

Peer Review File

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Reviewer A

The paper describes a case report on a female with metastatic lung adenocarcinoma and an ALK-RNF144A fusion, a HIP1-ALK fusion and a RB1 loss-of-function variant. The patient received treatment with multiple lines of ALK-directed TKIs plus/minus angiogenesis inhibitors, chemotherapy and radiotherapy. At the time of disease progression, squamous cell carcinoma with ALK-RNF144A and HIP1-ALK fusions was diagnosed. Treatment with lorlatinib plus nab-paclitaxel plus anlotinib resulted in stable disease and the patient is alive at 18 months. This case is of interest because of the complex molecule alterations and the transformation of an adenocarcinoma into a squamous cell carcinoma.

Comments

1) Add the smoking status of the patient.

Reply: Thank you for your suggestion. We have added the smoking status of the patient in the Case presentation (see page 4, line 103).

2) Mention the administration of radiotherapy in the abstract.

Reply: Thank you for your opinion. We have added the administration of radiotherapy in the abstract (see page 3, line 49).

3) Mention in the abstract after which line of treatment a squamous cell carcinoma did emerge.

Reply: Thank you very much. As requested, we have revised the paragraph in the abstract (see page 3, line 49-51), which now reads as follows:

Disease progression accompanied by a squamous cell carcinoma transformation was indicated after ALK-TKI combined with anti-angiogenesis and both ALK-RNF144A and HIP1-ALK fusions were retained in the tumor.

Reviewer B

Authors described a rare lung cancer patient harboring ALK-RNF144A fusion, HIP1-ALK fusion and RB1 loss-of-function variant. I appreciate the in-depth investigation of a single case using immunohistochemistry and NGS, as well as the subsequent discussions on the molecular mechanisms and treatment strategies.

We sometimes experience such a clinical course of EGFR or ALK-positive lung cancer. I am not sure whether combined treatment with ALK-TKI, chemotherapy, and anti-angiogenesis is best for the patient because of a single case. Could you please express it more subtly?

Reply: We thank the reviewer for the comment and agree that the description of best efficacy of combination therapy is not appropriate. As requested, we have revised the paragraph in the discussion (see page 8-9, line 236-241; page 10, line 276-277).

Reviewer C

1. Figure 2

No “CT” in Figure 2 while it is explained. Please revise.

Reply: Thank you very much. As your request, we have revised the section (Page 21, line 592).

2. Figure 2C and Figure 2D

Please send us the figure with higher resolution in JPG/TIFF, as the current ones are not clear enough.

Reply: Thank you for your suggestion and we will send Figure2C and Figure 2D with higher resolution.

3. Figure 3A

Please explain the meaning of the arrows

Reply: Thank you for your suggestion. We have explained the meaning of the arrows (Page 22, line 607).

4. Figure 3B

Please explain the meaning of two circles

Reply: Thank you for your suggestion. We have explained the meaning of two circles (Page 22, line 609).

5. Figure 3C

Please explain the meaning of the circle

Reply: Thank you for your suggestion. We have explained the meaning of the circle (Page 22, line 611).

6. Figure 3D

Please explain the meaning of the circle

Reply: Thank you for your suggestion. We have explained the meaning of the circle (Page 22, line 612-613).

7. Figure 3E

Please explain the meaning of the arrows

Reply: Thank you for your suggestion. We have explained the meaning of the arrows (Page 22, line 614-615).

8. Figure 3G

Please explain the meaning of the arrows

Reply: Thank you for your suggestion. We have explained the meaning of the arrows (Page 22, line 619-620).