Peer Review File

Article information: http://dx.doi.org/10.21037/tlcr-20-331

**-Article Type: Review Article**
**Manuscript ID: TLCR-2019-CNSCLC-03(TLCR-20-331)**
**Title: How to select the best upfront therapy for metastatic disease? Focus on ALK**

**Reviewer #1**

With pleasure I have read the overview of the paper Focus on ALK which presents an update on ALK use in the clinic. I understand that this is an invited paper for a special issue of TLCR. The paper is clearly written and addresses all the major items involved.

**Comment 1:** However: In the 2019 edition of TLCR (Vol 8, Supplement 3 (November 2019): Translational Lung Cancer Research (Targeted Therapies in NSCLC: An Evolving Landscape) A group of Italian scientists report on the same subject reporting most of the findings in the current paper (perhaps they are the same authors of this manuscript).

I therefore would recommend that additional information is presented on the different variants of the ALK and add an informative figure.

- ➔ Reply 1: Thank you for your comment. We decided to add another informative figure, Figure 2 to show comparison of median PFS among Phase 3 ALK TKI trials.

**Comment 2:** Figure 1 does not add much to the content of the paper.

- ➔ Reply 2: Thank you or your comment. We appreciate your feedback but decided to keep figure 1 in the paper since it provides an overview of drug development for *ALK*+ lung cancer. Figure 1 has also been updated to show that brigatinib was just approved in the first line setting.

**Comment 3:** The tables could also be more extensive presenting what kind of studies are currently ongoing

- ➔ Reply 3: Table 2 was added to include combination of ALK TKIs and immune checkpoint combinations being studied with available data.

**Reviewer #2**

The Authors summarized the best evidence for the first line treatment of patients with ALK rearranged NSCLC. The review is quite exhaustive and well written. My suggestions:

**Comment 1:** In the Abstract, a comment on ceritinib should be added.

- ➔ Reply 1: Thank you for your comments. We have added ceritinib into the abstract.

**Comment 2:** In the Introduction, Ref 5 refers to ceritinib that is not mentioned in the text. Ceritinib is not cited also in the end of introduction, where there is a comment on brigatinib and lorlatinib approved for second of further lines of therapy.

- ➔ Reply 2: Thank you for your feedback. Ceritinib was added to the end of introduction to indicate that it is also approved in second line therapy along with brigatinib and lorlatinib. Brigatinib was also added as FDA first line approved.

**Comment 3:** In Crizotinib section, the Authors should add a comment on 4 year OS rate of 56% (Mok T, ESMO 2017).

- ➔ Reply 3: Thank you for your comments. Four-year OS was added based on Mok et al in the crizotinib section.

**Comment 4:** In alectinib section, the Authors should comment also J-ALEX and ALESIA trials. Moreover, some criticism of ALEX study should be discussed (see Besse B, ESMO 2017). They can also comment the results of Cohort A of B-FAST study (Gadgeel, ESMO 2019).

- ➔ Reply 4: Thank you for your comments. Data from J-ALEX, ALESIA, and B-FAST were added in the alectinib section. The authors reviewed the Besse et al ESMO 2017 discussion on "which is the best upfront TKI" which focused on advocating for the use of crizotinib first-line. We did not feel the arguments applied to this review article and decided not to include this source.

**Comment 5:** In section 3, it should be discussed the lack of a benefit in OS with alectinib vs crizotinib and the results of some studies of real world, reporting very long OS with crizotinib (Duruisseaux, Oncotarget 2017; Gainor, Clin Cancer Res 2015; Chiari, Lung Cancer 2015; Ito, J Thor Oncol 2016).

- ➔ Reply 5: Thank you for your comments. The authors respectfully disagree to the statement "lack of a benefit in OS with alectinib vs crizotinib" and we here cite the updated OS analysis from ALEX (J Clin Oncol 38:2020 suppl; abstr 9518). However, we do acknowledge the several retrospective evaluations of

sequential use of crizotinib followed by a second gen ALK inhibitor and have cited the references that were suggested.

**Comment 6:** The paragraph of toxicities (sub-section e.) should be more detailed, in particular for crizotinib, ceritinib, alectinib and brigatinib.

➔ Reply 6: Thank you for your comments. We have added more details in to the toxicities section as suggested.

**Comment 7:** The sub-section f, should be reported as a different section (4.) and not as a sub-section. The same for cost effectiveness sub-section (it should be reported separately).

➔ Reply 7: Thank you for your suggestions. We have created separate sections.