Peer Review File

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Reviewer A:

Comment1: Line 39: “each year have ALK+ tumors”. Please re-phrase the sentence as there are not only patients with advanced disasease, but all stages. We don’t know whether it is “each year” as the rate does not need to be stable. Furthermore, instead of “have” use “harbor”. So, e.g. “About 5% of NSCLC patients are being diagnosed with tumor harboring ALK-fusion". I know the term “ALK+”, but you use in the title “ALK-positive", so maybe it will be a better style to be consequent and use “ALK-positive” or ALK-rearranged" “term in the whole article.

Reply1: we have modified our text as advised.

Changes in the text: See Page1. Line 9-10

Comment2: Line 42: It will be more important for readers to be informed about the TNM stage in the abstract instead of some limited information about “T” status only.

Reply2: we have added TNM stage in the abstract.

Changes in the text: See Page1. Line 16-17

Comment3: Line 43: “Anaplastic lymphoma kinase (EML4-ALK fusion positive) was detected”. We do not detect kinase as such, but ALK gene in rearranged form. Please, simply re-phrase to “EML4-ALK fusion, variant... was detected”. You have already in the abstract develop the abbreviation ALK, so you do not need to repeat it. Furthermore, instead of “fusion positive” it is enough “fusion”.

Reply3: we have modified our text as advised.

Changes in the text: See Page1. Line 13

Comment 4: Line 49: We do already know that Alectinib is feasible and has a good safety profile in advanced stage form other studies, where there also were patients with stage III. Your case demonstrated rather the possibility of using Alectinib as downstaging for subsequent definitive treatment and this should be highlighted. Please remove “conversion” from this context.

Reply4: we have removed “conversion” from this context.

Changes in the text: See Page1. Line 18

Comment 5: Line 55: New data form ESMO 2023 showed also impressive effect of neoadjuvant chemo- and immunotherapy for NSCLC patients WITHOUT genomic alterations. So, chemotherapy has a limited effect, but not chemo- and immunotherapy.

It is also important not to mix different subgroups of NSCLC. It is OK to mention generally such an approach – neoadjuvant treatment for advanced disease -, but in your case, this is about neoadjuvant targeted therapy as downstaging in NSCLC patients with genomic defined target.

“The use of novel therapeutic agents in neoadjuvant therapy for non-small cell lung cancer (NSCLC) is an emerging area of research aimed at achieving higher cure rates” - we need citation here and underlining that these effects have been reported in NSCLC patients without druggable genomic alterations.
Reply5: we have modified our text as advised.
Changes in the text: See Page2. Line 5-8

Comment 6: Line 58: “Although neoadjuvant therapy may delay surgery”. New data from ESMO 2023 show that neoadjuvant therapy does not always delay surgery. Therefore, add “may sometimes delay surgery”.
Reply6: we have added “may sometimes delay surgery”.
Changes in the text: See Page2. Line 8

Comment 7: Line 60: Please do not start the sentence with “And”
Line 63: “ongoing[2].” Space between “ongoing” and “[2].” is missing
Line 66: “NEO-adjuvant therapy”. Please change to “neoadjuvant”. You do not need to use capital letters for “neo”.
Line 71: please remove “characterized by dark red phlegm”, as the term hemoptysis is sufficient.
Reply7: we have modified our text as advised.
Changes in the text: See Page2.

Comment 8: Line 76: “The carcinoembryonic antigen concentration was 5.63 ng/mL (reference range, 0.00–5.00 ng/mL)”. How does this information contribute to the case as it is slightly increased?
Reply8: I'm sorry that the CEA I wrote is wrong, and I have modified it in the text.
Changes in the text: See Page3. Line 4

Comment 9: Line 78: please underline that N2 status was not rebiopsy confirmed.
Line 80: “Anaplastic lymphoma kinase (EML4-ALK fusion positive) was detected” - please refer to my comment regarding line 43.
Reply9: we have modified our text as advised.
Changes in the text: See Page2.

Comment 10: Line 84: “ALK+NSCLC.” - space is missing between “ALK+” and “NSCLC”. Please also refer to my comments in line 39.
Reply10: we have modified our text as advised.
Changes in the text: See Page3. Line 11

Comment 11: Line 86: please remove “at” and
“The carcinoembryonic antigen concentration was 5.63 ng/mL (reference range, 0.00–5.00

ng/mL), which was significantly lower than that before targeted therapy." You have previously mentioned the same CEA value in lines 76/77.

Reply11: we have modified our text as advised. I'm sorry that the CEA I wrote before was wrong, and I have modified it.

Changes in the text: See Page3.

Comment 12: Line 93: "as were"? - please re-phrease as it is not understandable.

Reply12: we have modified our text as advised.

Changes in the text: See Page3. Line 20，21

Comment 13: Line 97: As the remaining tumor was reduced to 0.4 x 0.7 cm (stage IB), please discuss why you did not consider definitive irradiation as SBRT?

Line 103: Please provide arguments for the entire left pneumonectomy for such a little remaining tumor. Please provide arguments why you did not consider less traumatic and potentially invalidating treatment as SBRT (e.g., non-homogeneous tumor structure? variable density? localization? etc.?)

Reply13: When we treated the patient with aletinib, the tumor was significantly reduced. The desire of the patient and his family to have the next sugery is very strong. After the discussion of many experts, and considering that the curative effect of radiotherapy may not be valid. Overall, we performed surgical treatment on the patient.

The planned surgical modalities were left inferior lobectomy. Thoracoscopic exploration showed that the left hilum of the lung showed dense fibrotic changes, the lower lobe trachea and pulmonary veins could not be separated by thoracoscopy. So the patient was converted to thoracotomy for left pneumonectomy.

Comment 14: Line 109: please develop "PCR" abbreviation as used here the first time.

Line 118: "NSCLC[3]." - space is missing between "NSCLC" and "[3]#. There are many places in the article with the same problem.

Reply14: we have modified our text as advised.

Changes in the text: See Page4. Line 15

Comment 15: Line 117/118: "...inhibitors (EGFR-TKIs) are the most common type of targeted adjuvant therapy for NSCLC". Instead "most common" change "the only currently approved". So, there is only EGFR-TKI approved in adjuvant setting. The next will be Alectinib from ALINA study (ESMO 2023). It is not correct to write "for NSCLC", as it is not for the entire NSCLC.

Reply15: we have modified our text as advised. As for the question of " for NSCLC ", we believe that NSCLC is a broad definition, in order to better lead to the following text.

Changes in the text: See Page5. Line 1

Comment 16: Line: 128: "ALK rearrangement is a poor prognostic factor for patients with resectable NSCLC.". Please explain why it is for "resectable NSCLC" and not for all stages?

Reply16: Because our patient underwent the removal of the left lung, we mainly studied resectable non-small cell lung cancer in this article, rather than all stages.

Comment 17: Line 129: In a previous study" - which previous study?
and
"ALK was positive in...". It is a kind of slang/colloquial language. Please re-phrase to "ALK-fusion was detected in..."
Reply17: "Previous study" is in Reference 9. A study about 764 resectable NSCLC patients.
Changes in the text: See Page5. Line 13

Comment 18: Line 131: "the mutation rate is low"- please explain what do you mean by this statement?
Do you mean up-front ALK-mutations co-existing with ALK-fusion? What is the meaning of ALK-mutation in this context?
Reply18: we have modified our text as advised.
Changes in the text: See Page5. Line 15

Comment 19: Line 132/133: "approximately 75,000 patients are diagnosed" - where in the world is this number of patients diagnosed? In which stage then, as you refer to perioperative data?
Reply19: We cited it from the reference 11

Comment 20: Line 134: "Chemotherapy is still the main perioperative treatment for patients with ALK+ NSCLC." - do you mean adjuvant chemotherapy for early stages? Please refer to the new data from ALINA study (ESMO 2023), so chemotherapy will not be the "main perioperative treatment".
Reply20: we have deleted that sentence

Comment 21: Line 150: "as a conversion" - please remove "conversion" from this context.
Reply21: we have modified our text as advised.
Changes in the text: See Page6. Line 12

Comment 22: Line 154/156: "According to the ADAURA study, osimertinib requires 3 years of oral administration after surgery, but patients with advanced ALK+ NSCLC have longer progression-free survival and overall survival." Please explain the connection between these two statements as it is not understandable for readers.
Reply22: we have modified our text as advised.
Changes in the text: See Page6. Line 15,16

Comment 23: Line 160: "and RET-TKI" - please remove it as the efficacy of Alectinib in RET-tumors is very limited and not used.
Reply23: we have modified our text as advised.
Changes in the text: See Page7. Line 2

Diskussion and conclusion generally:
Please include in the discussion other challenges:
Comment 24: - your patient was not diagnosed with PET/CT, but only with CT, which can cause the risk of insufficient staging
Reply24: The patient underwent PEC-CT examination two months after taking alectinib. Information about PETCT examination is provided in this text. Patients were staged according to tracheoscopy.

Comment 25: - was MRI of brain considered before definitive surgery as it is a standard
Reply25: The patient's brain MRI showed no abnormalities. We added it in Page 4, Line 4

Comment 26: - patients with druggable genomic alterations (here ALK-fusion) in stage III, where otherwise concomitant chemo- and radiotherapy followed by adjuvant immunotherapy is standard in this stage, but on the other hand we can expect high efficacy
- underline that the case demonstrated very effective downstaging and mad the definitive treatment possible. “Downstaging” here is a key word
- as mentioned before: provide good arguments for such an extensive and potentially traumatic surgery? Was is really necessary to perform pneumonectomy versus lobectomy versus SBRT?
Reply26: we have modified our text as advised.
Changes in the text: See Page6. Line 18-20, Page7. Line 5,6

Comment 27: Besides: please correct the spaces/missing spaces between the words in the text
Reply27: we have modified our text as advised.

Reviewer B:
The authors described the case of a 52 years old woman treated with alectinib in the perioperatively setting for ALK+ NSCLC.
Overall, this is an interesting case report that adds relevant evidence of alectinib efficacy in this scenario, where mature data of prospective trials are missing. However, I would suggest some revisions that I hope can improve the quality of the manuscript.
Major revisions:
Comment 1:- The title is misleading and should be changed; what kind of transformation do the authors refer to?
- Abstract should be re-written and focused on the key messages of this report (e.g. the baseline tumor size is not necessary at this point).
Reply1: we have modified our text as advised.

Comment 2:- Did the authors evaluate whether or not the patient was resectable before the starting of alectinib? It is not clear what was the main aim of neoadjuvant alectinib in this case: convert unresectabe to resectable/achieve a mediastinal downstaging/improving survival?
Reply2: We evaluated the patient prior to initiation of alectinib treatment, and the patient was

in stage cT4N2M0,ⅢB, and surgery was not feasible. Alectinib is used for neoadjuvant therapy.

Comment 3:- The authors should present this case in a more balanced and critical view, since the patient achieved a significant downsizing of the tumor but she underwent a pneumonectomy instead of the planned left inferior lobectomy. The authors should discuss also post-TKI fibrosis and how this affected the surgical approach.

Minor revisions:

Reply3: We are sorry to say that we have considered the issue of post-TKI fibrosis, but due to the relatively few cases at present, it is difficult for us to discuss the causes of its formation, the impact on surgical methods and the prevention methods.

Comment 4:- Line 60: ALNEO trial reference is not correct and should be replaced with PMID: 33762169.

Reply4: we have modified our text as advised.

Changes in the text: See Page2. Line 13

Comment 5:- Line 78: Please add the edition of TNM classification. At this point it is not clear how did the authors conduct the initial staging. Did the patient undergo mediastinal staging of PET-FDG? Was a CT scan of the brain-abdomen performed?

Reply5: we have modified our text as advised. We did tracheoscopy and staging, so we did not stage PET-FDG. No abnormalities were found on brain MRI and abdominal CT.

Changes in the text: See Page3. Line 6, Page4. Line5

Comment 6:- Line 83: It is not correct to define alectinib as a better choice than traditional chemotherapy or radiotherapy since there are no prospective comparative data. Preliminary data of phase III ALINA trial suggest a benefit of alectinib over chemotherapy in DFS but in the adjuvant rather than neoadjuvant setting. Authors should add and discuss the recent results of ALINA trial presented at ESMO 2023.

Reply6: Here we're just saying that based on the results of some previous cases. It is only a reference to the experience of predecessors, and it is not a conclusion on the efficacy. So we think it is right here. But we can also. But we can also make changes upon request.

Changes in the text: See Page3. Line 11

Comment 7:- Line 86: alectinib was administered for two and a half months prior surgery: why did the authors choose this specific duration?

Reply7: It's based on three cycles of neoadjuvant therapy, about two and a half months

Comment 8:- Line 91: information about pre-TKI chest CT is redundant.

Reply8: Our purpose is to list the relevant examination information of the patients as far as possible so that readers can understand more comprehensively, and also to compare the changes of CT before and after TKI therapy.

Comment 9:- Line 94: Restaging after neoadjuvant alectinib was evaluated with PET, which cannot be compared with the preoperative CT. Why did the author choose this imaging

technique? Did they consider a preoperative PET?
Reply9: We performed two bronchoscopies before and after alectinib treatment, and the staging was determined according to the bronchoscopy. PETCT was done before surgery
Comment 10:- Line 109: please use pCR instead of PCR.
Reply10: we have modified our text as advised.
Changes in the text: See Page4. Line 15

Comment 11:- Line 117: Discussion starts with a comment on EGFR-TKI efficacy in the adjuvant setting, which is not the focus of the present case report.
Reply11: This is to introduce the advantages of TKI adjuvant therapy over conventional chemotherapy, and then to better elucidate the latter. And this is not a big part of it, if you insist on deleting this paragraph, we can also delete this paragraph

Comment 12:- Line 118: Updated OS results of EVAN study have been published (PMID: 36027483) and discussion should be updated.
Reply12: we have modified our text as advised.
Changes in the text: See Page5. Line 4

Comment 13:- Line 124: Please add ADAURA reference (PMID: 32955177 and 37272535)
Reply13: we have modified our text as advised.
Changes in the text: See Page5. Line 8

Comment 14:- Line 125: ADAURA study did not demonstrate the superiority of adjuvant osimertinib over chemotherapy, but instead the efficacy of osimertinib regardless of previous chemotherapy, so we could not draw definitive conclusion regarding the best adjuvant treatment. Authors should specify this.
Reply14: we have modified our text as advised.
Changes in the text: See Page5. Line 9

Comment 15:- Line 145: I would mitigate the sentence of ‘striking effect’ of neoadjuvant alectinib
Reply15: we have modified our text as advised.
Changes in the text: See Page6. Line 8

Comment 16:- Line 148: can the authors explain in which terms did the patient choose the surgical intervention?
Reply16: The patient and his family strongly requested surgery and the removal of the tumor.

Comment 17:- Line 160: alectinib is a second-generation ALK-TKI and not a RET-TKI, even if it was also shown to block the growth of cells with RET fusions.
Reply17: we have modified our text as advised.
Changes in the text: See Page7. Line 2

Comment 18:- Authors should cite this relevant case series of salvage surgery after first-line alectinib: PMID 37061413.
Reply18: we have modified our text as advised.
Changes in the text: See Page6. Line 3

Comment 19:- If available, an image of histological sample at surgery could be added
- Please use extended names before using acronyms (e.g. Pathologic complete response before pCR).
Reply19: Sorry, we can't find that.

Reviewer C:
Several questions:
Comment 1. What are rhe exainations done for the diagnosis and for the staging.
Reply1: The patient underwent chest CT, PET-CT, cerebral MRI, abdominal CT, bone ECT, tracheoscopy, and pathological examination.

Comment 2. Why have you proposed this option? Has the patient the choice between rhe 2 options?
Reply2: We gave the patient two options, the first was to continue oral alectinib treatment and the second was to have surgery. Because the patient and his family had a strong desire for surgery, we performed surgery on the patient.

Comment 3. Is it recorded in a study? Ethical committee? Inform consent?
Reply3: Yes, we all have them. They were all submitted with the article.

Comment 4. Why have you proposed the treatment for 2.5 months?
Reply4: It's based on three cycles of neoadjuvant therapy, about two and a half months.

Comment 5. Review the English.
Reply5: We have done it.