Peer Review File

Article Information: http://dx.doi.org/10.21037/apm-20-1477

Reviewer A

Nice figures. This manuscript shared a quite complicated case report which the NSCLC patient occurred resistance to osimertinib. The authors found quite a few mutations and applied therapy by a combination of EGFR-TKIs and brigatinib plus cetuximab. The outcome is favourable. This case report could fill our experience handling such a complicated case, making itself potentially publishable at Annals of Palliative Medicine. However, there are some issues to be addressed.

Thanks a lot for your appreciation and constructive comments on our manuscript.

Comment 1. Title. The present title is confusing by using 1st/3rd/2nd. Besides, just clearly give out the prognosis instead of hiding it.

Reply 1: Thanks for the critical question.

Changes in the text: We have modified the title and running title. All changes have been tracked in the revised-highlighted manuscript. See page 1, line 1-4, line 18-19.

Comment 2. Keywords. Need refinding to be better searched.

Reply 2: Thanks for the critical question.

Changes in the text: We have modified the keywords. All changes have been tracked in the revised-highlighted manuscript. See page 4, line 57-58.

Comment 3. Abstract. Too short. Make sure there are 200~350 words. Add the outcome and prognosis (how long the PFS or OS). Add practical takeaway lessons.

Reply 3: Thanks for the critical question.

Changes in the text: we have modified the abstract and the latest follow-up have been added. All changes have been tracked in the revised-highlighted manuscript. See page 3-4, line 25-55.

Comment 4. Introduction. Too superficial. A lot of background information is missing. It's not smoothly presently.

Reply 4: Thanks for the critical question.

Changes in the text: We have re-edit the introduction. All changes have been tracked in the revised-highlighted manuscript. See page 5, line 61-77.

Comment 5. Case presentation. Carry out each medication's name, dosage and duration. Besides, the therapies are quite complicated. Add the rationale for each treatment. And, present the latest follow-up information too.

Reply 5: Thanks for the critical question.
Changes in the text: We have modified the whole case and renew the information until now. Afatinib was added when EGFR G724S and C797S re-occurred at July 2020 after 3 months of almonertinib and reached PR. We added the rationale for treatment. Figure 1, 2, 4 and figure legends were updated. All changes have been tracked in the revised-highlighted manuscript. See page 7-8, line 102-139; page 15-16, line 276, 280-285, 296-297.

Comment 6. Discussion. Not in-depth enough. Add one separate paragraph to list both strengths and limitations. Together, discuss in more details, making the discussion part informative and comparing the findings with other cases.
Reply 6: Thanks for the critical question.
Changes in the text: To follow your advice, we have added a separate paragraph discussing the strengths and limitation of our case (paragraph 4). Meanwhile, we also modified the whole discussion part. Comparing the findings with other cases were interpreted in paragraph 2 & 4. All changes have been tracked in the revised-highlighted manuscript. See page 9-11, line 146-151, 169-177, 190-203.

Reviewer B

This is an interesting case report which illustrates the complexity of EGFR mutations and their evolution under therapy. This illustrates also the absolute need of performing at least liquid biopsies, at best tissue biopsies at each time of progression.
Thanks a lot for your appreciation and constructive comments on our manuscript.

Major comment 1. The English language needs extensive review as sometimes it is quite impossible to be sure of what the authors mean and this is quite misleading.
Reply 1: Thanks for the critical question. The manuscript has been reviewed by a native English speaker to correct the linguistic errors in the text. All changes have been tracked in the revised-highlighted manuscript.

Minor comments 1. More details should be given about the seven-year history of previous adenocarcinoma before metastatic presentation: initial stage, type of surgery, reason for administration of chemotherapy (induction, adjuvant, palliative?)
Reply 1: Thanks for the critical question.
Changes in the text: We have added these in the beginning of the case presentation part. All changes have been tracked in the revised-highlighted manuscript. See page 6, line 80-93.

Minor comments 2. What about the evolution of brain metastases after whole brain irradiation?
Reply 2: The brain metastasis is SD in the beginning (from Oct. 2017- May 2019);

however, the patient got paralysis in May 2019 because of PD. And no brain MR test was done form that time, for preventing the risk of long time staying in MR room.
Changes in the text: No changes in the text.

Minor comments 3. The authors speak about "acceptable adverse evnet" which is not meaningful. More details should be given.
Reply 3: Thanks for the critical question.
Changes in the text: The adverse event during therapy is grade 1/2 skin rash, We added the details in the case presentation. All changes have been tracked in the revised-highlighted manuscript. See page 8, line 123, 128, 138-139.

Minor comments 4. What about assessment of the disease after april 2020?
Reply 4: Thanks for the critical question.
Changes in the text: We have renewed the story of this case. Afatinib was added when EGFR G724S and C797S re-occurred at July 2020 after 3 months of almonertinib and reached PR. Figure 1, 2, 4 and figure legends were updated. All changes have been tracked in the revised-highlighted manuscript. See page 8, line 133-139; page 15-16, line 276, 280-285, 296-297.