Peer Review File

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Reviewer A

Comment 1: Line 56: postoperative adjuvant chemotherapy? The patient did not receive complete resection. There were visceral pleura and diaphragm metastasis. In addition, they described partial resection (in Figure 2A legend on page 14). They may describe systemic chemotherapy instead of postoperative adjuvant chemotherapy.

Reply 1: Thanks for your comments and suggestions. After consideration, it should indeed be described here as systemic chemotherapy rather than postoperative adjuvant chemotherapy. However, in Figure 2A legend, the partial resection described refers to the partial resection of the right lung middle lobe, which is not directly related to whether the lesion has been completely resected.

Changes in the text: We have modified our text as advised (see Page 4, line 75, see Page 13, line 285, see Page 13, line 294). As follow: "systemic chemotherapy".

Comment 2: Line 57: cisplatinum (75 mg/m2, d1–3, 21 d) -> cisplatinum (75 mg/m2, d1, 21 d)?

Reply 2: Thanks for your comments. By reconfirming, the dose of cisplatinum was 75 mg/m2, and then the calculated total dose was divided into three parts and given to the patient on the first day, the second day and the third day, respectively. It is expressed as " cisplatinum (75 mg/m2, d1–3, 21 d)".

Changes in the text: We haven't made any changes.

Comment 3: Line 57: Why did authors treat the patient with CDDP/PEM/Beva? Bevacizumab is usually not used soon after invasive surgery.

Reply 3: Thanks for your comments. On this point, we carefully reviewed the instructions for bevacizumab: bevacizumab should not be started for at least 28 days after major surgery, or should wait until the surgical wound has fully healed before

starting bevacizumab treatment. First, the patient underwent surgery on July 31, 2017, and it has been more than 28 days by September 2, 2017 (bevacizumab treatment). In addition, the patient's surgical wound has completely healed. It is reasonable for patients to receive bevacizumab.

Changes in the text: We haven't made any changes.

Comment 4: Line 110: Why did the authors think almonertinib is a potentially feasible therapeutic regimen for the targeted therapy of NSCLC with EGFR ex20ins mutations? Please explain in detail.

Reply 4: Thanks for your comments and suggestions. EGFR ex20ins mutation is a rare mutation, and studies have shown that irreversible EGFR-TKIs can be effective for NSCLC patients with this rare EGFR mutations. Almonertinib, as the third generation EGFR-TKI, can irreversibly bind to EGFR ATP binding region, and it is suitable for the treatment of NSCLC patients with disease progression and T790M drug resistance mutation positive after EGFR-TKI treatment. And almonertinib has a favorable therapeutic effect in EGFR+ multiple targets inhibition. Therefore, we believe that almonertinib is a potentially feasible therapeutic regimen for the targeted therapy of NSCLC patients with EGFR ex20ins mutations.

Changes in the text: We have modified our text as advised (see Page 7, line 141). As follow: "Almonertinib, as the third generation EGFR-TKI, can irreversibly bind to EGFR ATP binding region, and it is suitable for the treatment of NSCLC patients with disease progression and T790M drug resistance mutation positive after other EGFR-TKI treatment."

Comment 5: Line 134: Osimertinib-> osimertinib

Reply 5: Thanks for your comments. We have changed to osimertinib.

Changes in the text: We have modified our text as advised (see Page 8, line 173). As follow: "osimertinib".

Comment 6: P15: In figure legend, third biopsy was described. Was second biopsy

specimen surgically resected tumor?

Reply 6: Thanks for your comments. The second biopsy specimen was a surgically resected tumor in the middle lobe of the right lung.

Changes in the text: We haven't made any changes.

Comment 7: Finally, I am not sure whether the refractory tumor to poziotinib had actually maintained EGFR ex20ins mutation. The mutation status may change after treatment with poziotinib. Please explain the fact as a limitation.

Reply 7: Thanks for your comments and suggestions. We have communicated with the patient when changing the targeted drug treatment regimens. Taking into account their own economic conditions and physical tolerance, the patient did not undergo further puncture biopsy and genetic testing. Therefore, it is not possible to determine whether the mutation state of the patient has changed after sequential treatment of afatinib and poziotinib. When we selected almonertinib to treat this patient, we still followed the NGS results of the initial treatment with targeted drugs. This is indeed a limitation.

Changes in the text: We haven't made any changes.

Reviewer B

Comment 1: Whether this woman (patients) had comorbidities (chronic diseases and the need to administer medications) The degree of their correction can by specified.

Reply 1: Thanks for your comments. This woman (patient) had no comorbidities (chronic diseases and the need to administer medications).

Changes in the text: We have modified our text as advised (see Page 3, line 56). As follow: "In July 2017, a 54-year-old Chinese woman who had never smoked and had no underlying disease was admitted to the hospital with cough and expectoration."

Comment 2: Whether this woman (patients) had symptoms toxicity of treatment with targeted therapy?

Reply 2: Thanks for your comments. This patient developed intermittent diarrhea and

dry skin during treatment with poziotinib. There were no toxic symptoms when taking afatinib and almonertinib.

Changes in the text: We have modified our text as advised (see Page 5, line 96, see Page 5, line 101). As follow: "During this period, the patient did not complain of toxic symptoms." As follow: "During the treatment, the patient developed intermittent diarrhea and dry skin."

Reviewer C

Comment 1: Almonertinib is a third-generation small molecule EGFR TKI, which can irreversibly and highly selectively inhibit EGFR sensitive mutations (such as exon 19 deletion and L858R mutation) and T790M resistance mutations and has been approved in China for the treatment of patients with EGFR T790M mutation—positive non–small cell lung cancer (NSCLC) who have progressed on or after other EGFR TKI therapy.

Reply 1: Thanks for your comments and suggestions. We have adopted some of your views.

Changes in the text: We have modified our text as advised (see Page 7, line 141). As follow: "Almonertinib, as the third generation EGFR-TKI, can irreversibly bind to EGFR ATP binding region, and it is suitable for the treatment of NSCLC patients with disease progression and T790M drug resistance mutation positive after other EGFR-TKI treatment."

Comment 2: Its approval was based on findings from the open-label phase II APOLLO study, in which treatment with almonertinib led to an objective response rate of 68.9% and a disease control rate of 93.4% in in patients with recurrent NSCLC harbouring EGFR T790M mutations. The median progression-free survival was 12.3 months and almonertinib induced an objective response rate of 61.5% in patients with CNS metastasis.

Reply 2: Thanks for your comments and suggestions. After consideration, we have not quoted it in the article yet.

Changes in the text: We haven't made any changes.

Comment 3: Then, go on to state, as you have, "EGFR ex20ins mutations are present in approximately 0.1% to 4% of all non-small cell lung cancer (NSCLC) and account for 4% to 12% of all EGFR mutations (2,3). The most common EGFR ex20ins mutation is A767_V769dup (2)" It would be helpful to state what is the most favourable progression-free survival in these patients with current best therapy.

Reply 3: Thanks for your comments and suggestions.

Changes in the text: We haven't made any changes.

Comment 4: It seems that the patient was not fully compliant with treatments prescribed to her. Did the patient comply fully with treatment with poziotinib?

Reply 4: Thanks for your comments. The patient did not fully comply with the doctor's advice during the period of chemotherapy, but during the period of taking poziotinib treatment, the patient would return to the outpatient clinic regularly and prescribe poziotinib drugs.

Changes in the text: We have modified our text as advised (see Page 5, line 101). As follow: "In June 2019, the patient's targeted therapy was changed to poziotinib (14 mg daily, P. O.) and her condition was stable during the regular treatment."

Comment 5: Following progression of the tumour after poziotinib, was osimertinib tried in this patient? What led the authors to consider adding almonertinib?

Reply 5: Thanks for your comments. Following progression of the tumor after poziotinib, the patient did not try osimertinib. At that time, we proposed two schemes of osimertinib and almonertinib to the patient, and also explained to the patient the differences in the price, efficacy and adverse reactions of the two drugs. Finally, the patient chose almonertinib.

Changes in the text: We haven't made any changes.

Reviewer D

Comment 1: It is interesting that almonertinib, a third generation EGFR TKI showed activity against a tumor with A767_V769dup EGFR mutation. And the duration of resonse was much long than poziotinib.

Reply 1: Thanks for your comments.

Changes in the text: We haven't made any changes.