as take-home messages and lessons for the clinical implications of the findings.

Reviewer D

1. Ref 9 and Ref 23 are the same. Please revise.
Reply: We deleted the duplicate one and numbered references consecutively in the order.

2. The authors mentioned “study...”, while two references were cited. Change “study” to “studies” or delete one citation. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.


120 LMs and poor performance status (19). Another study suggested that aumolertinib
121 monotherapy or combination therapy demonstrated superior activity for LMs of
122 advanced EGFRmutated NSCLC, ORR was 54.5%, DCR was 81.8 % and median PFS
123 was 8.1 months (20, 21).

Reply: We have deleted one citation.

3. The authors mentioned “reports...”, while only one reference was cited. Change “reports” to “report” or add more citations. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.

aumolertinib had efficacy in an EGFR-mutant brain metastases model (18). In previous reports, high-dose aumolertinib was treated for patients with catastrophic symptoms of LMs and poor performance status (19). Another study suggested that aumolertinib

Reply: We have changed “reports” to “report”.