Peer Review File

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Review Comments

Reviewer A

As these are Clinical Cases, it should be titled "Uncommon EGFR mutations: Clinical Cases and State of the art".

Likewise, if possible, CT images and evolution should be included.

Reply 1: Thanks for your suggestions. Title has been modified as suggested and CT and PET-CT images were added

Changes in the text: Page 1, line 1 / additional file including Case 1 and Case 2 images

Reviewer B

THE DESCRIPTION OF TWO CASES OF UNCOMMON MUTATIONS IS WORTHY. Notwithstanding , if it is possible adding images of radiographic response and pathology, immunohistochemistry or other it could be more understandable.

Secondly, if a diagram with the location of the mutations according with the already described could be of major interest.

Finally update the information regarding exon EGFR exon 20 insertion mutations. See Riely et al. Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with EGFR exon 20 insertion mutations from a phase I/II trial. Cancer Discovery 2021.

Reply: Thanks for your suggestions. CT and PET-CT images were added. Updated data from recent trials testing mobocertinib, amivantanab and poziotinib were added.

Changes in the text: Page 2, line 47-51 / additional file including Case 1 and Case 2 images

Reviewer C

The authors described two patients with non-small cell lung cancer (NSCLC) harboring uncommon EGFR mutations—namely, exon 20 insertion and exon 18 deletion/insertion—in their case report. The patient with EGFR exon 20 insertion was treated successfully with osimertinib, but the other patient with

EGFR exon 18 deletion/insertion failed to be treated with osimertinib. It is important to report such cases because uncommon EGFR mutations are rare.
However, I believe that some points remain unresolved in this manuscript; hence, there is insufficient merit to warrant the publication of this manuscript as is.

Comments:
The authors should precisely discuss the uncommon EGFR mutations, exon 20 D770 N771 insG and exon 18 delE709_T710insD. There should be more citations for published articles that refer to these mutations.
Were there any reports of osimertinib being used for patients with NSCLC with uncommon EGFR mutations? The authors should discuss the relationship between osimertinib and uncommon EGFR mutations.

Reply: Thanks for your suggestions. Updated data from recent trials testing mobocertinib, amivantanab and poziotinib in exon 20 insert mutations were added. Reports from trails testing osimertinib for uncommon mutations have been included.

Changes in the text: Page 2, line 47-51 / Page 3, line 59 – 61 and Page 5, Page 6, line 129 - 131

Reviewer D

This manuscript reports the treatment outcomes of upfront osimertinib for two NSCLC patients with uncommon EGFR mutations (exon 20 insertion and exon 18 deletion). The manuscript is interesting and adds new insights for the treatment of uncommon EGRF mutation. There are some minor comments.

Comments:
1. It would be more informative to the readers if the authors could provide the chest CT images before and after osimertinib treatment.
2. The patients with uncommon EGFR mutation is a heterogeneous population. The treatment decision should be tailored to specific mutations. The best treatment response of osimertinib for exon 18 del was stable disease in the previous study (J Clin Oncol. 2020;38(5):488-495). The authors need to summarize the published evidences of 2nd or 3rd generation EGFR-TKIs for exon 20 insertion and exon 18 del in the Discussion section.
3. The authors chose upfront osimertinib for case 1 with EGFR exon 20 insertion.

The authors need to address recently available therapeutic options for EGFR exon 20 insertion such as amivantamab, mobocertinib, and poziotinib.

Reply: Thanks for your suggestions.

1. CT and PET-CT scan imagese were added.
2. Published evidences of 2nd or 3rd generation EGFR-TKIs for exon 20 insertion and exon 18 del were discussed in the Discussion section.
3. Updated data from recent trials testing mobocertinib, amivantanab and poziotinib in exon 20 insert mutations were added. Reports from trials testing osimertinib for uncommon mutations have been included.

Changes in the text: Additional file including Case 1 and Case 2 images / Page 2, line 47-51 / Page 6, line 129-131

Reviewer E

Case 1: How did you analyze the mutation status? Please describe the details. Are there any case reports or research articles in patients with the same mutation?

Reply: Thanks for your suggestions. Published evidences of 2nd or 3rd generation EGFR-TKIs for exon 20 insertion and exon 18 del were discussed in the Discussion section.
Changes in the text: Page 6, line 129-131

Reviewer F

In this paper the authors reported two cases of NSCLC with EGFR minor mutation treated with osimertinib. There are already many reports regarding this issue. I am not for sure true importance of these specific mutations presented here, but if the authors want to publish this report, more deep insights are mandatory regarding incidence of these mutations, in vivo sensitivity data, reasons of the sensitivity of these mutations, etc.

Major points:

1) I think there are already several databases available on the web or published paper. Please cite such information, even though there are no perfect database.

Minor points:

1) There are no images suggesting response / failure of these two cases.

Reply: Thanks for your suggestions.

1. CT and PET-CT scan images were added.
2. Reference to published paper and databases were updated according to your suggestion.

Published evidences of 2nd or 3rd generation EGFR-TKIs for exon 20 insertion and exon 18 del were discussed in the Discussion section.

Changes in the text: Additional file including Case 1 and Case 2 images / Page 2, line 44-46 / Page 6, line 129-131

Reviewer G

The authors reported two cases with uncommon EGFR mutations, exon 20 D770 N771 insG and delE709_T710insD. The both cases were treated by osimertinib. The authors summarized the clinical causes and generally clearly presented; however, the following issues should be addressed.

1. To clearly indicate the treatment progressions, it would be informative to illustrate the clinical courses of the both cases from the diagnosis to the end of osimertinib treatment. In particular, the clinical course of the case 2 is hard to understand.

2. The representative CT images before and after osimertinib treatment would be useful.

3. Some papers already showed that 1st generation-TKIs have weak efficacies against uncommon EGFR mutation, while 2nd generation TKI, afatinib, showed significantly superiority over 1st generation-TKIs. (Lung Cancer. 2019 Jan;127:169-171.) Furthermore, a recent meta-analysis summarized the clinical efficacy of afatinib in patients with uncommon EGFR mutations (J Thorac Oncol. 2020 May;15(5):803-815.). The reviewer highly recommends to refer these papers and discuss the therapeutic strategy comparing afatinib and osimertinib for NSCLC patients with uncommon EGFR mutations.

Reply: Thanks for your suggestions.

1. A revised description of Case 2 was included.
2. CT and PET-CT scan images were added.
3. Reference to published paper and databases were updated according to your suggestion.

Changes in the text: Additional file including Case 1 and Case 2 images / Page 5, line 107-108 / Page 2, line 47-51