Peer Review File

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Reviewer A

The authors retrospectively analyzed 15 cases in which Alectinib was continued even after progression of disease (PD), and considered the significance of continued Alectinib usage. While they concluded that there were benefits to continuing Alectinib in many cases, there are several issues that need to be addressed.

1

It is important to document the reasons for the initial progression of disease (PD) with Alectinib. This includes specifying whether the PD originated from the primary lesion, if there were emerging brain metastases, the appearance of bone metastases, or other specific reasons.

Reply: Thanks for your advice, and we agree that the importance of adding a description of progressions with prior alectinib in the study. We have added the information of progression with prior alectinib. All 15 patients in this study experienced oligometastases, and all of these progressions were considered to have originated from the primary lesion based on imaging surveillance. Of these, 6 (40.0%) patients developed emerging CNS metastases and 1 (6.67%) developed novel bone metastases.

Changes in the text: The above emerging brain and bone metastases are shown in Page23/Table 2 and Page7/Line204-205.

#2

In relation to #1 and based on the discussion, it is anticipated that many cases underwent subsequent radiation therapy as the next line of treatment, suggesting a prevalence of oligometastases, such as brain metastases. However, the significance of objective response rate (ORR) after the first progression of disease (PD) needs to be carefully considered. For instance, if oligo brain metastases emerged, received radiation therapy, and subsequently exhibited shrinkage, the efficacy might be attributed to the radiation treatment rather than Alectinib. This response rate could potentially lead to misinterpretation.

It is imperative to provide specific details for each case, elucidating why PD occurred with Alectinib and outlining the subsequent treatments administered. The reviewer recommends mentioning more explicitly the rationale for continuing Alectinib while concurrently administering local treatments for oligometastases.

Reply: Thank you for your valuable advice. All patients suffered oligoprogression in the study. Sincerely, we cannot ignore the significance of local therapy including radiotherapy, and in the Results and Discussion of our paper, we have emphasized more on the fact that the therapy for most of the patients after progression was continued alectinib in combination with local therapy. According to the existing guideline, it is recommended that patients with ALK-positive oligoprogression or CNS progression should either continue with their original ALK-TKI in combination with local therapy or be switched to other ALK-TKIs.The aim of the present study was to highlight the fact that continuation of alectinib in combination with local therapy after oligoprogression or CNS progression of patients with ALK-positive NSCLC treated with

alectinib, even without switching to another ALK-TKI, demonstrated a good efficacy. Specific details of each case are shown in the Supplementary Data.
Changes in the text: Specific details are shown in Supplementary Data.
We emphasized the reason and the efficacy of combination therapy in Page2/Line 39-42, Page3/Line 45-48, Page3/Line 56-57, Page3/Line 63-67, Page4/ Line 98-101,Page5/Line 125-133, Page5/Line135-138, Page8/Line241-243, Page11/Line 324-343, and Page12/Line 364-368.

＃3 Line 145

'ECOG score' should be 'ECOG performance status' or 'ECOG PS'
Reply: Thank you for your advice, the above error has been changed.
Changes in the text: Page12/Line 196-197.

#4 Table 1
'ECOG' should be 'ECOG performance status' or 'ECOG PS'
Reply: Thank you for your advice, the above error has been changed.
Changes in the text: Page22-23/Table 1 and Table 2.

#5 Figure 2
It appears that the units for the X-axis are not provided.
Reply: Thank you for your advice, the above error has been changed. The unit of the X-axis in Figure 2 is month.
Changes in the text: Page25/Figure 2.

Reviewer B

The article presented by the authors entitled "Efficacy and safety of alectinib continuation in alectinib-refractory anaplastic lymphoma kinase-rearranged (ALK-positive) patients with non-small cell lung cancer: a retrospective cohort study" shows an investigation of the use of Alectinib after progression to Alectinib in NSCLC.
To begin this review, I would like to comment that the authors have produced a very valuable article, and their main contribution is the originality of the results they present. The article does not allow valid conclusions to be drawn about the reason with Alectinib should be proposed after progression but constitute an interesting case series in this setting. There are currently no studies that evaluate the role of Alectinib after progression disease although in clinical practise many physicians continue Alectinib in case of oligoprogression.
In addition to the above, it is true that the article has important methodological deficiencies and shortcomings in its results, so the results should be taken with great caution. The main drawback of the article is its lack of biological plausibility, as there is no biological or molecular explanation at a theoretical level to explain the results obtained. Therefore, the article presents a great advantage by showing very novel results that could have a great influence on the treatment of ALK-mutated NSCLC, however, in contrast, the results present serious deficiencies at the methodological level.
Overall, the article is well written, easy to read and easy to understand. The language is also

adequate, and I do not think it needs editing. The figures are the necessary and correct ones.

INTRODUCTION

Major changes:

The introduction is well written. Anyway, it could be implemented with data regarding

- the difference between oligoprogression and progression in patients with Alk rearranged NSCLC (doi: 10.3390/cancers14030718)

Reply: Thanks for your advice, we have added the difference between oligoprogression, CNS progression and systemic progression in patients with ALK rearranged NSCLC according the article in Introduction.

Changes in the text: Page4/Line 93-105.

- the role of resistance mechanisms (on target/off target) in ALK population (doi: 10.7573/dic.2022-3-1)

Reply: Thanks for your advice, we have added the role of resistance mechanisms (on target/off target) in ALK population according the article in Introduction.

Changes in the text: Page4/Line 106-108.

Minor changes

Although Lorlatinib is not still approved in the country of author some data regarding phase II trial after Alectinib should be included.

Reply: Thanks for your advice, we have added the data of phase II trial after alectinib in Introduction.

Changes in the text: Page5/Line 125-133.

METHODS

Minor changes "The study excluded patients who had a smoking history, certain tumor conditions, a treatment history, disease progression…".

I believe that authors should specify why do they excluded these patients and in particular what kind of "certain tumor conditions" they had.

Reply: Thanks for your advice, that was a mistake in our writing work. We didn't exclude the patients who smoked. We have checked and modified the exclusion criteria as "patients who had uncertain tumor conditions and who were lost to follow-up".

Changes in the text: Page6/Line 147-149.

RESULTS

Major changes: in methods authors said that excluded patients with smoking history but in table 1 there is 1 patient smoker, please explain.

The main issue regards the right explanation of the number of oligoprogression (eventually specifying where) and systemic progression. I think that a table including all 15 patients including those informations could be useful. Anyway the results should be written in a more easy way.

Reply: 1. Thanks for your advice, that was a mistake in our writing work. We didn't exclude the patients who smoked. We have checked and modified our exclusion criteria.

2.We uploaded the supplementary table including the information of 15 patients. We also shown more details about prior alectinib use in Table 1 and more information about continued alectinib in Table 2.
Changes in the text: Page6/Line 147-149, Page22-23/Table 1, Table 2 and Supplementary Data.

DISCUSSION
Major changes
The discussion is easy to understand. Anyway, I would focus mostly on
- resistance (many trials demonstrated that rechallenge with a first generation ALK could be useful doi: 10.1158/2159-8290.CD-17-1256)
Reply: Thanks for your advice. We have talk about the potential benefit of continuing prior TKI and the problem about highly resistant complex ALK mutations after sequential ALK-TKI in Discussion.
Changes in the text: Page9/Line 247-251.

- research of possible predictive biomarkers in course of Alectinib (es. doi: 10.3390/cancers15133422.)
Reply: Thanks for your advice. We have talk about the necessity about the predictive biomarker in alectinib use according the article.
Changes in the text: Page11/Line 343-346.

- exploring the synergistic effects of Alectinib and radiotherapy or chemotherapy or VEGFR
Reply: Thanks for your advice. We have talk about the synergistic effects of alectinib and radiotherapy or chemotherapy or VEGFR.
Changes in the text: Page11/Line 324-339.

Minor changes
I do not find any sentence regarding the limitations of the study.
Reply: Thanks for your advice. We have shown the limitations of the study at Line 46-360. And we have shown more limitation and prospect in Line 343-346.
Changes in the text: Page11/Line 343-346 and Page11-12/ Line 347-361.

In conclusion, this manuscript is really interesting but some data should be implemented focusing on the role of Alectinib after oligoprogression versus systemic progression disease.
Reply: Thanks for your advice. All patients suffered oligoprogression or CNS progression in the study. we have added the difference between oligoprogression, CNS progression, and systemic progression in patients with ALK rearranged NSCLC according the article in Introduction.
Changes in the text: Page4/Line 93-105.

Reviewer C

An interesting study exploring a current topic in lung cancer.
Some changes are needed.

Firstly, some expressions are a bit "wordy". Thus, a linguistic revision is recommended due to the presence of some grammar mistakes and oversights. We suggest a professional service.
Reply: Thanks for your advice. We organized a professional team including native speakers to polish and revise the article according to your suggestions, and corrected the relevant grammatical errors and descriptions not in line with academic norms.
Changes in the text: All the paper.

Secondly, the introduction section should be expanded and the authors should briefly discuss the changing treatment scenario for lung cancer, and add some recently published papers, only for a matter of consistency (PMID: 35326555; PMID: 36064585; PMID: 35031442 ; PMID: 37535194).
Reply: Thanks for your advice. We have expanded the INTRODUCTION about lung cancer and treatment scenario according to the articles and cite these articles.
Changes in the text: Page3-4/Line 77-84.

How do the authors think that this paper may impact clinical practice? Please, kindly speculate more in regards to the translational and practical implications of this interesting study.
Reply: Thanks for your advice. We have expanded the DISCUSSION about how the paper will influence the clinical pratice.
Changes in the text: Page11/Line 324-343.

The first paragraphs of the Discussion section repeat some parts and concepts of the Introduction. I would directly start with a Discussion of the results.
Reply: Thanks for your advice. We've deleted the part of Discussion that was duplicative of Introduction and got straight to the point of discussing our findings, making the discussion more concise and meaningful
Changes in the text: Page8-9/Line 241-248.

What are the main strengths and limitations of the current study? Please, kindly describe and report.
Reply: Thanks for your advice. Our strength is in providing a therapy that can provide sustained benefit to alectinib-resistant patients who continue alectinib in combination with other treatments. This therapy avoids the creation of complex mutations and offers the opportunity for subsequent third-generation-TKI therapy. Our limitation is that we failed to further explore the potential population that could benefit more from continued aleitinib.
Changes in the text: Page9/Line 343-346 and Page11-12/Line 347-361.

Reviewer D

1) Alectinib therapy is the only available choose after drug resistance in China?
Reply: Thank you for your advice. Aleitinib is not the only choice for ALK-positive NSCLC patients after drug resistance. According to the existing agreement, it is recommended that

patients with ALK-positive oligoprogression or CNS progression should either continue with their original ALK-TKI in combination with local therapy or be switched to other ALK-TKIs. For alectinib-resistant patients, treatment can be switched to the third-generation ALK-TKI loratinib and other second-generation ALK-TKIs, which can also be continued with alectinib and combined with other therapy. The aim of our study was to highlight the fact that continuation of alectinib in combination with other therapy after oligoprogression or CNS progression of patients with ALK-positive NSCLC treated with alectinib, even without switching to another ALK-TKI, demonstrated a significant efficacy and it balances the treatment of TKI-sensitive clones, possible off-target TKI-insensitive clones, avoiding the generation of complex resistance and providing more possibilities for subsequent third-generation ALK-TKI therapy. We have clarified more in the paper.
Changes in the text: Page3/Line 39-42, Page4/Line 98-101, Page9/Line 248-250, and Page11/Line 368-372.

2) This retrospective cohort study included a total of 15 patients from10 institutions in China. why the sample is too small?

Reply: Thank you for your advice. The small sample size is firstly due to the rarity of ALK-positive patients in NSCLC. Patients with ALK-positive NSCLC constitute approximately 3–7% of all NSCLC cases. Secondly, the better prognosis of ALK-positive NSCLC compared to other lung cancer patients led to limited follow-up of ALK-TKI-resistant patients. Even so, some patients in the above population did not use alectinib as first- or second-line therapy, leading to exclusion from this study. In a limited number of patients who had developed resistance to alectinib with first- or second-line use, the majority of patients changed TKIs despite guidelines recommending that ALK-TKIs may not be changed in the case of oligoprogression. In summary, our sample size was limited because of the rarity of the population included in our study. But because of this, our study demonstrated the value of providing options for drug-resistant patients.
Changes in the text: Page12/Line 354-356.

3) Can the authors give more info about the institutions?

Reply: Thanks to your advice, we show detailed center information in the supplementary material.
Changes in the text: Supplementary data.

4) Suggest to reported the study protocol at appendix

Reply： Thanks to your advice. We have organized the study protocol and uploaded it in the supplementary material
Changes in the text: Study protocol.

Reviewer E

Editorial note: As some comments were pointed out by line numbers, we've attached the peer-review version for your reference.

Efficacy and safety of alectinib continuation in alectinib-refractory anaplastic lymphoma

kinase-rearranged (ALK-positive) patients with non-small cell lung cancer: a retrospective cohort study.

Thank you for the article regarding continuing Alectinib beyond progression in ALK-positive NSCLC presented from a retrospective view.
Hereby my comments/questions:

Key findings
- what does it mean “a significant majority”? Can you provide percent of patients progressing on Alectinib and median time to progression?
Reply：Thanks to your advice. According to the ALEX Global Study, alectinib in the untreated ALK-positive NSCLC population resulted in 34.8 months of mPFS, with a median follow-up of 37.8 months as of November 30, 2018, as of the most recent report from 2020. And the progression disease occurred in a total of 53.3% of patients. We've rechecked the descriptions to make sure the article is rigorous. We have made changes in the highlight box, Abstract and Introduction based on your comments.
(Mok T, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8):1056-1064. doi:10.1016/j.annonc.2020.04.478)
Changes in the text: Page2/Line28(highlight box), Page3/Line 38-40 and Page4/Line 94-98.

Abstract/Line 38 and Line 75: instead of “disease relapse” it should be “disease progression”.
Reply：Thanks to your advice. We have amended the description to achieve a more rigorous presentation. The “disease relapse” in Line40 has been removed due to more concise and understandable discussions
Changes in the text: Page2/Line40 and Page4/Line96.

Line 39: “*ALK*-TKI”. This description is not correct. Names of the genes must always be written in italics, but not names of proteins should not be written in italics and in the context of TKI. The target for TKI is not the *ALK*-gene, but ALK-protein. Therefore, you must look through all the manuscript and correct all **“*ALK*-TKI”** to “**ALK-TKI**”, thank you.
Reply：Thanks to your advice. We apologize that we overlooked the difference between the two in our previous work. We have eliminated the italicization of ALK in all ALK-TKIs and modified the italics of other TKIs, such as EGFR-TKI.
Changes in the text: All the manuscript.

3Line 41: “third-generation of ALK-TKIs have not yet been approved…”. It is **not** the reason why you explore treatment beyond progression with Alectinib. There are many different acquired resistance mechanisms upon Alectinib like off-target resistance with e.g., *RET*-fusion or *MET*-amplifikation (1,2), or phenotypical changes like EMT, where Lorlatinib is not effective at all (1). So, the reason is rather to investigate whether treatment beyond progression may be applicable and relevant in some *ALK*-positive patients whose disease has progressed on Alectinib. Otherwise, it may be misleading for the readers.
Reply：Thanks to your advice. We apologize for failing to describe a clear strategy for selecting

therapeutic agents based on acquired resistance mechanisms after oligoprogression progression or CNS progression of alectinib. As the presentation of Abstract should be more concise, we have removed the relevant descriptions in the abstract. However, we have provided a detailed description in the Introduction.
Changes in the text: Page3/Line 44-46 and Page4-6/Line 98-144.

Line 45: "… who experienced disease progression". How was it assessed? Radiographically only or with rebiopsies?
Reply：Thanks to your advice. We apologize for not clarifying the methods of assessing disease progression in detail in previous manuscripts. The disease progression was assessed based on radiological surveillance. Due to limitations on the length of the abstract, we have elaborated in the Methods of the manuscript.
Changes in the text: Page6/Line 159-160.

Line 48: why ORR is written in italics?
Reply：Thanks to your advice. Sorry, this is a typo. We've removed the italics and corrected it
Changes in the text: Page3/Line 60.

Line 70: "…act on the *ALK* receptor tyrosine kinase". The target for ALK-TKI is ALK protein, not *ALK* gene. Therefore, please do not write it in italics.
Reply：Thanks to your advice. We've corrected it and checked the full text.
Changes in the text: Page4/Line 82 and all the manuscript.

Line 72: "… ALK-TKIs have seen three generations…" Please re-phrase, since ALK-TKIs are not supposed to see anything.
Reply：Thanks to your advice. We've re-phrase it and we will avoid such mistakes in the future.
Changes in the text: Page4/Line 84-86.

Line 84: you state that "It has been reported that the continuation of ALK-TKI therapy after the development of resistance can provide sustained benefits to patients (13,18)." If, so it may be used and no third-generation will be needed: "However, at the initiation of the present study, third generation ALK-TKIs had not yet been approved for clinical use in China". So, it is important to understand that third generation of ALK-TKI not always is the solution for all patients with progression on Alectinib. So, it is rather crucial to identify and characterize the patients who most likely may benefit form treatment with Alectinib beyond progression.
Reply：Thanks to your advice. We apologize for failing to describe a clear strategy for selecting therapeutic agents based on the mechanism of acquired resistance after oligoprogression of alectinib or CNS progression. We have revised the Introduction to take into account your previous comments.
Changes in the text: Page5-6/Line 116-144.

Line 99: ". The study excluded patients who had a, smoking history, certain tumour conditions, a treatment history, disease progression, and unknown safety information, and who were lost to follow-up". Please remove comma between "a" and "smoking". Why patients with smoking

history were excluded? What does it mean “certain tumour conditions”? Why the patients with disease progression were excluded while you investigate these patients with disease progression? The sentence is confusing. Please re-phrase.
Reply: Thanks for your advice, that was a mistake in our writing work. We didn’t exclude the patients who smoked. We have checked and modified the exclusion criteria as “patients who had uncertain tumor conditions and who were lost to follow-up”.
Changes in the text: Page6/Line 160-162.

Line 118: remove space between “the” and “objective”.
Reply: Thanks for your advice. We've re-phrased it and we will avoid such mistakes in the future.
Changes in the text: Page7/Line 180.

Line 116/117: “… and the second median progression-free survival (mPFS). However, 2 of the 15 patients received Alectinib as second line. So, for these patients it will be the third mPFS, not second. Please, take it into account.
Reply: Thanks for your advice. We apologize for our previous sloppy statement and we have re-phrased it as “The primary objective of the study was to evaluate the safety and the median progression-free survival (mPFS) of the continued alectinib, as assessed by the investigators”
Changes in the text: Page7/Line 178-180.

Line 145: “Three patients had previously undergone treatment with other ALK-TKIs”. It is confusing as you have presented in the Table 1 that only 2 patients received Alectinib as second line and 13 patients as the first line. Please specify, how many patients received Alectinib as first line and how many as second line and specify what “other ALK-TKI medications” were, thank you. In the Table 1 there are three (not two) patients treated with ALK-TKI before Alectinib, not two patients. It is quite confusing. When we treat a patient with different therapies, we would rather count the consecutive therapies, and not whether Alk-TKI was first line as ALK-TKI after chemotherapy. So, if you have three patients treated with ALK-TKI (which one? Crizotinib?) before Alectinib, and at the same time you have two patients treated with chemotherapy, so one patient may have been treated with ALK-TKI and chemotherapy before Alectinib. Is this true?
Reply: Thanks for your advice. We apologize for not stating the prior TKI treatment, prior chemotherapy. According to the practice of clinical oncology, the replacement of treatment line is due to progressive disease. In fact, in the real world, due to the long wait for genetic test results, chemotherapy usually are given first to avoid tumor progression due to treatment delay. Thereafter, if the genetic test suggests the existence of driver gene, chemotherapy can be discontinued to take the targeted drug. Just for the above reason, two patients with first-line alectinib had prior chemotherapy exposure. Among the 3 patients with prior exposure to ALK-TKI before alectinib, 2 were treated with the first-generation ALK-TKI crizotinib as first-line therapy, and 1 was treated with crizotinib without progression and then switched to aleitinib in pursuit of better efficacy, which was counted as a first-line aleitinib-treated patient. We explain this in detail in the text as follows:
“As shown in Supplementary Data, patient No.9 received 1 cycle of chemotherapy after

diagnosis while awaiting the result of the genetic test, followed by crizotinib in combination with cranial gamma knife radiosurgery and alectinib after the progression of the prior treatment. Patient No. 3 was treated with crizotinib for 2.5 months, which was then discontinued based on individual decision, followed by alectinib for better efficacy. Patient No.2 received 1 cycle of chemotherapy during the post-diagnostic genetic test and thereafter received alectinib. Other patients who received first-line treatment with alectinib were previously untreated." In addition, we show the specific treatment history in the Supplentary data.
Changes in the text: Page8/Line 211-219.

Line 147/150: If 10 patients were simultaneously treated with local ablation therapy while continuing Alectinib, and two patients received Alectinib in monotherapy beyond progression, and three patients received chemotherapy upon Alectinib – so there are different patients' profiles and different forms of treatment beyond progression. Therefore, it is difficult to assess all these patients, as they have been treated differently, where radiotherapy and chemotherapy could have more impact on response than monotherapy with Alectinib.
Reply: Thanks for your advice. Sincerely, we cannot ignore the significance of other therapies, and in the Results and Discussion of our paper, we have emphasized more on the fact that the therapy for most of the patients after progression was continued alectinib in combination with other therapy. According to the existing guideline, it is recommended that patients with ALK-positive oligoprogression or CNS progression should either continue with their original ALK-TKI in combination with local therapy or be switched to other ALK-TKIs. The aim of the present study was to highlight the fact that continuation of alectinib in combination with other therapy after oligoprogression or CNS progression of patients with ALK-positive NSCLC treated with alectinib, even without switching to another ALK-TKI, demonstrated a good efficacy. In addition, in Figure 2, the swim plots we drew to show the PFS of patients receiving different combination therapies were also designed to demonstrate the fact.
Changes in the text: We emphasized the reason and the efficacy of combination therapy in Page2/Highligt box, Page3/Line 40-42, Page3/Line 53, Page3/Line62, Page4/ Line 66-67,Page5/Line 111-114, Page5/Line119-131, Page8-9/Line237-239, Page9/Line 264-268, and Page9-10/Line 271-274, Page12/Line 355-368, Page13/Line 403-406.

Line 162: the conclusion of 46,6% ORR represents the whole group (n=15) differently treated beyond progression. Such conclusion is remarkable biased.
Reply: Thanks for your advice. In the same vein as the previous reply, we cannot ignore the significance of localized treatments, including radiotherapy, and in the results and discussion of our paper, we emphasize more that the treatment for the majority of patients after progression is to continue alectinib in combination with other therapies, so as not to mislead the reader.
Changes in the text: We emphasized the reason and the efficacy of combination therapy in Page2/Highligt box, Page3/Line 40-42, Page3/Line 53, Page3/Line62, Page4/ Line 66-67,Page5/Line 111-114, Page5/Line119-131, Page8-9/Line237-239, Page9/Line 264-268, and Page9-10/Line 271-274, Page12/Line 355-368, Page13/Line 403-406.

Line 185/186 and lines 78/79 are the same.
Reply: Thanks for your advice. As a result of your reminding us, we have realized the

repetitions and redundancies in our previous manuscript, and we have further revised it to make it more concise.
Changes in the text: Page5/Line 114-116 and Page10/Line279-280.

Line 186/187: it is not quite correct as a time-factor here is needed. Acquired resistance is commonly considered when the progression occurs after 6 months of treatment. Contrary to intrinsic resistance where progression occurs earlier and before 6 months of treatment.
Reply: Thanks for your advice. We apologize for our oversight, the previous definition was really sloppy. We have revised the description of acquired resistance with your comments
Changes in the text: Page10/Line 280-282.

Line 186-203: This part of manuscript refers to "drug-holidays", where re-sensitizing may be obtained after treatment break in EGFR-mutated NSCLC patients. It seems not be relevant to the main question debated in this article and should be removed.
Reply: Thanks for your advice. We reread this section with your comments and do feel confused. The description in our previous manuscript was intended to present evidence for continuing the original TKI therapy. However, our improper articulation caused this section to seem irrelevant to the issues discussed in this paper, and we have revised this section. We believe that it is not enough to state the feasibility of continuing the original TKI only from the perspective of clinical data such as progression-free survival, and the mechanism behind it should also serve as strong evidence. We consider that this section should be retained with modifications
Changes in the text: Page10/Line 293-296.

Line 237/238: "… the subsequent treatment approach depends on the location of the resistance within the ALK domain". It is not quite true. It depends on the type of resistance, which may be on-target (secondary ALK-mutations localized in the kinase domaine) or off-target. Please, rephrase the sentence.
Reply: Thanks for your advice. We have corrected the above error. We will avoid such problems in the future.
Changes in the text: Page11/Line 334-337.
Line 239: "third generation ALK-TKI" – which ALK-TKI do you mean? You repeat very often third generation Alk-TKI without specifying. Do you mean Lorlatinib or other third generation ALK-TKI, which are still not available in the clinic?
Reply: Thanks for your advice. Since there is now only one third-generation ALK-TKI, loratinib, on the market, we have overlooked this subtle difference, leading to such a loose description. We will do our best to avoid such errors in our future work. We have corrected the error.
Changes in the text: Page11/Line 337-339.

Line 247: "When alectinib becomes resistant, it can still be used in combination with chemotherapy or third-generation drugs...". Do you mean combination of Alectinib with third generation of ALK-TKI? Which drugs do you mean?
Reply: Thanks for your advice. We apologize for our sloppy presentation and we have revised the above sentence as "When alectinib becomes resistant again, it can still be used in combination with chemotherapy or switch to another ALK-TKI such as lorlatinib, depending

on the underlying resistance mechanism.”.
Changes in the text: Page12/Line 346-348.

Line 274: “especially in patients in whose who experienced asymptomatic or limited progression”. I can agree with this statement, but it does not tell us whether there were these two patients who continued monotherapy with Alectinib, or patients treated with either radiotherapy or chemotherapy. Furthermore, if the progression was limited or asymptomatic, why combination with radiation therapy or chemotherapy should be required?
Reply: Thanks for your advice. We previously had a loose presentation, and our cohort was all patients with oligoprogression or CNS progression. The previous presentation was intended to include the two patients who continued to use alectinib monotherapy, who were indeed asymptomatic, but this presentation was ultimately discarded in view of the standardization. The choice of whether or not to combine other therapies should be based on the reality of each patient's situation and the physician's decision. The conclusion section has been changed as “In our study, we found that continuing alectinib treatment combined with other necessary therapy after the oligoprogression or CNS progression of the first- or second-line alectinib in patients with ALK-positive NSCLC yielded a favorable response and maintained safety. Our findings suggest that instead of immediately switching to another ALK-TKI, continuing alectinib combined with other necessary therapies after the oligoprogression or CNS progression of the first- or second-line therapy alectinib may offer greater survival benefits to patients.”
Changes in the text: Page12-13/Line 403-411.

Reassuming, most patients, about 53%, did not receive any benefit from continued Alectinib. Therefore, what is the role of treatment with Alectinib beyond progression, while the majority of patients do not respond. Was it legitimized to continue Alectinib then, without knowing the potential resistance mechanism? The most important question is who the patients are who benefit from continuing Alectinib beyond progression. Are there any characteristic features, like those (good PS, asymptomatic progression, long primer response to the treatment, etc.) found in treating patients with Crizotinib beyond progression (3). Small group of patients, where majority come from 10 different institutions may increase bias. Furthermore, the genomic diagnostics of ALK-fusion is not provided (ALK-IHC? ALK-FISH? ALK-NGS?). Therefore, the group may also include patients with intrinsic resistance. Additionally, the group constitutes mostly by males (10/15). Is this representative for the Chinese population in contrary to data showing the higher prevalence of females? The discussion may also address more attention to the patients with progression in the brain. How were they treated beyond progression? Finally, the term of “treatment beyond progression” will be more understandable for readers as is has been commonly used in the relevant literature for this topic. So, the title may also be re-phrased, e.g., “…. Alectinib continuation beyond progression in NSCLC-patients with ALK-rearrangement…”
Reply: Thanks for your advice. We have carefully thought about and discussed your comments. 1.The 46.6% ORR achieved by the treatment regimen thereafter is not low for patients with aleitinib resistance. Loratinib treatment in patients with ALK-positive NSCLC who progressed on alectinib only achieved an ORR of 40%, and similarly, brigatinib achieved an ORR of 29.1%.

(PMID:30892989, 36096442) With rising numbers of treatment lines, tumors become progressively more refractory and therefore response rates gradually decline.

2. We apologize that we have not clarified the mechanism and background of this therapy in the previous manuscripts. For TKI therapy in ALK-positive patients, the choice of their next treatment regimen is not based only on progressive disease as determined by the RECIST criteria. Progression can be divided into oligoprogression, central nervous system (CNS) progression, and systemic progression. Oligoprogression is defined as a disease that progresses in a limited number of sites. CNS progression is defined as progression involving only the central nervous system. When the disease suffers progression in more sites, it is defined as systemic progression. According to established guidelines, patients with advanced NSCLC who experience oligoprogression or CNS progression while undergoing ALK-TKIs treatment have the option to continue with their current ALK-TKI therapy combined with local therapy or switch to an alternative ALK-TKI. It can be considered that oligoprogression or CNS progression does not necessarily indicate a complete failure of the prior TKI treatment, but rather it may be due to heterogeneity within and between tumors. Although ALK-TKI replacement is desirable in this scenario, several studies have indicated that sequential ALK-TKIs treatment may ultimately result in the development of highly resistant complex ALK mutations, which could potentially limit patient survival benefits. Above all, continued alectinib in combination with other necessary therapies is a good option in this scenario. We have carefully revised the article to ensure that the above mechanisms are demonstrated.

3. We strongly agree that it is essential to identify the subgroup that will potentially benefit from continued alectinib therapy. In our study, all patients experienced oligo-progression or CNS progression and showed good efficacy. Therefore, in combination with previous reports, it should be feasible to continue the original ALK-TKI in combination with other therapies in this subgroup. And we have carefully read and discussed your comments and have added to the manuscript some descriptions of possible biomarkers to predict the benefit of continued alectinib and the necessity to explore biomarkers.

4. We agree with you. However, it was determined by the rarity of the population included in this study. Firstly, Patients with ALK-positive NSCLC constitute approximately 3–7% of all NSCLC cases. Secondly, the better prognosis of ALK-positive NSCLC compared to other lung cancer patients led to limited follow-up of ALK-TKI-resistant patients. Even so, some patients in the above population did not use alectinib as first- or second-line therapy, leading to exclusion from this study. In a limited number of patients who had developed resistance to alectinib with first- or second-line use, the majority of patients changed TKIs despite guidelines recommending that ALK-TKIs may not be changed in the case of oligoprogression. In summary, our sample size was limited because of the rarity of the population included in our study. But that is what makes our research all the more valuable. We hope that when this study is seen by much wider readers, there will be a large sample of clinical studies to further substantiate.

5. Because of the rarity of re-biopsy in the real world, we have not been able to report the results of genetic testing again after patient progression. The greatest difficulty with re-biopsy is the high frequency of brain metastases, given the safety concerns. it is rare for re-biopsy to be performed in patients with oligometastases, considering the existence of TKI-sensitive clones, the progression usually due to tumor heterogeneity. We have written it as a limitation in the manuscript to avoid misleading the reader.

6. In ALK-positive NSCLC in Asia, there are still slightly more female than men. With your reminder, we checked the Supplementary Data, which is the original data for this study, found that there were some errors in the manuscript and table1. In the original data it was recorded that there were 5 cases of males and 10 cases of females, we have changed this error. We apologize and we will avoid such mistakes in the future.
7. In our study, a total of 75% of patients with CNS progression received cranial radiotherapy. In addition, one received chemotherapy and another received bevacizumab. We have discussed in the manuscript to meet the requirements of the readers.
8. Thank you very much for your advice. We also agree that "beyond progression" is better than the original wordings. We have changed the title as you suggested.
Changes in the text: Page4-5/Line 101-114, Page12/Line 355-360, Page12-13/Line 372-380 and Page13/Line 385-393.

Ref.

1. Urbanska, E. M., Sørensen, J. B., Melchior, L. C. et al., Costa, J. C. et al. Changing ALK-TKI-Resistance Mechanisms in Rebiopsies of ALK-Rearranged NSCLC: ALK- and BRAF-Mutations Followed by Epithelial-Mesenchymal Transition. International journal of molecular sciences, 21(8), 2847. https://doi.org/10.3390/ijms21082847.

2. Dagogo-Jack, Ibiayi et al. "Efficacy and Tolerability of ALK/MET Combinations in Patients With ALK-Rearranged Lung Cancer with Acquired MET Amplification: A Retrospective Analysis." JTO clinical and research reports vol. 4,8 100534. 1 Jun. 2023, doi: 10.1016/j.jtocrr.2023.100534. https://www.jtocrr.org/article/S2666-3643(23)00073-5/fulltext.

3. Ou SH, Jänne PA, Bartlett CH, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. Ann Oncol 2014; 25:415-22.