

## Peer Review File

Article information: <https://dx.doi.org/10.21037/tlcr-23-658>

### Reviewer A

- 1) First, the title needs to specify the clinical research design of this study such as a retrospective cohort study.

Reply 1: Thank you for your advice. See page 1, line 4.

- 2) Second, the abstract needs some revisions. The background did not indicate the research question to be answered in this study. The methods did not describe the inclusion criteria of subjects, the assessment of baseline clinical factors and test of ALK-rearrangements and co-existing alterations, follow up procedures, and measurement of prognosis outcomes. The results need to first briefly describe the clinical characteristics of the subjects and its overall prognosis outcomes. The conclusion should not repeat the findings, and please have comments for the clinical implications of the findings.

Reply 2: Thank you for your proposal. The background section has been revised. See page 2, lines 43-44. Detailed methods are described in the methodological section of the text. So it's not described much in the abstract. We have revised the results and conclusions. See page 2, lines 50-52; page 3, lines 73-74.

- 3) Third, the introduction of the main text needs to analyze the limitations and knowledge gaps of prior studies and describe the potential clinical implications of this study.

Reply 3: We have added and modified the introduction part of the text. See page 4, lines 107-131; page 5, lines 144-147.

- 4) Fourth, in the methodology of the main text, the authors need to accurately describe the clinical research design and sample size estimation of this study, as well as the data collection of baseline clinical factors and follow up procedures. My concern for this part is the small sample size, which is not adequate for the proposed analysis. In statistics, please consider multivariable regression analysis to adjust for potential confounding effects.

Reply 4: Thank you very much for your advice. We have revised and supplemented the methodology. See page 5, lines 156-163; page 7, lines 207-214. In addition, we analyzed the baseline level of each group, and the baseline among the groups was balanced.

- 5) Finally, please consider to cite several related papers: 1. Sasaki T, Yoshida R, Nitani K, Watanabe T, Tenma T, Kida R, Mori C, Umekage Y, Hirai N, Minami Y, Okumura S. Detection of resistance mutations in patients with anaplastic lymphoma kinase-rearranged lung cancer through liquid biopsy. *Transl Lung Cancer Res* 2023;12(7):1445-1453. doi:

10.21037/tlcr-22-671. 2. Zhou S, Sun G, Wang J, Zhang H. Anaplastic lymphoma kinase (ALK) rearrangement in adult renal cell carcinoma with lung metastasis: a case report and literature review. *Transl Androl Urol* 2020;9(6):2855-2861. doi: 10.21037/tau-20-1343. 3. Chen MF, Chaft JE. Early-stage anaplastic lymphoma kinase (ALK)-positive lung cancer: a narrative review. *Transl Lung Cancer Res* 2023;12(2):337-345. doi: 10.21037/tlcr-22-631. 4. Hida T. Anaplastic lymphoma kinase inhibitor development: enhanced delivery to the central nervous system. *Transl Lung Cancer Res* 2023;12(8):1822-1825. doi: 10.21037/tlcr-23-43.

Reply 5: We quoted the recommended references. See reference, 14, 22, 23, 37.

### **Reviewer B**

The paper titled “Efficacy of alectinib in lung adenocarcinoma patients with different anaplastic lymphoma kinase (ALK)-rearrangements and co-existing alterations-a retrospective study” is interesting. In this study, the efficacy of alectinib in different types of ALK-rearrangements varied slightly. TP53 and TSC1 co-mutations were identified as detrimental factors affecting efficacy. In addition, we found that two patients carrying specific ALK-rearrangements still respond to alectinib treatment. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply 1: Thank you for your proposal. We have revised the Abstract and Introduction sections. See page 2, lines 43-44; page 5, lines 141-157.

2) Suggest summarizing the recent developments in our understanding and treatment of tumors with ALK alterations.

Reply 2: Thank you for your advice. We have added this content in the introduction section. See page 4, lines 110-131.

3) It is recommended to increase comparative analysis with other drugs, which may make the entire study more complete.

Reply 3: Thank you for your suggestion. This is a good suggestion. Considering our study mainly focuses on the efficacy of alectinib on different ALK rearrangement types, so there is no comparative analysis with other drugs. In future research, we will focus on research from this perspective.

4) This study is a retrospective analysis, which is likely to cause some deviations in the results. It needs to be further confirmed by multi-center clinical trials.

Reply 4: Thank you for your suggestion. We discussed this issue in the discussion section. See page 12, lines 388-389.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Complex genetic alterations contribute to rapid disease progression in an ALK rearrangement lung adenocarcinoma patient: a case report, *Transl Cancer Res*, PMID: 35116617”. It is recommended to quote this article.

Reply 5: We have supplemented the content of the introduction and cited this reference. See Ref. 17; Page 4, lines 110-131.

6) The number of patient samples in this study is too small, and a large sample study should be added for verification.

Reply 6: We discussed this limitation in the discussion section. See page 12, lines 385-389.

7) With the discovery of new drug targets and the continuous emergence of new combination treatment options, what breakthroughs will there be in the treatment of lung adenocarcinoma in the future? What inspiration can this study provide? It is recommended to add relevant content to the discussion.

Reply 7: Thank you for your suggestion, we have added the corresponding content in the discussion. See pages 11-12, lines 366-383.

#### Reviewer C

##### 1. Reference

a. **In the text**, references should be identified using numbers in **round brackets** in which they appear consecutively. **Please revise the whole text.**

[e.g., “*The First International Consensus Conference on Laparoscopic Liver Surgery was held in Louisville in 2008 (3).*”].

Reply: Have revised.

14 cancer (NSCLC) and account for 4–6% of LADCs. The *ALK* gene is located on  
15 chromosome 2, and chromosomal rearrangements lead to the ectopic expression of the  
16 tyrosine kinase-containing part of *ALK* and its structural activation [1]. *ALK*  
17 rearrangements lead to ligand-independent dimerization and hyperactivation of pro-

b. The authors mentioned “**studies...**”, while only one reference was cited. Change “Studies” to “study” or add more citations. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.

Reply: Have revised.

Our previous *studies have* analyzed the efficacy of alectinib in real-world ALK-rearranged patients [27].

c. **In reference list**, if there are more than three authors, **name only the first three and then use “et al”** and names of journals should be abbreviated in the style used in PubMed.

Format should be: Author 1, Author 2, Author 3, et al. Title of the article. Journal Abbreviation name Year; Volume: Page numbers.

Example ( $\leq 3$  authors):

[e.g. Resnick MJ, Bassett JC, Clark PE. Management of superficial and muscle-invasive urothelial cancers of the bladder. *Curr Opin Oncol* 2013;25:281-8.];

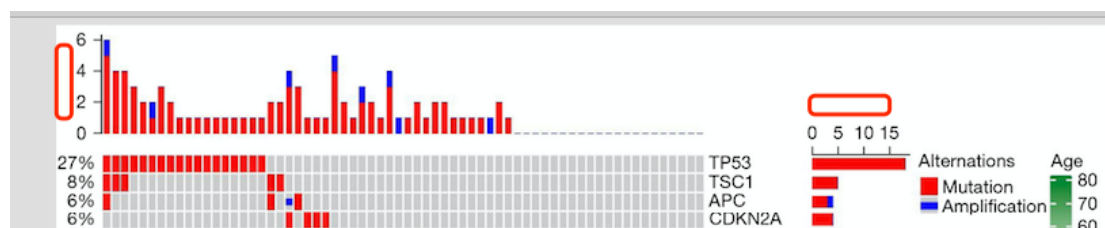
Example ( $> 3$  authors):

[e.g. Park S, Jee SH, Shin HR, et al. Attributable fraction of tobacco smoking on cancer using population-based nationwide cancer incidence and mortality data in Korea. *BMC Cancer* 2014;14:406-17.]

Reply: Have revised.

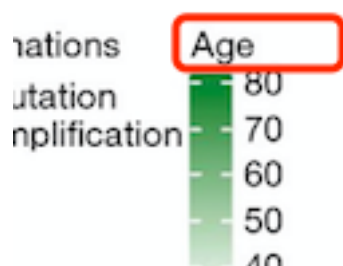
## 2. Figure 1

a. Please add description to the axis.



Reply: Have added.

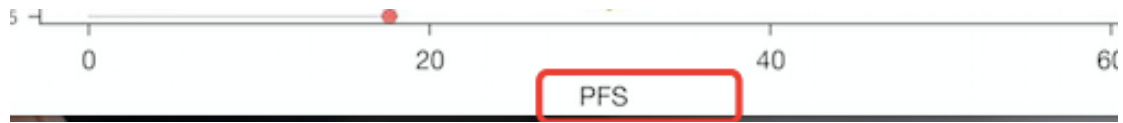
b. Please add the unit (years).



Reply: Have added.

### 3. Figure 3

Please add the unit of “PDF”.



Reply: Have added.

### 4. Figure 7

It is “800” in the main text, but it is “0.8” in figure. Please check and revise.

311 December 2019, a bone scan showed new lesions in the skull. From 21 January 2020,  
312 pemetrexed + carboplatin regimen chemotherapy (pemetrexed 800 mg + carboplatin  
313 500 mg) was used, and oral alectinib was continued, at the same time with incadronate  
314 disodium to treat the bone metastases. ←

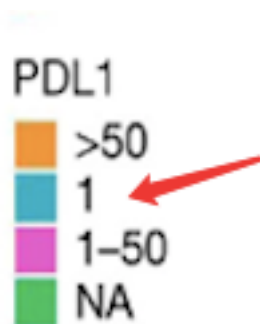
▼  
Jan. 21. 2020

AC (pemetrexed 0.8 + carboplatin 500 mg)  
(alectinib 600 mg, D2 + incadronate  
disodium 10 mg)

Reply: We have modified the figure.

### 5. Figure 1

Should it be “< 1”? Please check and revise.



Reply: We have modified the figure.