Peer Review File
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Comment 1: Lines 168-170: "Despite impressive gains in PFS and survival benefits compared to wild-type groups, the phase III trials discussed above have not yet demonstrated statistically significant improvements in overall survival" -> the ALEX trial has already demonstrated significant OS benefit (Ref. 18), and the ALTA-1L also: i) when correcting for cross-over and ii) for patients with brain metastases at baseline, despite the cross-over (Ref. https://pubmed.ncbi.nlm.nih.gov/34537440/ -> this important reference is missing and should be added).

Reply 1: Thank you for your suggestion. In lines 203-205 we refer to the finding that there has been no statistically significant benefit in OS demonstrated on pre-planned statistical analysis and acknowledge that OS benefit has been demonstrated after correcting for cross-over and on post-hoc sub-group analysis. We have incorporated the updated results from ALTA-1L.

Changes in text: We have added the data on improvements in OS found for the group of patients with baseline brain metastases from ALTA-1L (lines 233-237), reference 23.

Comment 2: Lines 172: "When statistical adjustment (rank preserving structural failure time model) was applied to account for the effect of cross-over in an updated survival analysis from..." -> such a correction has also been published for ALTA-1L and should be discussed and cited as well (ref. https://pubmed.ncbi.nlm.nih.gov/34537440/, see above).

Reply 2: Noted, we have added this to the discussion.

Changes in text: Lines 212-222 discuss findings of improved OS after correction for cross-over in the ALTA-1L trial (reference 23).

Comment 3: Lines 170-171: "This is likely in part due to effects of cross-over and utilization of effective post-study treatment". The wording is somehow misleading, because cross-over was not permitted in most trials (ALEX, eXalt3, CROWN), and only allowed in ALTA-1L (and in the PROFILE 1014, which is already mentioned). Maybe it is better to just clarify which studies permitted and which did not permit cross-over.

Reply 3: Acknowledged. Statement added detailing which trials allowed cross-over.

Changes in text: Statement detailing which studies allowed crossover lines 205-206.

Comment 4: lines 209-211: "When considering quality of life impacts of CNS progression, the marked CNS activity of lorlatinib is a substantial step-forward in the

management of ALK+ aNSCLC.": it is kind of artificial to consider this in isolation, because at the same time lorlatinib also adversely impacts CNS-related quality of life due to neurologic side effects (ref. 32 cited by the authors).

Reply 4: Have deleted this sentence.

Changes in text: Have deleted this sentence from line 266.

Comment 5: Lines 232-234: the authors could also add that in many patients (approximately one third) CNS events resolved without intervention in the CROWN study (ref. 32).

Reply 5: Thank you – have added

Changes in text: Added in lines 295-297 (now reference 35)

Comment 6: Lines 250-252: "For those patients who receive crizotinib in the first line, second-line therapy may be with either lorlatinib, alectinib or brigatinib" -> I do not completely agree here for two reasons: i) lorlatinib is not approved for use directly after crizotinib, neither by the FDA not by the EMA; ii) considering available data, brigatinib has consistently shown greater benefit after crizotinib with mPFS 13-17 months (Gettinger Lanc Oncol 2016, Kim/Ahn JCO/JTO 2017, Camidge JTO 2021 [the cross-over in ALTA-1L, final analysis]) compared to alectinib (mPFS 8-9 months, Ou JCO 2016, Shaw Lanc Oncol 2016) and even lorlatinib (mPFS 11 months, Shaw JCO 2019 EXP2+3A).

Reply 6: We have attempted to avoid cross-trial comparisons and thus have left the recommendations quite broad. However, considering that lorlatinib is not approved in this setting, we have reworded this sentence.

Changes in text: Reworded sentence line 315.

Comment 7: Lines 256-258: "In particular, the G1202R mutation confers resistance to many of the 2nd generation ALK inhibitors, but tumours may remain sensitive to lorlatinib" -> these are data after alectinib and ceritinib. After brigatinib, which is also a second generation inhibitor, not one single patient had G1202R among 29 evaluable (https://pubmed.ncbi.nlm.nih.gov/34537440/ suppl. Table 5).

Reply 7: Acknowledged, have amended to be more specific.

Changes in text: Line 321 have removed ‘some of the second-generation TKIs’ and replaced with ‘alectinib and ceritinib’.

Comment 8: Lines 117-119: "with a 12-month cumulative incidence of CNS

progression rate of 22.4% for those on crizotinib compared to 7.8% for those on brigatinib (HR 0.30, 95% CI 0.17-0.53)" -> could you please check the source of these data? As far as I know, there was indeed an updated analysis of the cumulative incidence of CNS progression at the time of the ATLA-1L second interim analysis (cut-off June 2019), but this result is not reported in the JCO publication, which you reference at this point (ref. 14). The results presented in the NEJM publication (ref. 13) are somewhat different (they come from the first interim analysis).

Reply 8: Thank you for pointing this out, reference has been updated.

Changes in text: Reference updated – reference 15 is European Medicine Agency report

Comment 9: Line 63: Hiro -> Hiroyuki.

Reply 9: Thank you, have amended.

Changes in text: Line 64 amended.

Comment 10: Line 96: Dose of alectinib differs in ALEX (1200 mg/day) and J-ALEX (600 mg/day).
The description of the doses may be addressed. Please discuss whether the dose difference affected their results.

Reply 10: Have added some discussion around this. The lower dose of alectinib used in J-ALEX was chosen for regulatory reasons and did not appear to impact results.

Changes in text: Lines 113- 116 now discuss the different doses received in ALEX/ALESIA and ALEX.

Comment 11: Line 108: Ref 11 (J-ALEX) was published (Epub) in 2017 May 10. Ref 10 (ALEX) was published (Epub) in 2017 Jun 6. The description of "Findings were in keeping from the ALEX trial" was not right, I think. Final overall survival analysis from the phase III J-ALEX study was recently published (ESMO Open 2022;7:100527). Authors may add the survival data.

Reply 11: Thank you – amended and added final OS data from J-ALEX.

Changes in text: Final OS data from J-ALEX added to lines 116-118, reference 12.

Comment 12: Line 193 and Table 1: ceretinib -> ceritinib.

Reply 12: Thank you.

Changes in text: Amended in text and in table.

Comment 13: The review however does not contain any information on the differences between the different trials in the patient selection (with the exception that it was mentioned in the ALTA 1 L trial that prior chemotherapy was allowed). Especially whether treated or untreated brain mets were allowed should be mentioned in the review. Also, when describing the end point PFS, it should be made clear, that in certain trials, independent review committee PFS and in others investigator assessed PFS was reported, with the INV assessed PFS being weaker especially in a context of no cross over and potentially no access to subsequent treatment outside of a trial (ALEX). Furthermore, regarding the treatment of G1202R with lorlatinib, there are also data and new case reports indicating that G1202R might not be adequately be treated by lorlatinib. This should also be mentioned. The authors should be commened for including the aspect of sequential therapy in the review. However potential attrition rates between 1st and 2nd line therapy are not mentioned. Also, the rate and type of subsequent treatment in the mentioned trials are not included. This would largely increase the quality of the review.

Reply 13:

- Have included more information on patient selection in lines 185-198.
- Independent review committee PFS vs investigator PFS is indicated in Table 2 and is now discussed in text in lines 198-199.
- Have included new reference regarding response rates to lorlatinib when G1202R mutations/deletions present vs when additional compound mutations present in lines 322-325 (reference 40).
- The limitation of retrospective studies with relation to potential attrition rates between 1st and 3nd line therapies and the lack of date on subsequent treatments is now discussed in lines 244-251.

Comment 14: The reviewer recommends to list the percentages of interstitial lung diseases caused by each ALK inhibitor in the clinical trial into ‘Management of toxicity (from line 213)’ part since interstitial lung disease is one of the serious adverse events that can lead to treatment discontinuation in clinic.

Reply 14: Although this is an important toxicity, this is reported differently across the different trials (ie some report only ILD leading to treatment discontinuation, some report ILD of any grade, some report ILD if it was a serious adverse event) and so comparative comments are challenging. We have added information about the likely lower rates of ILD/pneumonitis with other ALK-inhibitors.

Changes in text: We have added information about the likely lower rates of ILD/pneumonitis with other ALK-inhibitors in lines 279-281.

Comment 15: Some preclinical studies mentioned about the mechanisms of resistance to ALK inhibitors by ALK-independent mechanisms (e.g. bypass-signal from other RTKs). (Clin Cancer Res. 2020 Jun 1;26(11):2535-2545.), (Cancer Sci. 2022 Sep 10.

doi: 10.1111/cas.), (J Thorac Oncol. 2020 May;15(5):752-765.), (Cancer Res. 2016 Mar 15;76(6):1506-16.).

Also, Dardaei L, et. al., reported that combined ALK and SHP2 inhibition may be a promising therapeutic strategy for resistant cancers driven by several different ALK-independent mechanisms underlying resistance. (Nat Med. 2018 May;24(4):512-517.) The reviewer suggests to add the above information in a couple of sentences in 'Beyond first-line' part (from line 248).

Reply 15: Thank you – have included.

Changes in text: Lines 325-333 (references 41, 42 and 43).

Comment 16: The correct name of Dr. Mano is 'Hiroyuki Mano'.

Reply 16: Thank you.

Changes in text: Amended.

Comment 17: Line 21: There are 5 (not 6) FDA-approved ALK inhibitors - would suggest clarifying.

Reply 17: Have edited to specify 5 FDA approved ALK inhibitors, previously was referring to 6 approved world-wide which includes ensartinib (approved only in China).

Comment 18: Lines 83-86: In this section, it may benefit the readers to define and specify 2nd- versus 3rd-generation ALK TKIs leading into the next section.

Reply 18: Have added specification of second vs third generation inhibitors into lines 120-121.

Comment 19: Lines 180-182: Would suggest adding in the median PFS for brigatinib from ALTA-1L in this summary statement and also specifying for each mPFS whether this was by BIRC versus investigator assessment; it may be worth adding in parenthesis the mPFS by BIRC for alectinib from global ALEX as the other trials used efficacy by BIRC.

Reply 19: Have added to lines 218-221.

Comment 20: Line 199: I believe ALTA-1L reported PFS by BIRC (not investigator assessment as is stated in the manuscript) as the primary endpoint - please double check and correct.

Reply 20: Have amended this in line 219.

Comment 21: Line 200-201: CROWN also did not permit crossover (currently, manuscript states this was not permitted in global ALEX).

Reply 21: Have made clearer in lines 247-248.

Comment 22: Lines 205-206: These lines again discuss crossover which is also discussed in the preceding paragraph - could consolidate.

Reply 22: Have consolidated in lines 247-248.

Comment 23: Lines 212-214 and lines 234-238: These lines, separated apart, both comment on OS outcomes from ALTA-1L - would consolidate.

Reply 23: Have consolidated in lines 257-264.

Comment 24: Lines 224-231: If the authors would agree, could consider removing these lines to focus discussion on OS data with next-generation ALK TKIs as pertinent to the overall section.

Reply 24: Have removed this section.

Comment 25: Lines 243-245: This may not be the best example relevant to the section - seems out of context.

Reply 25: Agree, have replaced with more general discussion on strengths/limitations of such observational studies in lines 302-306.

Comment 26: Line 271: There are 5 FDA-approved ALK TKIs, not 6.

Reply 26: Have clarified FDA-approved.

Comment 27: Lines 280-282: Could the authors please add in the pulmonary toxicity frequencies with the other next-gen ALK T HIs aside from brigatinib?

Reply 27: Have added in lines 352-357.

Comment 28: Line 318: Would the authors consider editing the sentence “second-line therapy with lorlatinib is recommended” to “second-line therapy with lorlatinib is an option”? This is because lorlatinib may not be preferred if there is evidence of actionable off-target mechanism of resistance (such as MET amplification) or histologic transformation.

Reply 28: Have edited in line 400.

Comment 29: Line 320: The authors could add a brief sentence stating the topic of mechanisms of resistance to ALK TKIs are discussed in detail in a separate review of this series.

Reply 29: Have added in lines 406-407.