

Dear editor:

Thank you very much for your letter regarding our manuscript (Manuscript NO.: 69115, Case Report) together with the comments from the reviewers. According to reviewer's valuable comments, we have revised the relevant part in the original manuscript. And we also responded point by point to the reviewer's comments as listed below. And we resubmitted our modified manuscript, together with point-to-point responses to reviewer. We hope it is more acceptable for publication. Thank you very much for your kind and continued attention.

Reviewer 1: The manuscript is nicely written, and well organized

**Re: Thank you.**

Reviewer 2: 1. I see that in conclusion patients with PDL1 expression greater than 25%, L858R mutation, smoking history or pemetrexed treatment may benefit from immunotherapy. I see that he does not have any history of smoking [is it both active and passive - please clarify], second I did not see PDL1 expression mentioned in the manuscript in this patient - can you please mention the PDL1 expression.

**Re: Thank you for the valuable comment. This patient has no history of active or passive smoking. We clarify in the text. As you pointed out, the expression level of PD-L1 plays an important role in guiding treatment. However, due to the shortage of puncture samples, this patient has not been tested for PD-L1 expression levels.**

2. Although first-generation TKI such as erlotinib or gefitinib used to be the standard front-line treatment for advanced EGFR mutant non-small cell lung cancer, new data improved survival outcomes with front-line of osimertinib compared with the first-generation tyrosine kinase inhibitors. In the phase 3 FLAURA clinical trial, comprising of approximately 550 patients with advanced EGFR mutated non-small cell lung cancer, osimertinib improved progression free survival, duration of response as well as overall survival [18.9 months versus 10.2 months for progression free survival, 17.2 months versus 8.5

months for duration of response, 38.6 months versus 31.8 months for overall survival]. Also grade 3 toxicities were lower in patients with osimertinib. What was the reason for choosing gefitinib in this patient.

Re: Thank you for the valuable comment. As you pointed out, the previous study showed the front-line of osimertinib improved survival outcomes compared with the first-generation TKIs. Unfortunately, due to the high price of Osimertinib in China, the patient could not afford it and received gefitinib which was recommended as the first-line treatment at that time.

2. It was mentioned that patient did not have T790M mutation - which are responsible for approximately 50% of the patients with acquired resistance to early generation tyrosine kinase inhibitors. Other mechanisms include MET gene amplification, sometimes they can be histological transformation of the lung cancer as well which can contribute to resistance. Is anything else identified in this patient apart from not having T790M mutation.

Re: Thank you for the valuable comment. At this time, no MET gene amplification or histological transformation was identified in this patient apart from not having T790M mutation. The potential mechanisms of the acquired resistance to early generation TKIs need to be further studied.

3. Also it is worth mentioning IMpower 150 clinical trial, where addition of Atezolizumab to combination chemotherapy with carboplatin and paclitaxel along with wedge of targeted therapy with bevacizumab - this clinical trial has approximately 110 patients with EGFR mutations or ALK translocation who progresses on prior targeted therapy with an improvement in progression free survival. There was also some evidence in phase 3 trials with bevacizumab and ramucicamab combinations with erlotinib improved progression free survival but not overall survival.

Re: Thank you for the valuable comment. We cited this important content in the revised text.

4. Thank you for discussing Atlantic clinical trial. Although there was some benefit in patients with PDL 1 expression greater than 25% [ 97 patient were

EGFR positive, 77 patients with greater than 25% of tumor cells expressing PDL1] - 8 patients completed 12 months of treatment, 93 patients discontinued treatment [almost 86 patients due to disease progression] - progression free survival was similar in patients with PDL 1 expression less than or greater than 25% but overall survival was better in patients with PDL 1 greater than 25% with approximately around 13 months versus 10 months with PDL 1 levels less than 25%. I agree that we need more prospective trials in this group of patients to see if there is any benefit from single agent immunotherapy.

Re: Thank you for the valuable comment.

5. Also regarding second line of treatment with chemotherapy followed by immunotherapy as third line of treatment, it is reasonable to consider this approach, is there any contraindication for considering a combination of carboplatin pemetrexed and pembrolizumab was not considered as a second line of treatment which can be followed by pemetrexed and pembrolizumab maintenance.

Re: Thank you for the valuable comment. A combination of carboplatin pemetrexed and pembrolizumab followed by pemetrexed and pembrolizumab maintenance may be a better choice, however, pembrolizumab plus chemotherapy had not been approved at that time in China. We chose second line of treatment with chemotherapy followed by immunotherapy as third line of treatment.

6. Is there any data on pembrolizumab monotherapy in patients with EGFR mutant advanced lung cancer, that progressed on targeted therapy third line setting and beyond. Is it based on Atlantic trial - this patient was treated with pembrolizumab [they allowed to prior lines of therapy including targeted therapy with tyrosine kinase inhibitors and platinum based therapy before being treated with durvalumab]

Re: Thank you for the valuable comment. The data on third line setting and beyond of pembrolizumab monotherapy in patients with EGFR mutant advanced lung cancer that progressed on targeted therapy remains limited.

Yes, it is based on the ATLANTIC trial which showed that the clinical activity of durvalumab in patients with EGFR+ NSCLC with  $\geq 25\%$  of tumour cells expressing PD-L1 was encouraging.

Reviewer 3: This study is interesting in its results and will be interesting for oncologists and chemotherapists.

Re: Thank you for the valuable comment.

Reviewer 4: While this case is interesting, it is not new. Moreover, the PFS in the timeline figure is only 5 months although in the text it mention 10 months!. This The usage of immunotherapy is not recommended for EGFR-mutatnt NSCLC patients unless there is depletion of the EGFR targeted therapy. There is some evidence for efficacy in patients with PDK1 $>25\%$  (see below) when used in further lines of treatment. Please see: Yu S, Liu D, Shen B, Shi M, Feng J. Immunotherapy strategy of EGFR mutant lung cancer. Am J Cancer Res. 2018;8(10):2106-2115. Published 2018 Oct 1. and Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Garassino MC, Cho BC, Kim JH, Mazières J, Vansteenkiste J, Lena H, Corral Jaime J, Gray JE, Powderly J, Chouaid C, Bidoli P, Wheatley-Price P, Park K, Soo RA, Huang Y, Wadsworth C, Dennis PA, Rizvi NA, ATLANTIC Investigators. Lancet Oncol. 2018 Apr; 19(4):521-536.

Re: Thank you for the valuable comment. We are so sorry for mistake in the timeline picture and revised it in the revised text. In this study, we mainly aimed to describe a case report illustrative of potential treatment benefit from immunotherapy in EGFR-positive patients with NSCLC harboring specific mutations despite the general opinion that these patients are immunotherapy-resistant. And chemotherapy and immunotherapy are also recommended for EGFR-mutant NSCLC patients if the disease progressed on gefitinib treatment (NCCN Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer).

Reviewer 5: 1. Why the authors did not use 2nd generation TKIs? Absence of

T790M mutation exclude the chance? 2. Biomarkers for this effectiveness should be searched for more robustly such as PDL1 FISH and/or CD8 infiltration in the tumors.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Re: Thank you for the valuable comment. As you pointed out, 2nd generation TKIs would be the better choice. Unfortunately, due to the high price of osimertinib, the patient could not afford it and received the chemotherapy as the second-line treatment at that time. As you pointed out, the expression level of PD-L1 FISH and/or CD8 infiltration in the tumors play an important role in guiding treatment. However, due to the shortage of puncture samples, this patient has not been tested for PD-L1 FISH and/or CD8 infiltration.