Peer Review File

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Comment 1: The review article in my view is rather confusing. Involvement of the CNS occurs not only in EGFR and ALK fusions in NSCLC, but as well in RET fusions and in 40% of K-RAS mutant NSCLC. Involvement of CNS occurs often in triple negative breast cancer and melanoma.

Reply 1: Adjusted abstract to avoid implication that only ALK- or EGFR-positive disease is associated with brain metastasis formation.

Comment 2: Treatment options should be better explained including radiotherapy and neurological surgery.

Reply 2: Thank you for this note. The local therapies section has been adjusted to clarify the role of surgery, RT, and combined approaches.

Comment 3: The mechanism underlying brain metastases should be explained as well new therapeutic targets.

Reply 3: Hopefully the elaboration within the “Background” section describes a sufficient level of details.

Comment 4: Long noncoding RNAs that contribute to the development of brain metastasis have not been described.

Reply 4: Mention of lncRNAs has been added to the “Background” as well. Thank you.

Comment 5: The authors described a review article focusing on the treatment of brain metastases in patients with NSCLC, especially harboring ALK fusion. This review paper includes some interesting findings, but I have several concerns need to be addressed. The background section needs to be shortened. The authors should only mention why brain metastases of lung cancer is an unresolved problem and what they discuss in this paper.

Reply 5: Thank you for this feedback. The background is significantly shortened and focused on why this topic is relevant.

Comment 6: On page 7, J-ALEX study (doi: 10.1016/S0140-6736(17)30565-2) comparing alectinib and crizotinib in ALK-positive lung cancer should be cited and added to the table.

Reply 6: Good catch. The J-ALEX study and CNS subanalyses are now added to the main text and table.

Comment 7: On page 7, line 242, iORR of brigatinib was 46 to 67%.

Reply 7: This has been updated in the text and table.

Comment 8: On page 10, the trial investigating the combination of alectinib and bevacizumab was already published (DOI: 10.1016/j.esmoop.2021.100342)

Reply 8: Thank you. The data from the MGH series has been included, but I have left the mention of the trial currently ongoing in Mexico in the future work at the end.

Comment 9: Authors showed good overview discussions about the ALK mutation positive population with brain metastases. My opinion is that the review can be more helpful if authors focus more on recent advances, and making general principles part briefer. Line 53-66: Authors' explanation of the divergent genetic alterations is important, but I suggest shortening this discussion in to 5-7 sentences. Instead, I recommend adding a paragraph about the brain metastases specific to ALK mutation positive populations. Potential readers want to know if ALK mutation positive populations require any special clincial approach prior to management of brain metastases.

Reply 9: Thank you for this suggestion. The section on divergence has been shortened and the remainder of the background (re)focused on the development of and approach to ALK-positive disease.

Comment 10: Line 114-130: These are general principles when approaching brain metastases. Brain MRI and symptom assessment. I advise making this paragraph brief.

Reply 10: As above, hopefully the adjustments are now logically but not exhaustively descriptive.

Comment 11: Line 250: Please insert comma before starting a new sentence.

Reply 11: Punctuation added. Thank you.

Comment 12: Line 315: Mentioned neurologic problems are relatively frequently encountered situations. A paragraph explaining how the neurologic adverse events can be relieved or shortening the duration of the symptoms can be helpful for clinicians. How symptom can be managed, or the AEs can be screened early can be explained here.

Reply 12: This has now been mentioned within the "Systemic Treatment" and "Symptomatic Management" sections. Thank you.

Comment 13: *If word limit does not deter, I recommend adding a brief chapter on future perspectives in approaching ALK mutation population with brain metastases. Identifying ALK fusion variants (DOI: 10.1016/j.ejca.2022.07.026), confirming ALK TKI resistance mechanism such as G1202R mutation can be mentioned.

Reply 13: Good idea. These suggestions have been incorporated with additional discussion within the "Systemic Therapy" section that highlights ALK-positive variants and the implications on response to treatment.

Comment 14: The relationship between VEGF expression and brain metastases is also an important point. Please briefly describe the relationship in the BACKGROUND.

Reply 14: Thank you for this suggestion. A brief description of the role of VEGF has been added to the "Background" section and in the rationale for a trial under "Systemic Therapy".

Comment 15: Please summarize at the end of the DISCUSSION how to distinguish between local therapies and systemic therapies and how we should be used in combination to provide the best treatment.

Reply 15: The "Systemic Therapy" section now attempts to address this point. Please let me know if this remains unclear. Thank you!

Comment 16: I feel the SUMMARY is too long. Please put the current limitations and future issues at the end of the DISCUSSION and make the SUMMARY brief.

Reply 16: This is a fair suggestion. The "Summary" has been shortened to focus on high level concepts.

Comment 17: The abstract is confusing.Please eliminate the first two meaningless sentences and replace it with a single sentence discussing the incidence of brain mets in patients with NSCLC, Lung adenocarcinomas, and ALK fusion Lung adenocarcinomas.

Reply 17: Thank you for letting us know. The abstract has been substantially shortened and simplified.

Comment 18: The background section should be 2-3 paragraphs dealing with the incidence of brain metastases and the primary tumors associated with them. You should then discuss the incidence of NSCLC brain mets and center on lung adenocarcinomas and the various genetic aberrations. You should then mention why you are focusing on ALK positive tumors.

Reply 18: The “Background” section has been substantially shortened and focused with attention paid to why ALK-positive disease is clinically relevant to target.

Comment 19: Material and methods should then come next. Almost half of the article is centered on how intracranial metastases develop, but this section is not correlated with ALK positive disease in particular. Please focus this section and correlate with ALK fusion disease.

Reply 19: The development of ALK-positive brain metastases is now much more clearly highlight within the background section. Thank you.

Comment 20: At the present time, it can take 2 weeks to obtain genetic information that leads to the ALK diagnosis. The authors should provide clinical information that would lead one to suspect ALK fusion disease at diagnosis and make recommendations while awaiting the diagnosis, ie should a patient with multiple lesions with 2-3 large lesions between 2-3 cm undergo radiosurgery to the large lesions while awaiting the genetic diagnosis or undergo whole brain radiation?

Reply 20: This is a good point. A pragmatic approach to molecular characterization has been added in the first paragraph of “General Principles”

Comment 21: References 1-4 are antiquated. Find new references and update this paragraph.

Reply 21: These references have been replaced. Thanks!

Comment 22: References 40, 43, and 44 are old and need to be replaced. You can use the MD ANDERSON studies that you included by Brown and Mahajan here.

Reply 22: This is reasonable; these references have been updated.

Comment 23: Line 197 - should be patients with minimal "extracranial" disease burden.

Reply 23: Fair enough; this has been updated.

Comment 24: Lines 204 -209--- When discussing the QUARTZ trial the authors should mention that the patients in this trial were selected because they were considered unsuitable for SRS or surgery and that their median time from diagnosis to randomization was 25 days and that treatment was further delayed.

Reply 24: This is a good point of clarification. The text has been updated to reflect this. Thank you.

Comment 25: lines 270-284- The authors should discuss the CNS side effects of lorlatinib.

Reply 25: Good idea. A paragraph about AEs and SAEs of ALK TKIs has been added to the “Systemic Therapy” section.

Comment 26: The authors should conclude with which agent they would treat a patient with upfront brain metastases and how this may or may not differ from patients with metastatic disease and no brain metastases. Which ALK agent is best? The authors should also address the treatment of brain mets in patients who are currently receiving an ALK TKI.

Reply 26: The “Systemic Therapy” section has been updated to reflect our recommendation. Thank you.

Comment 27: The background section appears very long according to the objective of the review and with to much ref ie 33 and without a focus on NSCLC and more particularly ALK NSCLC ….

Reply 27: The background has been significantly shortened. Thank you.

Comment 28: Paragraphs starting line 113 and paragraph starting line 124 is too general and probably no relevant for thoracic oncologists

Reply 28: That is reasonable. Where appropriate, paragraphs have been moved to the “General Principles” section.

Comment 29: Again, paragraph starting line 131 seems not relevant.

Reply 29: This paragraph has been rewritten to keep the topic in focus. Thank you.

Comment 30: The ref 40 is very old ref and refers to another’s situations, not ALK NSLC patients.

Reply 30: Fair point. This is a highly cited source – acknowledging the age – within neuro-oncology that emphasizes the role for a wide differential diagnosis. It may be superfluous and has been removed.

Comment 31: Results of bibliography research is not reported (a flow chart will help).

Reply 31: The “Methods” section has been elaborated. Thank you.

Comment 32: An important key point is missed: the protective effect of the ALT TKI to prevent cerebral met in patients without cerebral Met at the diagnosis. There are several papers on this topic.

Reply 32: Good point. This has been highlighted in several areas within the text, including the “Abstract”, “Systemic Therapies”, and “Summary” sections.

Comment 33: Comment and responses between authors remains on the submitted manuscript.

Reply 33: thank you for catching this. These notes have been removed.

Comment 34: The background can be significantly shortened. That said, it is fine to have some of the information/background on the general NSCLC brain metastasis biology as this is not something that is offered in other reviews in this series. In fact, much of the CNS efficacy data of available ALK TKIs will also be discussed in other reviews, so this biology aspect offers a unique angle. Perhaps the authors can try and integrate how the knowledge of this information may direct avenues for investigation of TKI-resistant CNS met biology in ALK+ lung cancer? The basic information regarding imaging of brain metastases and biopsy on page 4 can probably be omitted.

In addition, I would encourage authors to incorporate data on the high CNS tropism of ALK+ lung cancers (and can compare to other genomic subtypes such as EGFR, ROS1, RET, etc) (for reference, see Gainor et al JCO Precis Oncol 2017 and Drilon et al., J Thorac Oncol 2018) and what implications this may have on surveillance for brain mets in this patient population. I would also encourage authors to consider adding a section on not only treatment of brain metastases that have already occurred but also discussing the CNS-protective effects of ALK TKIs as relevant to this and implications for clinical trial design in incorporating CNS efficacy endpoints and corresponding study assessments (which may also be applicable to other tumor subtypes or types with high frequency of CNS mets).

Please explicitly discuss how to think about local therapy versus using CNS-penetrant TKIs upfront +/- brain RT in this patient population. There have been studies looking at this topic in EGFR/ALK (for example, Thomas NJ et al., J Thora Oncol 2022; Magnuson et al., J Clin Oncol 2017; Saida et al., Thorac Cancer 2019).

While the authors cite the consensus recommendations from ASCO-SNO-ASTRO to use upfront treatment with alectinib, brigatinib, or ceritinib for patients with ALK+ lung cancer with brain metastases, ceritinib is known to be less CNS-active is generally not preferred in this setting.

It would be interesting to think about / discuss how some TKIs are found to be CNS-penetrant and active, versus some TKIs (such as lorlatinib) being intentionally

developed to cross the BBB. In developing CNS-active agents, what are considerations to be taken into account? What are the optimal characteristics for such compounds during drug development process? This discussion could be incorporated after discussing the CNS tropism of different subsets of lung cancers, especially ALK+ lung cancer, and then followed by implications for trial design, before then going into the CNS-specific data of the available ALK TKIs, including data on CNS-protective effect in patients without baseline brain metastases, followed by discussion of local therapy (RT) vs upfront TKI, and then thoughts on resistant CNS met biology/genomics and potential therapeutic strategies to target such ALK TKI-resistant CNS metastases in the future.

Reply 34: Thank you for your thoughtful suggestions. We have incorporated essentially all of the recommended changes and added content where appropriate. There is now a more focused description of ALK-positive brain metastasis formation and supplemental data regarding the development of resistance to AKI. The inclusion of ROS and RET within the background does provide some interesting contrast and highlights the importance of CNS tropism seen with ALK (and EGFR) disease. Furthermore, COI forms have been completed, and the requisite formatting updates have been made.