

## Peer Review File

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### Reviewer A

Studies evaluating the clinical value of ALK-TKIs based on one or two dimensions have been conducted. And this paper provides a comprehensive assessment of first-line drug use in ALK-positive non-small cell lung cancer patients based on six dimensions: safety, effectiveness, economy, suitability, accessibility, and innovation, to provide a basis for national policy and system improvement. This is a useful piece of information that may guide drug selection for ALK-positive patients.

The following are some of my comments:

-Introduction There are some repetitive concepts and theories in the first and second paragraphs, and given the focus of this article on patients with ALK-rearrangements in non-small cell lung cancer, perhaps patients could be introduced to ALK-rearrangements and their prevalence, the unique clinical characteristics of this patient population in the first paragraph while removing other unnecessary information.

-Methods The paper mentions that a total of 24 experts were selected. If possible, can the authors explain the specific selection process of these 24 experts and whether the clinical specialties of "five experts in clinical medicine" were all oncologists?

-What is the exact meaning of the grade grading in Table 1, is it divided into 3 grades or 3 boards? I hope the author can give a detailed explanation if it is convenient.

-Effectiveness Among ALK-positive patients, ALK-positive patients with brain metastases are a group of concern, and perhaps the authors could consider the further analysis of the effectiveness of ALK-TKIs from this perspective.

-Page 11 lines 341-343 "The interview results showed that physicians highly recommended alectinib, and they reported high levels of patient compliance with this drug." What are the reasons for highly recommending alectinib by the experts? Did the authors set up the recommendation reason details in advance for quantitation and were the recommendation strengths of other ALK-TKIs counted and compared, and how was patient compliance assessed, please explain in detail.

-Discussion This section is a slightly longer summary of the article's 6 dimensions of evaluating ALK-TKIs and could perhaps be summarized in more concise language.

**Comment 1:** Introduction There are some repetitive concepts and theories in the first and second paragraphs, and given the focus of this article on patients with ALK-rearrangements in non-small cell lung cancer, perhaps patients could be introduced to ALK-rearrangements and their prevalence, the unique clinical characteristics of this patient population in the first paragraph while removing other unnecessary information.

**Reply 1:** Thank you very much for the valuable comment provided by the expert. We have streamlined and deleted the repetitive parts in the first paragraph of the introduction in accordance with expert opinions.

**Changes in the text:** We have modified our text as deleted the sentences of “In 2020, the number of lung cancer-induced deaths worldwide was estimated at 1.8 million.” (see Page 3, lines 79) and “has the highest mortality rate among all malignancy-related deaths and” (see Page 3, line 80).

**Comment 2: Methods** The paper mentions that a total of 24 experts were selected. If possible, can the authors explain the specific selection process of these 24 experts and whether the clinical specialties of “five experts in clinical medicine” were all oncologists?

**Reply 2:** Thank you very much for the valuable comment provided by the expert. According to the division of China, we select secondary and tertiary medical institutions in five major regions of the country, namely, the eastern, western, southern, northern, and central regions. Each medical institution selects one expert, with a total of 24 experts. The clinical specialties of “five experts in clinical medicine” were all oncologists.

**Changes in the text:** we added some content of “five major regions eastern (western, southern, northern, and central regions.) of China, and each expert comes from a different medical institution.” in the text (see Page 4, lines 132-134); Besides, the content of “five experts in clinical medicine” was modified to “five experts in oncology medicine” (see Page 4, line 135).

**Comment 3:** What is the exact meaning of the grade grading in Table 1, is it divided into 3 grades or 3 boards? I hope the author can give a detailed explanation if it is convenient.

**Reply 3:** Thank you very much for the valuable comment provided by the expert. Some of the contents we describe here are not clear enough. The evaluation indicators here are mainly primary, secondary, and tertiary indicators. The third level indicators are included in the second level indicators, and the second level indicators are included in the first level indicators. The corresponding contents in the article has been modified.

**Changes in the text:** We have modified our text as advised (see Table 1).

**Comment 4: Effectiveness Among ALK-positive patients, ALK-positive patients with brain metastases are a group of concern, and perhaps the authors could consider the further analysis of the effectiveness of ALK-TKIs from this perspective.**

**Reply 4:** Thank you very much for the valuable comment provided by the expert. ALK-positive patients with brain metastases are indeed an important group, and our study did not include this group, which is also a limited part of the study. In the future, it is planned to evaluate the medication of patients with brain metastases separately based on the opinions provided by experts.

**Comment 5: Page 11 lines 341-343 “The interview results showed that physicians highly recommended alectinib, and they reported high levels of patient compliance with this drug.” What are the reasons for highly recommending alectinib by the experts?**

**Did the authors set up the recommendation reason details in advance for quantitation and were the recommendation strengths of other ALK-TKIs counted and compared, and how was patient compliance assessed? Please explain in detail.**

**Reply 5:** Thank you very much for the valuable comment provided by the expert. We mainly interview clinical oncologists to understand the clinical recommendations for these drugs. For several ALK-TKIs, the clinical acceptability of alectinib is high in terms of safety and effectiveness; We found that patients’ satisfaction with alectinib treatment was relatively high and their compliance was relatively good, through investigating the treatment effectiveness and satisfaction of patients.

**Comment 6: Discussion This section is a slightly longer summary of the article’s 6 dimensions of evaluating ALK-TKIs and could perhaps be summarized in more concise language.**

**Reply 6:** Thank you very much for the valuable comment provided by the expert. We have modified the section of discussion as advised.

**Changes in the text:** The content of the discussion section has been modified and adjusted.

## **Reviewer B**

Overall, a pretty comprehensive article. Some comments as below:

Some of the results mentioned should be under the respective section under methodology. For example "A meta-analysis and systematic review were conducted to determine the incidence of  $\geq$  grade 3 AEs. The incidence of  $\geq$  grade 3 AEs was systematically compared between six ALK-TKI first-line drugs for ALK-positive advanced NSCLC. Clinical randomized controlled trials were included, excluding single-arm and unavailable full-text studies. The study population was ALK-positive patients with advanced NSCLC. The databases searched included PubMed, Web of Science, and the ClinicalTrial website. The retrieval period was from the establishment of the databases until June 30, 2022. Finally, nine studies were included (15-23) with a total of 2,508 patients."

Methodology should include all these data from the results section.

Second-generation brigatinib and third-generation lorlatinib were launched abroad in 2017 and 2018, respectively, but not until 2022 in China. How then did the authors investigate the clinical value of these two ALK inhibitors in Asians in the local setting across the different parameters?

However, alectinib and crizotinib have been recommended as first-line treatments by several clinical guidelines. brigatinib, ceritinib, and lorlatinib were also recommended by various guidelines.

Please reference the guidelines. The article lacks appropriate citations especially in the discussion sections. What are your evidences for the statements?

"Based on the current prices of brigatinib and lorlatinib in our country, they are not economical." You must assume that readers are not only from China and many will have no idea what are the cost of these drugs currently in your country. You can give a rough estimate in USD for the different drugs listed in your country per year of treatment.

How is this article helpful to the rest of the world? Can you generalised your findings?

The discussion is very chunky. You should paragraph them with just ONE main idea in each paragraph followed by your supporting evidences and citations.

Abstract: Real-world studies are needed to explore the clinical use of ALK-TKIs, and the system established remains to be further verified in clinical practice.

Discussion: Future work will require real-world studies to explore the real-life clinical applications of ALK-TKIs.

Comment: While these statements have some truth, there have already been many real-world studies reported in the ALK setting. IF we are focusing on Asians, there are already real-world studies from Southeast Asian countries. Pls reference and cite accordingly.

Your conclusion in the abstract does not match the conclusion of the article.

**Comment 1: Some of the results mentioned should be under the respective section under methodology. For example "A meta-analysis and systematic review were conducted to determine the incidence of  $\geq$  grade 3 AEs. The incidence of  $\geq$  grade 3 AEs was systematically compared between six ALK-TKI first-line drugs for ALK-positive advanced NSCLC. Clinical randomized controlled trials were included, excluding single-arm and unavailable full-text studies. The study population was ALK-positive patients with advanced NSCLC. The databases searched included PubMed, Web of Science, and the ClinicalTrial website. The retrieval period was from the establishment of the databases until June 30, 2022. Finally, nine studies were included (15-23) with a total of 2,508 patients."**

**Methodology should include all these data from the results section.**

**Reply 1:** Thank you very much for the valuable comment provided by the expert. We have modified our text as advised.

**Changes in the text:** The content related to safety, effectiveness, and economy in the results has been modified to the section of methodology (see Page 6, lines 171-179, Page 6-7, lines 193-203, Page 7, lines 222-226).

**Comment 2: Second-generation brigatinib and third-generation lorlatinib were launched abroad in 2017 and 2018, respectively, but not until 2022 in China. How then did the authors investigate the clinical value of these two ALK inhibitors in Asians in the local setting across the different parameters?**

**Reply 2:** Thank you very much for the valuable comment provided by the expert. This study is mainly based on evidence-based data. When comprehensive clinical evaluation of drugs is conducted, the RCTs included in the study can be large samples based on Chinese populations, multicenter data/evidence, or international multicenter data/evidence containing Chinese populations. Our study included clinical studies that included data from Asian populations, and the results of the Asian population data analysis were consistent with the research results. Based on these considerations, although the brigatinib and lorlatinib were recently listed in China, we also included them in our comprehensive evaluation.

**Comment 3: However, alectinib and crizotinib have been recommended as first-line treatments by several clinical guidelines. brigatinib, ceritinib, and lorlatinib were also recommended by various guidelines.**

**Please reference the guidelines. The article lacks appropriate citations especially in the discussion sections. What are your evidences for the statements?**

**Reply 3:** Thank you very much for the valuable comment provided by the expert. Relevant guidelines for reference have been cited in the article.

**Changes in the text:** We have modified our text as advised (see Page 14, lines 447-448).

**Comment 4: "Based on the current prices of brigatinib and lorlatinib in our country, they are not economical." You must assume that readers are not only from China and many will have no idea what are the cost of these drugs currently in your country. You can give a rough estimate in USD for the different drugs listed in your country per year of treatment.**

**Reply 4:** Thank you very much for the valuable comment provided by the expert. The cost of different drugs treated per each year in our country has been roughly estimated USD for the different drugs in the text.

**Changes in the text:** We have modified our text in the discussion section as advised (see Page 14, lines 468-470).

**Comment 5: How is this article helpful to the rest of the world? Can you generalised your findings?**

**Reply 5:** Thank you very much for the valuable comment provided by the expert. This study integrates and analyzes evidence-based medical evidence to investigate the clinical comprehensive value of anti-tumor drugs from different dimensions, achieving scientific, homogeneous, and standardized clinical comprehensive evaluation of anti-

tumor drugs, providing reference for clinical rational drug use and directory access in hospitals, and providing a basis for the improvement of national policies and systems. We also hope that our research results can provide certain ideas and methods for other countries to carry out similar comprehensive drug evaluation, including anti-tumor drugs and other drugs, in order to promote certain reference for the safe and reasonable use of drugs.

**Comment 6: The discussion is very chunky. You should paragraph them with just ONE main idea in each paragraph followed by your supporting evidences and citations.**

**Reply 6:** Thank you very much for the valuable comment provided by the expert. The discussion section has been deleted and streamlined.

**Changes in the text:** We have modified our text as advised (see the discussion section).

**Comment 7: Abstract: Real-world studies are needed to explore the clinical use of ALK-TKIs, and the system established remains to be further verified in clinical practice.**

**Discussion: Future work will require real-world studies to explore the real-life clinical applications of ALK-TKIs.**

**Comment: While these statements have some truth, there have already been many real-world studies reported in the ALK setting. IF we are focusing on Asians, there are already real-world studies from Southeast Asian countries. Pls reference and cite accordingly.**

**Reply 7:** Thank you very much for the valuable comment provided by the expert. Relevant references to real-world studies of Asian populations have been cited. Most real-world research is based on the situation in different countries. Currently, the application situation in the real world in China is viewed from a multi-dimensional perspective, and some areas need to be further explored to investigate its real application situation in the Chinese population. Therefore, we also hope to understand the application of ALK-TKIs in China through real world research.

**Changes in the text:** We have modified our text as advised (see Page 15, lines 488-494).

**Comment 8: Your conclusion in the abstract does not match the conclusion of the article.**

**Reply 8:** Thank you very much for the valuable comment provided by the expert. The conclusion in the abstract and conclusions in the article have been adjusted and supplemented.

**Changes in the text:** We have modified our text as advised (see Page 2, lines 55-56; Page 15, lines 498-499).

### **Reviewer C**

First of all, I would like to thank you for submitting your study on the comprehensive clinical value of ALK-TKIs in patients with ALK-positive advanced non-small cell lung cancer (NSCLC). I believe this is an important and interesting topic, and this research will help guide clinical practice and provide a basis for the rational use of antitumor drugs. In this article, you have conducted a comprehensive evaluation of various ALK-TKI drugs, detailing their advantages in terms of inhibitory capacity, blood-brain barrier permeability, and drug action mechanisms for different generations of ALK-TKIs. Furthermore, you have combined the results of clinical expert interviews, emphasizing the urgent clinical need for ALK-TKIs in cancer prevention and treatment. You have done a considerable amount of work in the design and implementation of the study. However, to make your paper more rigorous and persuasive, I suggest you consider the following points:

We believe that this paper has significant value in the comprehensive evaluation of ALK-TKI drugs and provides a strong basis for clinical practice. Following our suggestions for revisions to the paper, we look forward to seeing your improved manuscript.

**Comment 1: In the discussion section, I recommend providing a more detailed description of the toxicity and side effects of various ALK-TKI drugs, and comparing the specific side effects of different drugs. This will help readers gain a more comprehensive understanding of the advantages and disadvantages of various ALK-TKI drugs.**

**Reply 1:** Thank you very much for the valuable comment provided by the expert. Relevant adverse reactions of various ALK-TKI drugs have been supplemented in the discussion section.

**Changes in the text:** We have modified our text as advised (see Page 13, lines 419-433).



**Comment 2:** In terms of research limitations, you mentioned the need for future exploration of the real-world application of ALK-TKIs. We suggest that you provide a detailed explanation of the importance of empirical research in the discussion section, and how they might affect the comprehensive evaluation results of ALK-TKIs.

**Reply 2:** Thank you very much for the valuable comment provided by the expert. Real-world studies in Caucasian population studies have been conducted, but different ALK-TKIs have different market times in different countries. Therefore, we also hope to conduct some real world studies to understand the application of ALK-TKI in Chinese people.

**Changes in the text:** The reasons for conducting empirical research have been added to the limited content in the discussion (see Page 15, lines 488-494).