Input from manufacturer on the 2nd draft assessment

“ALECTINIB AS MONOTHERAPY FOR THE FIRST-LINE TREATMENT OF ADULT PATIENTS WITH ALK-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER”

Project ID: PTJA03

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA JA3 WP4 - Pharmaceuticals, PTJA03

Comments on the 2nd draft rapid assessment on alectinib as monotherapy for the first-line treatment of adult patients with alk-positive advanced non-small cell lung cancer

The objective of this reviewer form is to standardise the process of reviewing rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment on alectinib as monotherapy for the first-line treatment of adult patients with alk-positive advanced non-small cell lung cancer was open to review by the manufacturer between 15/01/2018 and 24/01/20181.

Comments received from

Manufacturer
Roche.

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments from Manufacturer

Page	Line	MAH	Comment	Reply from author
11	300	Roche	**Please modify** the from Appendix 1 to Appendix *6 - indirect treatment comparison*	Accepted
2	30	Roche	**Please correct** V1.1. version to 18.12.2017.	Accepted
12	324	Roche	The current text suggests caution in interpreting the results of the NMA because of heterogeneity between studies with respect to chemotherapy regimens and baseline prognostic factors (CNS metastases at baseline). The feasibility analysis submitted with the file acknowledges this heterogeneity and nonetheless concludes that the studies are similar enough to allow meaningful comparison. The difference in PFS in the chemotherapy arms between the PROFILE 1014 and ASCEND-4 studies is of a magnitude (median 7 months vs 8.1 months) that would be unlikely to impact the overall outcome, given the magnitude of PFS benefit seen for alectinib in the results of the NMA. The proportion of patients with CNS metastases was reported to be higher in ALEX (40%) than the other studies (approx. 30%). However, please note that the ALEX study design required CNS imaging at baseline whereas the other studies did not. This could lead to greater detection and reporting of CNS metastases in the ALEX study and overestimate the true differences at baseline. **Current text:** Because of the uncertainties involved and possible dependencies regarding the heterogeneity, assumptions on the results in the NMA, these results are considered with caution. **Proposed text:** While there is a degree of uncertainty around indirect treatment comparisons, given the magnitude of benefit (statistically significant benefit is shown across all scenarios with HR of 0.4 and upper limit of credible intervals no higher than 0.7) the results can be considered robust.	Not accepted - Overall there is too large uncertainty both on the adequacy of the model assumptions and the comparability, as described in Appendix 6. Vague prior analysis showed non-significant results, therefore results of base case are partly assumption driven, namely on the heterogeneity assumption. There is no indication, which degree of between-trial-heterogeneity still leads to significant results, since a sensitivity analysis for varying priors was not performed (except for the inclusion of the mentioned vague prior). See also comment on between-trial-heterogeneity and sensitivity analysis [page 23, line 630]
12	336	Roche	**Please add** in the word 'unadjusted' to ensure the results are from an analysis of unadjusted OS **Proposed text:** Unadjusted OS analysis; HR 0.85 (95% Credible interval, CrI, 0.41, 1.73).	Accepted

Page	Line	MAH	Comment	Reply from author
12	337	Roche	**Clarification and Proposed Correction**: Please note there was no endpoint "relapse rate" in the ALEX study.	Accepted
12	351	Roche	**Please add** the median PFS for the subgroup of patients with CNS metastases at baseline **Current text:** The PFS benefit was consistent for patients with CNS metastases at the baseline (HR 0.40, (95% CI, 0.25, 0.64) and without CNS metastases at the baseline (HR 0.51, (95% CI, 0.33, 0.80); median PFS for alectinib not estimable, 95% CI, not estimable to not estimable; median PFS for crizotinib 14.8 months, (95% CI, 10.8, 20.3 months), indicating benefit of alectinib over crizotinib in both subgroups (MAH submission). **Proposed text:** The PFS benefit was consistent for patients with CNS metastases at the baseline (HR 0.40, 95% CI, 0.25, 0.64); median PFS for alectinib not estimable (95% CI, 9.2 months to not estimable); median PFS for crizotinib 7.4 months (95% CI, 6.6, 9.6 months) and for patients without CNS metastases at the baseline (HR 0.51, 95% CI, 0.33, 0.80); median PFS for alectinib not estimable (95% CI, not estimable to not estimable); median PFS for crizotinib 14.8 months (95% CI, 10.8, 20.3 months), indicating a benefit of alectinib over crizotinib in both subgroups.	Accepted. Relevant, and in line with the corresponding information provided for the complementary subgroup (i.e. patients without CNS metastases at the baseline).
17	489	Roche	Roche suggests evaluating the totality of the patient-reported outcome evidence, which includes pre-specified descriptive mean change from baseline and proportion of improved/worsened analyses and to highlight a similar pattern of patient-reported benefit with alectinib that is consistent with its clinical efficacy and safety data. As stated in the body of the report (lines 1358 - 1359), patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. **Current text:** No statisticaly significant difference was found in HRQoL. **Proposed text:** Patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. However, the difference was not statistically significant.	Accepted but rewritten
12	363	Roche	Roche suggests adding the HR for CNS mets to the following statement. **Current text:** This finding was consistent in the subgroup of patients with CNS metastases at the baseline. The results should be interpreted with caution because of the uncertainties involved.	Partly accepted. Addition of NMA HRs for CNS metastases is accepted to be added. Original wording kept, however.

Page	Line	MAH	Comment	Reply from author
			Proposed text: Additionally, the subgroup of patients with CNS metastases at baseline demonstrated a statistically significantly longer PFS by IRC for alectinib versus ceritinib in the NMA, HR 0.30 (95% CrI, 0.13, 0.71), showing a benefit and consistency in results across the ITT and CNS sub groups.	
12	364	Roche	As noted in the comment from Roche on line 325, we feel that the results of the NMA can be considered robust. **Current text:** The results should be interpreted with caution because of the uncertainties involved. Proposed new text: While there is a degree of uncertainty around indirect treatment comparisons, given the magnitude of benefit (statistically significant benefit shown across scenarios with HR of 0.4 and upper limit of credible intervals no higher than 0.7) the results can be considered robust.	Not accepted - see comment to page 12, line 324, page 17, line 476 and page 23, line 630.
12	367-369	Roche	Roche suggests evaluating the totality of the patient-reported outcome evidence, which includes pre-specified descriptive mean change from baseline and proportion of improved/worsened analyses and highlight a similar pattern of patient-reported benefit with alectinib that is consistent with its clinical efficacy and safety data. **Current text:** A trend favouring alectinib over crizotinib was observed, a for patient-reported global health status/ health-related quality of life (HRQoL) (HR 0.72, 95% CI, 0.38–1.39), but it was not statistically significant. Such trends were seen in all patient-reported outcomes. **Proposed text:** A trend favouring alectinib over crizotinib was observed for patient-reported global health status/ health-related quality of life (HRQoL) (HR 0.72, 95% CI, 0.38–1.39). Overall, patients in the alectinib arm reported clinically meaningful improvement in HRQoL and improvement in multiple lung cancer symptoms for a longer duration of time than patients in the crizotinib arm, but the differences were not statistically significant.	Accepted
12	368	Roche	Consistency Proposal: Throughout the report, there are multiple ways to separate lower and upper limits for the 95% CIs and 95% CrIs e.g. commas, 'to' and '–' (dash). As in examples: - HR 0.72 (95% CI, 0.38, 1.39), HR 0.72 (95% CI, 0.38-1.39), HR 0.73 (95% CI, 0.38 to 1.39). For consistency, please can commas be used throughout.	Accepted

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12	378	Roche	**Please correct** "face" to "facial"	Not accepted. Written as in SmPC.
13	395	Roche	The current statement is incorrect. Hepatobiliary ADRs occur with higher incidence with ceritinib (60% liver laboratory abnormalities per Table 6.3) than with alecensa or crizotinib. In Ascend-4 hepatic transaminase increases (all grades) occurred in up to 91% of patients, Grade 3-4 increases in up to 34% of patients with ceritinib. These numbers are markedly higher than those for alectinib. **Current text:** Hepatobiliary disorders, including abnormal levels of liver transaminases, were least common with ceritinib, but were more common with crizotinib than alectinib. **Proposed text:** Hepatobiliary disorders, including abnormal levels of liver transaminases, were less common with alectinib than with crizotinib or ceritinib.	Partly accepted. It is agreed that the statement is incorrect, and should be removed. New text: "Abnormal liver laboratory results appeared least common with alectinib, while acknowledging that a comparison based on the varying items in the SmPCs is difficult.
13	410	Roche	Roche would prefer to add in the HR reported from the NMA within the safety section. **Current text:** The NMA indicates the presence of significantly fewer grade 3 or 4 AEs with alectinib than with ceritinib, and no significant differences were observed for discontinuations due to AEs. **Proposed text:** The results from the NMA indicate the presence of significantly fewer grade 3 or 4 AEs with alectinib than with ceritinib (HR:0.36 [95% CrI, 0.16, 0.79) while ceritinib resulted in significantly more grade 3-4 AEs than chemotherapy (HR:2.25 [95% CrI, 1.42, 3.61]). No significant differences were observed for discontinuations due to AEs.	Not accepted. Due partly to the uncertainties, these HRs are not considered necessary in the Summary section.
13	453	Roche	Please include the treatment duration in parenthesis. **Current text:** ...longer exposure to treatment... **Proposed text:** longer exposure to treatment (17.9 months versus 10.7 months for crizotinib)	Accepted
15	421	Roche	Propose Correction to table header. **Current text:** Summary of findings for alectinib, interim analysis 7 February 2017 **Propose Correction to text:** Summary of findings for alectinib, primary analysis 9 February 2017	Accepted
15	421	Roche	**Current text in Table 0.1 (row 2, column Comments)**: Despite investigator assessed PFS, consistent results with independently assessed PFS	Accepted

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			Proposed text: Of note, investigator assessed PFS was consistent with independently assessed PFS.	
15	421	Roche	**Proposed Change in row Time to CNS progression/column Relative Effect (95% CI): Please remove** the P value for consistency with all other HRs reported in the same column.	Partly accepted. The p-values were added for consistency when available.
15	421	Roche	Proposed Correction: Total proportion of patients with ≥1 AE: 100 % in either treatment arm. Correction to be made to 97% in either treatment arm. Note, in the "Discussion" section within the Summary of Relative Effectiveness Of Alecensa " the correct figure is noted (page 16, line 448): "The same numbers of adverse events of any grade were reported for both alectinib and crizotinib (97%) in the randomized phase-III ALEX trial."	Accepted
15	421	Roche	Proposed Correction: 'Time to deterioration in EORTC QLQ-30 global health score' - **Please change** to 'Time to deterioration in EORTC QLQ-C30 global health score' (see also page 16, line 437). **Current text:** 'Low baseline values' **Proposed text:** suggest to change to: 'low numbers of completed questionnaires at the baseline'	Accepted
16	381	Roche	Roche suggests adding the treatment duration in parenthesis. **Current text:** In a naïve comparison of the ADR frequencies in the SmPCs, and without consideration of the longer median treatment length for alectinib, **Proposed text:** In a naïve comparison of the ADR frequencies in the SmPCs, and without consideration of the longer median treatment length for alectinib (17.9 months versus 10.7 months for crizotinib),	Not accepted. The data is from SmPC where were several studies is includes with different treatment durations.
16	434	Roche	There was no statistical difference in ORR between alectinib and crizotinib, however the duration of response was significantly longer, which is consistent in keeping with the longer PFS, in the alectinib arm and this should be noted. **Current text:** In contrast, no statistically significant difference was found in the objective response rate (ORR), and only a numerical advantage for alectinib was found in the result for quality of life.	Accepted

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			Proposed text: The ORR was numerically higher with alectinib (83% vs 76%) although not statistically significantly different. However, the duration of response was significantly longer for alectinib with the majority of responses ongoing (median not yet reached vs 11.1 months in the crizotinib arm, p<0.0001).	
16	445	Roche	Please consider using the suggested text which more acccurately describes the methods used. **Current text:** In the indirect comparison of alectinib and the comparator ceritinib, the results were derived from the fixed effects NMA model. Due to the limited number of studies, no adjustment of patient characteristics was made at the study level. **Proposed text:** The methods for synthesizing the ALK+ mNSCLC clinical trial data are as recommended by the National Institute for Health and Care Excellence (NICE) in the UK and EUnetHTA. In the indirect comparison of alectinib and the comparator ceritinib, the results were derived from the fixed effects NMA model due to the limited number of studies. Since these standard validated methods for evidence synthesis were feasible, no additional adjustment of patient characteristics was made at the study level.	Not accepted - The proposed text suggests that in principle a properly conducted adjustment for patient characteristics was an option for this NMA, which is not the case (see also NMA report: "Note that there are insufficient studies and data to perform a covariate analysis or meta-regression." [NMA report, page 44]). It also suggests, that in a fixed effects NMA model, if it is "feasible", no adjustment for patient characteristics is necessary. We cannot confirm this statement.
16	470	Roche	The current text states that it is reasonable to assume the burden of toxicity is at least not worse than that of ceritinib, however Roche considers that the burden of toxicity for alectinib is less than that for ceritinib. The frequency of the very common toxicities such as liver enzyme abnormalities, nausea, diarrhea and vomiting are markedly lower for alectinib than for ceritinib. Both the indirect comparison using network meta-analysis and a comparison of the established adverse event frequencies in the SmPCs indicated an overall superior safety profile for alectinib vs ceritinib (as stated on line 1677 “Both analyses indicated an overall superior safety profile for alectinib over ceritinib, with the exception of a few non-serious adverse events” and in the body of the report). **Current text:** Due to the high degree of uncertainty naturally inherent in any indirect comparison, no firm or formal conclusion is possible. Based on the available data, it might be considered reasonable to assume that the overall burden of toxicity from alectinib is at least not	Not accepted. The results are presented in the preceding sentence: "Both analyses indicated an overall superior safety profile for alectinib over ceritinib, with the exception of a few non-serious adverse events." The overall conclusion on what assumption is possible based on these indirect comparisons stands, however.

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			worse than that of ceritinib. **Proposed text:** Due to the high degree of uncertainty naturally inherent in any indirect comparison, no firm or formal conclusion is possible. Nontheless, it is reasonable to assume that the overall burden of toxicity from alectinib is less than that of ceritinib based on available data (e.g., notably lower rates of common toxicities such as liver test abnormalities, nausea, diarrhea, and vomiting).	
16	473	Roche	**Propose to add** the estimated PFS gain of 19 months to highlight the clinical relevance as well as statistical significance. **Current text:** ...a statistically significant increase in PFS and is associated with a statistically significant longer time to CNS progression compared with crizotinib **Proposed text:** ... a statistically significant increase of 19 months in PFS and is associated with a statistically significant longer time to CNS progression compared with crizotinib	Partly accepted. This text has been added in the two discussion sections: While the median PFS was not reached in the alectinib arm for the investigator-based PFS, the IRC showed a difference in medians of 15.3 months (25.7 vs 10.4 months, respectively).
17	476	Roche	The current text questions the adequacy of the ITC and the conclusions drawn. Earlier text in this section suggests caution in interpreting the results of the NMA because of heterogeneity between studies with respect to chemotherapy regimens and baseline prognostic factors (CNS metastases at baseline). The feasibility analysis submitted with the file acknowledges this heterogeneity and nonetheless concludes that the studies are similar enough to allow meaningful comparison. The methods for synthesizing the ALK+ mNSCLC clinical trial data are as recommended by the National Institute for Health and Care Excellence (NICE) in the UK and EUnetHTA. Furthermore, given the magnitude of PFS benefit seen for alectinib (statistically significant benefit shown across the ITT and CNS subgroups and scenarios with HR of <= 0.4 and upper limit of credible intervals no higher than 0.7), the results of the NMA can be considered robust. **Current text:** From an indirect comparison, an advantage of alectinib versus ceritinib is indicated for PFS, but because of uncertainties regarding the adequacy of the comparison, this observed result has to be regarded as unsure. **Proposed text:** From an indirect comparison, an advantage of alectinib versus ceritinib is indicated for PFS by IRC for the ITT population as well as for the subgroup of patients with	Not accepted - Besides the questionable comparability of chemotherapy regimens and CNS metastases at baseline, other known and unknown prognostic factors might contribute to between-study heterogeneity. Furthermore the statements on between-study-heterogeneity included in this assessment refer to modelled variability within the same treatment comparison, not across treatment comparisons. The only sensitivity analysis that includes a different prior than the Dirac prior for the between-trial-heterogeneity of zero was the vague prior distribution and led to non-significant results. An additional sensitivity analysis is needed to derive the borderline between-trial-variability, that still concludes

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			CNS metastases at baseline. While there is a degree of uncertainty and limitations around indirect treatment comparisons, given the magnitude of benefit across the ITT and CNS subgroups, the results can be considered robust.	significance. A sensitivity analysis using different priors was requested by the authors, but not presented by the MAH. Therefore the magnitude of influence of the choice of a model with zero between-trial-heterogeneity is not known. The width of the credible intervals depend on the between-trial-heterogeneity assumption, therefore robustness cannot be deduced from the credible intervals of the hazard ratios.
17	480	Roche	Roche feels this statement is incomplete since also fewer severe events were reported with alectinib than with crizotinib, which also impacts quality of life. **Current text:** Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non serious adverse events that tend to affect quality of life. **Proposed text:** Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non serious adverse events and severe (Grade>=3) events that tend to affect quality of life.	Accepted, in principle. Wording modified to communicate that it is particularly those non-SAEs that tend to affect QoL that are less frequent for alectinib. Modified wording: "Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non-serious adverse events that tend to affect quality of life, as well as severe (Grade ≥3) events."
17	487	Roche	There are safety advantages for alectinib vs ceritinib. Both the indirect comparison using network meta-analysis and a comparison of the established adverse event frequencies in the SmPCs indicated an overall superior safety profile for alectinib over ceritinib (as stated in the body of the report - line 1677). The NMA indicates significantly lower risk of severe (Grade >=3 AEs) with alectinib and the comparison of SmPCs demonstrate markedly lower frequency of the very common GI and liver toxicities (nausea, vomiting, diarrhea and liver test abnormalities). These are ADRs that impact tolerability and everyday quality of life. Roche feels that these data should be reflected in the conclusion on safety. **Current text:** No conclusions in relative safety between alectinib and ceritinib should be	Accepted, with minor modification: "... suggest an overall superior safety profile of alectinib."

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			drawn from the indirect comparison, due to the inherent high degree of uncertainty in such analysis. **Proposed text:** While conclusions on relative safety compared with ceritinib should be made with caution, both the NMA and the comparison of the established AE profiles in the SmPCs indicate a superior safety profile of alectinib.	
17	489	Roche	Roche suggests evaluating the totality of the patient-reported outcome evidence, which includes pre-specified descriptive mean change from baseline and proportion of improved/worsened analyses and to highlight a similar pattern of patient-reported benefit with alectinib that is consistent with its clinical efficacy and safety data. As stated in the body of the report (lines 1358 - 1359), patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. **Current text:** No statisticaly significant difference was found in HRQoL. **Proposed text:** Patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. However, the difference was not statistically significant.	Accepted but rewritten
18	495	Roche	Table 1.1 Row Outcomes/Column Project Scope: **Please correct** in table "Primary endpoint: overall survival, progression-free survival" as OS was a key secondary endpoint and investigator-assessed PFS the primary endpoint of the ALEX study. **Propose Correction:** Primary endpoint: Investigator -assessed progression-free survival	Not accepted This table presents the prioritisations of endpoints by the EUnetHTA assessment team for the present evaluation. A footnote has been added to explain that it differs from the endpoints in the ALEX study
18	495	Roche	Table 1.1 Row Outcomes/Column Project Scope: **Please correct** in table cell "Primary endpoint: overall survival, progression-free survival" as OS was a key secondary endpoint and investigator-assessed PFS the primary endpoint of the ALEX study. **Current text:** Secondary endpoints: time to CNS progression, objective response rate, health-related quality of life, other patient-reported outcomes, CNS objective response rate, CNS duration of response **Propose to add** in Secondary Endpoint: Secondary endpoints: time to CNS progression, objective response rate, overall survival, health-related quality of life,	Not accepted This table presents the prioritisations of endpoints by the EUnetHTA assessment team for the present evaluation. A footnote has been added to explain that it differs from the endpoints in the ALEX study

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			other patient-reported outcomes, CNS objective response rate, CNS duration of response	
20	512	Roche	Please list Uniba on page 2 as a dedicated reviewer.	Uniba (Slovakia) was originally set up to be a dedicated reviewer, but were unable to assist at this time.
21	564	Roche	**Please correct** font of "Study selection" for consistency	Accepted
22	581	Roche	**Please can the following statement be added** that the PROFILE 1029 study was also included in the qualitative synthesis from the MAH dossier and is included in other aspects of this document.	Not accepted
22	607	Roche	**Please include as an additional bullet point (lines 607 - 610)**, the third analysis that was conducted of the adjusted OS data There should be three methods - 1, base case; 2, sensitivity analysis with PROFILE 1029; 3, sensitivity analysis with adjusted OS.	Not accepted The introductory sentence to the bullet points has instead been changed
22	609	Roche	PLease remove the quotation marks around sensitivity analysis. **Current text:** A 'sensitivity analysis', which in addition to the studies included in the base case **Proposed text:** A sensitivity analysis, which in addition to the studies included in the base case	Accepted
22	611	Roche	**Please modify** the following statement to help clarify the methods: **Current text:** First, the Bucher method was performed for the base case and the sensitivity analysis. **Proposed text:** First, an indirect treatment comparison using Bucher indirect comparison method was performed for the base case and the sensitivity analysis.	Accepted
23	630	Roche	Suggestion to clarify **Current text:** A proper sensitivity analysis regarding different informative priors of the between-study standard deviation was requested by the authors but not delivered by the MAH. Therefore in the evaluation of the indirect evidence it is possible to compare only the Bayesian fixed effects NMA with the Bayesian random effects NMA in terms of sensitivity. Response to **Current text:** Roche conducted a random effects analysis for the sensitivity	Not accepted - Moving away from the vague prior for between-study-heterogeneity and using more informative priors instead may compromise the results, since a part of the precision depends on chosen prior distribution. Using a fixed effects model corresponds to a random effects model using the most

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			analysis including PROFILE 1029 only. It has to be noted that there were only two studies for the contrast crizotinib vs chemotherapy and one study for all other contrasts. Roche used a vague prior for the between-studies standard deviation in the random effects models, assuming study heterogeneity has the same effect across all comparisons. There are insufficient data to relax this assumption. The vague prior seems appropriate given the lack of data. While a more informative prior could result in smaller 95% credible intervals this would imply more precision than can be justified by the data.	informative prior possible, namely a point prior, on between-trial-variability zero. According to the suggestion of the MAH this choice leads to highly assumption-driven results ("... this would imply more precision than can be justified by the data"). The only presented sensitivity analysis using another prior (the vague prior) showed negative results (suggesting sensitivity of the results to the assumptions). One requirement to save the generalisability of the numerically favourable result of alectinib in the fixed effects model (which used the un-validated assumptions of zero between-trial-variability) would have been a sensitivity analysis as requested by the authors, to conclude what degree of between-trial variability still results in a significant benefit regarding PFS (using for example point priors for between-trial-variance greater than zero).
24	676	Roche	**Please correct**: The reference should be made to Appendix 6 instead of to Appendix 1 **Current text:** third individual was involved to resolve this disagreement (17) (see Appendix 1 for details). **Proposed text:** third individual was involved to resolve this disagreement (17) (see Appendix 6 for details).	Accepted
24	684	Roche	Roche feels that to account for patients subjective experience(s) more than one patient would have strengthened patient representation.	A semi-structured in-depth interview of one hour was conducted with the patient. Limitations are presented in Discussion section. It was also noted that since only one patient

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				was involved, no general conclusions could be drawn.
25	704	Roche	**Please correct** reference: Table 2.1, last row: "Soria et al. [42].." to Soria et al. [51]	Accepted
25	704	Roche	**Please correct** Table 2.1: Row:Authors and year (study name): Solomon et al/Column: Intervention: the intervention is crizotinib (not ceritinib) Current text in cell: Ceritinib vs. chemotherapy **Corrected text:** Crizotinib vs. chemotherapy	Accepted
27	750	Roche	**Please specify** the version no of the European Guideline as the current version is pending to be updated with Alecensa & Ceritinib. The same comment is applicable for line 1000.	Accepted
29	782		**Please add** the approval date to the following text at line 786. **Current text:** On 12th October 2017 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product alectinib. The CHMP adopted an extension to the existing indication as follows: 'Alecensa as monotherapy is indicated for the first-line treatment of adult patients with (ALK)- positive advanced NSCLC'(19). **Proposed text:** On 12th October 2017 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product alectinib. The CHMP adopted an extension to the existing indication as follows: 'Alecensa as monotherapy is indicated for the first-line treatment of adult patients with (ALK)- positive advanced NSCLC'(19). The European Commission provided approval for Alecensa (alecetinib) as first line- treatment for ALK positive lung cancer on the 21st Dec 2017.	Accepted
33	932	Roche	**Current text:** Whether sex has an impact remains uncertain because of conflicting evidence (8, 32). Please **Note:** Reference no 8 "Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J. Non-Small Cell Lung 2375 Cancer. National Comprehensive Cancer Network; 2017" is a reference for NSCLC and not specifically for ALK + patients and the typical profile of an ALK patient which is predominantly women.	Not accepted. Ettinger et al. have a section specifically on ALK-positive NSCLC where they state that ALK+ NSCLC is more common in men. In addition a further reference was added
33	958	Roche	Roche suggest that the most common symptoms in patients with brain	Accepted

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			metastasis/metastases are also reflected within lines 958 - 959. **Current text:** Development of brain metastases is associated with an increase in symptoms; rates of fatigue, shortness of breath, nausea or vomiting and headaches. **Propose to add** the additional symptoms: The most common symptoms in patients with brain metastasis/metastases include seizures, weakness or numbness in parts of the body and mental status change (Reference: Link to reference abstract: http://journals.lww.com/continuum/Abstract/2012/04000/Brain_Metastases.7.aspx CONTINUUM: Lifelong Learning in Neurology: April 2012 - Volume 18 - Issue 2, Neuro-oncology - p 295–311 doi: 10.1212/01.CON.0000413659.12304.a6)	
33	1004	Roche	"Suggestion for elaboration on neurocognitive side effects of WBRT and other nonpharmacological interventions, by reflecting the most common symptoms in patients with post brain WBRT within lines 1004- 1007. **Current text:** Other local, nonpharmacological treatment options for brain metastases include WBRT, stereotactic radiosurgery and surgical resection, either alone or in combination or as sequential treatment. However, for limited brain metastases, WBRT is not used very often because of the neurocognitive side effects (8). **Propose to add** the additional symptoms: Other local, nonpharmacological treatment options for brain metastases include WBRT, stereotactic radiosurgery and surgical resection, either alone or in combination or as sequential treatment. However, for limited brain metastases, WBRT is not used very often because of the neurocognitive side effects (8). The most common symptoms in patients with post brain WBRT toxicity symptoms include headache, fatigue, somnolence, neurocognitive deficits such as decline in memory and change in mental status (Reference link - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656558/ McTyre, E., Scott, J., & Chinnaiyan, P. (2013). Whole brain radiotherapy for brain metastasis. Surgical Neurology International, 4(Suppl 4), S236–S244. http://doi.org/10.4103/2152-7806.111301	Accepted
34	1000	Roche	**Please specify** the version no of the European Guideline as the current version is pending to be updated with Alecensa & Ceritinib.	Accepted

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34	1001	Roche	Line 1001&1002. **Suggest to include** references in both sentences.	Accepted
35	1038	Roche	Line 1038: **Suggest for consistency** to use ALK positive or ALK-positive (with dash) throughout document.	Accepted
35	1043	Roche	line 1043, Table 4.1, row 2: "Total NSCLC incident population " is estimated to be 87% (not 82-86%) for the EU5 and based on the EU5 epidemiology forecasts which considered local data sources for each of the EU5 countries. EU28 was estimated based on the EU5 proportion of lung cancer patients that are of the NSCLC type. This lead to the following estimates: EU5: 187,011; EU28: 289,334. **Note:** The data in table 4.1 are not aligned with data provided by Roche. Please provide the sources in order to understand why there are lower estimates than in Roche sources.	Partly accepted: since the assumptions of the MAHs' calculations could not be reproduced by using the epidemiology data provided in the submission file; these data were used to perform own calculations. It was added that the country EU-5 absolute numbers were used to calculate the probabilities for e.g first-line, ALK positive eligible based on the total incident population. Applying these ranges to the total EU5/28 population led to slightly lower estimates.
35	1043	Roche	line 1043, Table 4.1, Row 3: "NSCLC locally advanced or metastatic" should rather be termed "NSCLC 1L eligible patients (i.e. patients recurrent from early stages and de-novo advanced or metastatic patients). This group is estimated to be 82% not 67-72%. This is a combination of recurrent patients from early stages (~19%) and de-novo advanced/metastatic patients (67%). For the EU5, this is expected to be 152,739 for the EU5 and 236,311 for EU28. **Note:** The data in table 4.1 are not aligned with data provided by Roche. Please outline the sources referred to understand why there are lower estimates than in Roche sources	Accepted
36	1053	Roche	Table 5.1, row 4 - **For consistency please use** "progression-free survival" (including dash) throughout document.	Accepted
36	1057	Roche	**Please correct** duplicate referencing: "ALEX (50)". Reference of ALEX study publication already present as (1)	Accepted
36	1080	Roche	**Please add** the information that only stage IIIB not amenable for multimodality treatment	Accepted

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			were eligibile to the ALEX study **Current text:** "... in previously untreated adult patients with ALK-rearranged (ALK-positive), stage IIIB or IV, ..." **Proposed text:** "... in previously untreated adult patients with ALK-rearranged (ALK-positive), stage IIIB not amenable for multimodality treatment or IV, ..."	
36	1083	Roche	**Please add** the information that key secondary endpoints are listed here, as there were more secondary efficacy endpoints in the ALEX study. **Current text:** "Secondary endpoints were IRC-assessed, time to CNS progression, ORR and OS." **Proposed text:** "Key secondary endpoints were IRC-assessed PFS, time to CNS progression, ORR and OS.'	Accepted
37	1099	Roche	**Please correct** from ceritinib to crizotinib. **Current text:** 171 of 172 patients randomised to receive ceritinib received ceritinib. **Proposed text:** 171 of 172 patients randomised to receive crizotinib received crizotinib.	Accepted
37	1106	Roche	**For consistency please use** "non-squamous" instead of "nonsquamous NSCLC" throughout document.	Accepted
37	1107	Roche	**Please correct Current text:** "performance status 0 2". **Proposed text:** "performance status 0-2"	Accepted
39	1143	Roche	**Please add** the missing Abbreviation for MAIN to Table 5.2; Also, **For consistency please use** the word positive instead of the + sign (per NEJM); Also **Please update** the astrix on PROFILE1029 to an (a) per the footnote.	Accepted
40	1154	Roche	**Please change** the range of males from 40-45% to 37 to 48% **Current text:** The proportion of male patients was largely similar across studies, approximately 40%–45%. **Proposed text:** The proportion of male patients was largely similar across studies, approximately 37 to 48%.	Accepted
40	1155	Roche	**Please add** 'percentage of males' to the text **Current text:** In ASCEND-4 a slightly larger difference between arms was observed	Accepted

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			Proposed text: In ASCEND-4, there was a slightly larger difference between arms in the precentage of males	
40	1165	Roche	The higher frequency of CNS mets at baseline observed in the ALEX study compared with PROFILE 1014 and ASCEND-4 may be due to the requirement for all patients to have CNS imaging at baseline in the ALEX study. We suggest to mention this information. **Current text:** There were higher frequencies in the ALEX study (approximately 40%) compared with less than 30% in PROFILE 1014 and approximately 30% in ASCEND-4. **Proposed text:** There were higher frequencies in the ALEX study (approximately 40%) compared with less than 30% in PROFILE 1014 and approximately 30% in ASCEND-4. The higher frequency of CNS metastases at baseline observed in the ALEX study may be explained by the requirement for all patients to have CNS imaging at baseline.	Accepted
41	1192	Roche	**Please correct** "progression free-survival " to "progression-free survival"	Accepted
41	1202	Roche	Median PFS duration by treatment arm are reported for patients without CNS mets at baseline only. For consistency, we suggest to add median PFS duration by treatment arm for patients with CNS mets at baseline. **Current text:** The PFS benefit was consistent for patients with CNS metastases at the baseline (HR 0.40, 95% CI 0.25–0.64) and without CNS metastases at the baseline (HR 0.51, 95% CI, 0.33, 0.80); median PFS for alectinib not estimable (95% CI not estimable to not estimable); median PFS for crizotinib 14.8 months (95% CI, 10.8, 20.3 months)), indicating a benefit of alectinib over crizotinib in both subgroups. **Proposed text:** The PFS benefit was consistent for patients with CNS metastases at the baseline (HR 0.40, 95% CI 0.25–0.64); median PFS for alectinib not estimable (95% CI 9.2 to not estimable); median PFS for crizotinib 7.4 months (95% CI, 6.6, 9.6 months) and without CNS metastases at the baseline (HR 0.51, 95% CI, 0.33, 0.80); median PFS for alectinib not estimable (95% CI not estimable to not estimable); median PFS for crizotinib 14.8 months (95% CI, 10.8, 20.3 months)), indicating a benefit of alectinib over crizotinib in both subgroups.	Accepted to include PFS estimates, but an alternative wording is used for legibility reasons.

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45	1250	Roche	**Please correct** missing brackets: **Current text:** (cause-specific HR 0.16, (95% CI, 0.10, 0.28)". Propose text: "(cause-specific HR 0.16, (95% CI, 0.10, 0.28))" [bracket missing]	Accepted
45	1257	Roche	Roche suggests commenting on CNS -ORR in the main text. The current report does not provide any comment on CNS-ORR in the CNS results section. The results have been reported in the Table 5.6. Given the clinical importance of CNS response in terms of patients' benefit (neurological symptoms, morbitidy associated with local radiotherapy), we suggest to also include these results. **Proposed text to be added following line 1257**: In ALEX, intracranial ORR was significantly improved with alectinib compared with crizotinib, irrespective of prior radiotherapy. Duration of CNS response with alectinib was longer in all patient subgroups than with crizotinib. Of note, a complete CNS response was more frequently observed in the alectinib arm. This was specifically observed for patients with measurable and/or non-measurable CNS metastases at baseline without prior radiotherapy where the complete response rate in the alectinib arm was 61.5% compared with 10.8% for the crizotinib arm, suggesting that the need for a potentially morbid local radiotherapy may be avoided in a majority of the alectinib patients.	Partly accepted. Agree to add information on CNS ORR by prior radiotherapy. The statement that duration of CNR response was longer, and the information on CR rates could not be verified in the publication referenced for these statements in the submission file, however (Gadgeel 2017). A CNS CR rate of 61%, if true, would be remarkable and therefore needs further substantiation. Furthermore, no information on statistical significance was found for the CNS ORR in the source publication, probably since these were exploratory endpoints.
47	1269	Roche	Please mention that the Random effects models were carried out as sensitivity analyses and results are also not reported in the text but are available in the appendix tables for OS and PFS **Current text:** An NMA was performed by the MAH company using Bayesian Markov chain Monte Carlo methods in WinBUGS, with a fixed effects and a random effects model. The NMA MAH base case was based on the fixed effects model and included the ALEX, ASCEND-4 and PROFILE 1014 studies. An alternative analysis was performed with the results included from the PROFILE 1029 study. **Proposed text:** An NMA was performed by the MAH company using Bayesian Markov chain Monte Carlo methods in WinBUGS, with a fixed effects and a random effects model. The NMA MAH base case as conducted using a fixed effects model and included the ALEX, ASCEND-4 and PROFILE 1014 studies. For the sensitivity analysis more than one study	Accepted

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			(PROFILE 1014 and PROFILE 1029) were available to evaluate the comparison between crizotinib and chemotherapy which allowed for both a fixed effects and random effects NMA to be conducted. Both sensitivity analyses were performed with the results included from the PROFILE 1029 study.	
47	1272	Roche	Please refer to the additional analyses as 'sensitivity analysis' instead of an 'alternative analysis' for consistency.	Accepted
48	1274	Roche	Suggest revision to interpretation of NMA results as follows: **Current text:** The results have to be interpreted with caution because of uncertainties regarding the adequacy of the NMA. **Proposed text:** The results should be interpreted with caution due to limitations in the analyses and data that may have affected the results. These are further addressed in Appendix 6.	Accepted
50	1282	Roche	**Please change** to state "Alectinib versus ceritinib (NMA)" since the ITC results will not be reported.	Accepted
50	1292	Roche	**Proposed Additions to Table 5.7**: Amend to include ORR by IRC for the ALEX study: 79% in the alectinib arm and 72% in the crizotinib arm (see FAS p35)	Accepted
50	1292	Roche	Table 5.7 **Please add** 'median' to PFS, months to clarify.	Accepted
50	1294	Roche	**Please update** the footnote in Table 5.7 to state Inv=investigator assessed	Accepted
51	1307	Roche	**Please correct** punctuation: **Current text:** "lower number of standard chemotherapy cycles. (See the discussion on baseline characteristics above.)". **Proposed text:** "lower number of standard chemotherapy cycles (see the discussion on baseline characteristics above)."	Accepted
51	1311	Roche	**Please add** data to support the statement. **Current text:** The ORR for crizotinib was consistent at approximately 75% in ALEX and PROFILE 1014 **Proposed text:** The ORR for crizotinib was 79% in ALEX and 74% in the PROFILE 1014	Not accepted but wording clarified
51	1315	Roche	Proposed change in Table 5.8: include '95% credible interval' instead of just 'credible	Accepted

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			interval'	
51	1315	Roche	**Please correct** Formatting: Please move the text "Bold indicates significance based on 95% credible intervals" to after the description of the HR and OR to clarify that the bold text signifies 95% CrI for both.	Accepted
52	1333	Roche	**Please add** a reference to the table with the HRs (Table 5.8) and caterpillar plots (Figure 5.7) in the sentence below. Currently, it appears that the text only links to the caterpillar plots and not to the table with the HRs. **Current text to correct reference**: The key efficacy findings for the fixed effects base case (including ALEX, ASCEND 4 and 1333 PROFILE 1014) were as follows (Figure 5.7, Figure 5.7) **Proposed text:** The key efficacy findings for the fixed effects base case (including ALEX, ASCEND 4 and 1333 PROFILE 1014) were as follows (Figure 5.7, Table 5.8)	Accepted
52	1335	Roche	**Please add** 'by IRC' following PFS **Current text:** Significantly longer PFS for alectinib versus ceritinib **Proposed text:** Significantly longer PFS by IRC for alectinib versus ceritinib	Accepted
52	1336	Roche	**Please add** 'by IRC' following PFS **Current text:** Significantly longer PFS in the subgroup of patients with CNS metastases at the baseline with alectinib versus ceritinib **Proposed text:** Significantly longer PFS by IRC in the subgroup of patients with CNS metastases at the baseline with alectinib versus ceritinib	Accepted
53	1353-1355	Roche	**Please add** additional context to data that among patients who did complete PRO data at baseline, compliance remained moderate-to-high thereafter. **Current text:** The proportions of compliance at the baseline were similar in both treatment arms, with 64% of patients in the alectinib arm and 66% of patients in the crizotinib arm completing the baseline patient-reported outcomes assessment. **Proposed text:** The proportions of compliance at the baseline were similar in both treatment arms, with 64% of patients in the alectinib arm and 66% of patients in the crizotinib arm completing the baseline patient-reported outcomes assessment. Among patients who had PRO baseline data, moderate-to-high compliance rates (60% or greater) throughout the study with the exception of Week 112 and 116 were observed in the	Partly accepted: It is not agreed that compliance rate is moderate to high.

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			alectinib-treated arm.	
53	1354	Roche	Suggest to change this sentence: **Current text:** "A patient reporting a point change in scale score that is greater than 10 is by the patient considered clinically significant and therefore also considered clinically meaningful." to the following: **Proposed text:** "A point change in scale score, reported by a patient, that is greater than 10 is considered clinically meaningful."	Accepted
57	1418	Roche	**Please modify** to use the generic names rather than commerical ones for consistency	Not accepted since it is according to SmPC
59	1458	Roche	Please include the treatment duration in parenthesis. **Current text:** ...longer median treatment length for alectinib... **Proposed text:** longer median treatment duration for alectinib (17.9 months versus 10.7 months for crizotinib)	Not accepted. The data is from SmPC where were several studies is includes with different treatment durations.
60	1472	Roche	The current statement is incorrect. Hepatobiliary ADRs occur with higher incidence with ceritinib (60% liver laboratory abnormalities per Table 6.3) than with alecensa or crizotinib. In Ascend-4 hepatic transaminase increases (all grades) occurred in up to 91% of patients, Grade 3-4 increases in up to 34% of patients with ceritinib. These numbers are markedly higher than those for alectinib. **Current text:** Hepatobiliary disorders, including abnormal levels of liver transaminases, were least common with ceritinib, but were more common with crizotinib than alectinib. **Proposed text:** Hepatobiliary disorders, including abnormal levels of liver transaminases, were less common with alectinib than with crizotinib or ceritinib.	Partly accepted. It is agreed that the statement is incorrect, and should be removed. New text: "Abnormal liver laboratory results appeared least common with alectinib, while acknowledging that a comparison based on the varying items in the SmPCs is difficult.
60	1487	Roche	Table 6.3. For consistency **Please add** any missing dashes missing in the table	Accepted
60	1487	Roche	Table 6.3. **Please correct**: Liver laboratory test abnormalities for Zykadia to 60.5% from Zykadia SmPC and not 60%	Not accepted: A footnote says that frequencies ≥5% have been abbreviated to have no decimal.
62	1507	Roche	**Please correct** missing bracket: "(0% vs. 2%) MAH submission file).". It should be "((0% vs.	Accepted

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			2%) MAH submission file)."	
63	1524	Roche	**Current text:** The statement 'The result is driven by the PROFILE 1014 crizotinib versus chemotherapy comparison" would benefit from the inclusion of additional information to justify this statement. **Proposed Additional Text**: Roche suggests adding in the caveats provided in the NMA report as follows: "In PROFILE 1014, data are Grade 3 or 4 elevations of ALT managed with dose interruptions or dose reductions. For ASCEND-4 and ALEX, data are any treatment interruptions or dose reductions due to an AE. Additionally, the differences in dose reductions or treatment interruptions may be due to differences in time on treatment/drug exposure".	Accepted
64	1560	Roche	Proposed deletion of **Current text:** Patients with bradycardia may be more likely to be harmed since symptomatic bradycardia can be aggravated with alectinib. Roche proposes to delete this statement since it is not based on available data. Moreover, SmPC does not preclude initiation of Alecensa treatment in patients with asymptomatic and symptomatic bradycardia and this is allowed as per prescribers clinical judgement. Cases of bradycardia reported with alectininib were largely asymptomatic and none of the cases led to withdrawal of Alecensa. Moreover, in case of symptomatic bradycardia, the SmPC states that: If patients experience symptomatic bradycardia or life-threatening events, concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products should be evaluated and Alecensa treatment should be adjusted as described in Table 2 (Dose modification advice for specified Adverse Drug Reactions). As such, the potential events of symptomatic bradycardia will be adequately managed with the SmPC guidance, avoiding aggravation of symptomatic bradycardia.	Partly accepted: Generally, patients with an pre-existing condition that overlaps the toxicity profile of alectinib might be considered at greater risk by the treatment. Patients with bradycardia may thus have an increased risk of symptomatic toxicity, since the pre-existing bradycardia might be aggravated with alectinib.
67	1591	Roche	**Current text:** the longer duration of response observed for alectinib versus ceritinib. **Please correct** to read: the longer duration of response observed for alectinib versus crizotinib	Accepted
67	1610	Roche	**Current text:** "Taken together, the results presented for OS have a high degree of	Partly accepted: **Changed** wording

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			uncertainty ('risk of bias')." We agree with the authors that the OS results have a high degree of uncertainty (low precision) but there is no reason to assume that the results from this RCT are biased. We therefore suggest to rephrase. **Proposed text:** "Taken together, the results presented for OS have a high degree of uncertainty (due to immaturity of the data)."	
67	1624	Roche	Please clarify that only OS outcomes are impacted by cross-over. See suggested change below. **Current text:** No significant differences were observed between alectinib and ceritinib with regard to OS. The results may be affected by treatment arm crossover and data immaturity (median OS was not observed for some treatment arms in the trials). **Proposed text:** No significant differences were observed between alectinib and ceritinib with regard to OS. The OS results may be affected by treatment arm crossover and data immaturity (median OS was not observed for some treatment arms in the trials).	Accepted
67	1626	Roche	**Please add** text to clarify the extent to which additional analyses were conducted to evaluate the impact of heterogeneity and difference estimates of uncertainty in the model (i.e., use of FE and RE models) **Proposed text:** A thorough feasibility assessment was conducted to evaluate the available evidence. Due to the paucity of RCT data for ALK+ mNSCLC in treatment naïve/first-line populations (data from 3 studies in the base case evidence network, 4 for the sensitivity analysis), there were limitations to the analysis that could be conducted. Therefore, the base case analysis was conducted using FE only. Three additional sensitivity analyses were conducted to evaluate the impact of heterogeneity within the NMA and ITC as well as a RE model including the PROFILE 1029 study.	Partly accepted - Inclusion of description of RE-NMA result by extending sentence "Analyses to check the sensitivity of the results for varying heterogeneity are not included in the submission." [page 67, line 1629] into "Analyses to check the sensitivity of the results for varying heterogeneity are not included in the submission, except for the computation of a random effects NMA with a vague a priori between-study-heterogeneity assumption. This analysis showed wide credible intervals leading to non-significant results and therefore reveals the dependency of the fixed effects NMA results on the assumed between-study-heterogeneity.". - Further details on the

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				sensitivity analysis are not included, since they were already presented before in the assessment and are not of main relevance in the discussion.
68	1639	Roche	Please consider the following clarifications to the points being made: **Current text:** There are further issues regarding the uncertainties in the NMA; for example: - There is inconsistency in the relative efficacy of crizotinib and ceritinib compared with alectinib in terms of OS and PFS HRs. **Proposed text:** Additional limitations to interpretation of the NMA results included: - The potential confounding of OS data due to cross-over that was allowed in three of the trials (PROFILE 1014, PROFILE 1029 and ASCEND-4) and immaturity of OS data reported; - The differences in the chemotherapy arms of the ASCEND-4 and PROFILE trials	Accepted
68	1641	Roche	The current bullet point does not reflect the decision to include the PROFILE 1029 study only in the sensitivity analysis nor does it represent a limitation of the NMA results. Roche's **Rationale** for excluding PROFILE 1029 from the Base Case: The PROFILE 1029 (crizotinib vs. chemotherapy in Asian patients only) was not included in the base case analysis, since PROFILE 1029 was conducting in only East Asian patients (100%) whereas the other studies populations were more closely matched the mixed Asian/non Asian population in ALEX. Additionally, there was a larger disparity bewteen arms for in CNS mets at baseline reported in PROFILE1029 (crizo; 20% vs. 31%) which may have increased the heterogeneity of the analysis. However, given the comparability of the treatment and diagnostic characteristics of the patient population (ALK+ NSCLC, treatment naive patients) in the study, PROFILE 1029 was included in a sensitivity analysis. Therefore, results from the study were used as a sensitivity analysis to determine the significance of race in driving results which was informed by the outcome of the analysis. Based on the similarity of the results from the FE model, one may conclude that differences in the proportion of CNS mets as well race are not substantial prognostic factors and do not substantially impact the NMA outcomes.	Partly accepted. The text has been updated.

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			Current text: - The results from the PROFILE 1029 clinical study were excluded in the base case result of the NMA. In an alternative analysis where the results from PROFILE 1029 were included in the NMA, the HRs were slightly lower. Therefore the exclusion of PROFILE 1029 does not affect the results in a major way. Proposed deletion of **Current text:** Roche recommend that this bullet is removed from the report because the **Rationale** for exclusion from the base case network and the similarity in results.	
68	1648	Roche	Please remove the hyphen from phase-III	Accepted
68	1652	Roche	Please include the treatment duration in parenthesis. **Current text:** ...longer exposure to treatment... **Proposed text:** : longer exposure to treatment (17.9 months versus 10.7 months for crizotinib)	Accepted
68	1659	Roche	Roche feels this statement is incomplete since also fewer severe events were reported with alectinib than with crizotinib, which also impacts quality of life. **Current text:** Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non serious adverse events that tend to affect quality of life. **Proposed text:** Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non serious adverse events and severe (Grade>=3) events that tend to affect quality of life.	Accepted, in principle. Wording modified to communicate that it is particularly those non-SAEs that tend to affect QoL that are less frequent for alectinib. Modified wording: Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non-serious adverse events that tend to affect quality of life, such as nausea, diarrhoea and vomiting as well as severe (Grade ≥3) events.
68	1679-1681	Roche	The current text states that it is reasonable to assume the burden of toxicity is at least not worse than that of ceritinib, however Roche considers that the burden of toxicity for alectinib is less than that for ceritinib. The frequency of the very common toxicities such as liver enzyme abnormalities, nausea, diarrhea and vomiting are markedly lower for alectinib	Not accepted. The results are presented in the preceding sentence: "Both analyses indicated an overall superior safety profile for alectinib over ceritinib, with the exception of a few non-

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			than for ceritinib. Both the indirect comparison using network meta-analysis and a comparison of the established adverse event frequencies in the SmPCs indicated an overall superior safety profile for alectinib vs ceritinib (as stated on line 1677 “Both analyses indicated an overall superior safety profile for alectinib over ceritinib, with the exception of a few non-serious adverse events” and in the body of the report). **Current text:** Due to the high degree of uncertainty naturally inherent in any indirect comparison, no firm or formal conclusion is possible. Based on the available data, it might be considered reasonable to assume that the overall burden of toxicity from alectinib is at least not worse than that of ceritinib. **Proposed text:** Due to the high degree of uncertainty naturally inherent in any indirect comparison, no firm or formal conclusion is possible. Nontheless, it is reasonable to assume that the overall burden of toxicity from alectinib is less than that of ceritinib based on available data (e.g., notably lower rates of common toxicities such as liver test abnormalities, nausea, diarrhea, and vomiting).	serious adverse events." The overall conclusion on what assumption is possible based on these indirect comparisons stands, however.
69	1684-1686	Roche	Roche recommmend evaluating the totality of the patient-reported outcome data, which includes pre-specified descriptive mean change from baseline and proportion of improved/worsened analyses and highlight a similar pattern of patient-reported benefit with alectinib that is consistent with its clinical efficacy and safety data. **Current text:** A trend favouring alectinib over crizotinib was observed for patient-reported global health status/HRQoL; however, it was not statistically significant. Such trends were seen in all patient reported outcomes. **Proposed text:** A trend favouring alectinib over crizotinib was observed, as for patient-reported global health status/ health-related quality of life (HRQoL) (HR 0.72, 95% CI, 0.38–1.39). Overall, patients in the alectinib arm reported clinically meaningful improvement in HRQoL and improvement in multiple lung cancer symptoms for a longer duration of time than patients in the crizotinib arm, but the differences were not statistically significant.	Accepted but rewritten.
69	1700	Roche	Please **Note:** The statement that data were not collected and reported in the study is incorrect. Data are collected and will be reported in the ALEX study final analysis - together	Accepted but rewritten.

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			with OS analysis (please refer to line 415 and 416). Anticancer treatment administered after progression or discontinuation of the study treatment (alectinib in the alectinib arm and crizotinib in the crizotinib arm) are collected in the ALEX study (cf. MAH submitted version of Appendix 1). Roche therefore suggest to delete the statement that "Data were not collected and reported in the study."	
69	1704	Roche	Proposed additional new text: However recent data show a higher 4-year OS rate of 70% with alectinib (AF001-JP) versus 56.6% for crizotinib (PROFILE1014) (WCLC Oct 2017)	Not accepted: Patient characteristics are not comparable
70	1707	Roche	Suggestion to add "the" before "high quality of evidence **Current text:** From direct comparison, based on high quality of evidence, alectinib demonstrates a statistically significant increase in PFS ... **Proposed text:** From direct comparison, based on the high quality of evidence, alectinib demonstrates a statistically significant increase in PFS with an estimated gain of 19 months ...	Partly accepted. This text has been added in the two discussion sections: While the median PFS was not reached in the alectinib arm for the investigator-based PFS, the IRC showed a difference in medians of 15.3 months (25.7 vs. 10.4 months, respectively).
70	1707	Roche	Please state the estimated gain in PFS in order to highlight the clinical relevance as well as the statistical significance of the finding. **Current text:** From direct comparison, based on high quality of evidence, alectinib demonstrates a statistically significant increase in PFS ... **Proposed text:** From direct comparison, based on high quality of evidence, alectinib demonstrates a statistically significant increase in PFS with an estimated gain of 19 months ...	Partly accepted. This text has been added in the two discussion sections: While the median PFS was not reached in the alectinib arm for the investigator-based PFS, the IRC showed a difference in medians of 15.3 months (25.7 vs. 10.4 months, respectively).
70	1708	Roche	Please highlight the clinical relevance of CNS progression. **Current text:** ...and is associated with a statistically significant longer time to CNS progression compared to crizotinib. **Proposed text:** ...and is associated with a statistically significant longer time to CNS progression compared to crizotinib. This is of high clinical relevance as CNS metastasis and progression affects both the symptoms and the quality of life, as well as the prognosis of	Accepted

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			the patients.	
70	1711	Roche	The current text questions the adequacy of the ITC and the conclusions drawn. This refers to caution in interpreting the results of the NMA because of heterogeneity between studies with respect to chemotherapy regimens and baseline prognostic factors (CNS metastases at baseline). The feasibility analysis submitted with the file acknowledges this heterogeneity and nonetheless concludes that the studies are similar enough to allow meaningful comparison. The methods for synthesizing the ALK+ mNSCLC clinical trial data are as recommended by the National Institute for Health and Care Excellence (NICE) in the UK and EUnetHTA and can be considered adequate. Furthermore, given the magnitude of PFS benefit seen for alectinib (statistically significant benefit shown across the ITT and CNS subgroups and scenarios with HR of <= 0.4 and upper limit of credible intervals no higher than 0.7), the results of the NMA can be considered robust. **Current text:** From an indirect comparison, an advantage of alectinib versus ceritinib is indicated for PFS, but because of uncertainties regarding the adequacy of the comparison, this observed result has to be regarded as unsure. **Proposed text:** From an indirect comparison, an advantage of alectinib versus ceritinib is indicated for PFS by IRC for the ITT population as well as for the subgroup of patients with CNS metastases at baseline. While there is a degree of uncertainty and limitations around indirect treatment comparisons, given the magnitude of benefit across the ITT and CNS subgroups, the results can be considered robust.	Not accepted: see comment to page 12 / line 324, page 17, line 476 and page 23, line 630.
70	1715	Roche	Roche feels this statement is incomplete since also fewer severe events were reported with alectinib than with crizotinib, which also impacts quality of life. **Current text:** Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non serious adverse events that tend to affect quality of life. **Proposed text:** Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non serious adverse events and severe (Grade>=3) events that tend to affect quality of life.	Accepted, in principle. Wording modified to communicate that it is particularly those non-SAEs that tend to affect QoL that are less frequent for alectinib. Modified wording: "Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to

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				non-serious adverse events that tend to affect quality of life, as well as severe (Grade ≥3) events."
70	1719	Roche	**Please add** that the events with lower frequency for alectinib are those that impact tolerability and QoL. **Current text:** Thus markedly lower frequencies for alectinib were reported for diarrhoea, vomiting and nausea. **Proposed text:** Thus markedly lower frequencies for alectinib were reported for diarrhoea, vomiting and nausea, events that impact tolerability and everyday quality of life.	Not accepted already mentioned in the same paragraph
70	1722	Roche	There are safety advantages for alectinib vs ceritinib. Both the indirect comparison using network meta-analysis and a comparison of the established adverse event frequencies in the SmPCs indicated an overall superior safety profile for alectinib over ceritinib (as stated in the body of the report - line 1677). The NMA indicates significantly lower risk of severe (Grade >=3 AEs) with alectinib and the comparison of SmPCs demonstrate markedly lower frequency of the very common GI and liver toxicities (nausea, vomiting, diarrhea and liver test abnormalities). These are ADRs that impact tolerability and everyday quality of life. Roche feels that these data should be reflected in the conclusion on safety. **Current text:** No conclusions in relative safety between alectinib and ceritinib should be drawn from the indirect comparison, due to the inherent high degree of uncertainty in such analysis. **Proposed text:** While conclusions on relative safety compared with ceritinib should be made with caution, both the NMA and the comparison of the established AE profiles in the SmPCs indicate a superior safety profile of alectinib.	Accepted, with minor modification: "... suggest an overall superior safety profile of alectinib
70	1724	Roche	Roche suggests evaluating the totality of the patient-reported outcome evidence, which includes pre-specified descriptive mean change from baseline and proportion of improved/worsened analyses and to highlight a similar pattern of patient-reported benefit with alectinib that is consistent with its clinical efficacy and safety data. As stated in the	Accepted but rewritten.

Page	Line	MAH	Comment	Reply from author
			body of the report (lines 1358 - 1359), patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. **Current text:** No statisticaly significant difference was found in HRQoL. **Proposed text:** Patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. However, the difference was not statistically significant.	
71	1726	Roche	**Note:** The Appendix on "EXTRAPOLATION OF PFS AND OS/SURVIVAL ANALYSIS" was provided by Roche in order to capture the full potential benefit of Alecitinb without restricting what has been provided in the ALEX trial so far. Table 1 of this Appendix provides very relevant information to the reader regarding the estimated mean progression-free survival and overall survival gain for alectinib compared to crizotinib. Furthermore, Table 1 highlights that the observed survival gain is only a small amount of the total expected survival gain Suggestion to consider: Please include in the assessment report the table in the executive summary of the survival modelling appendix.	Accepted
71	1737	Roche	Please capitalize weibull -> Weibull gompertz -> Gompertz	Accepted
72	1781	Roche	**Current text:** "The use of a parametric function requires that the unknown scale (λ) and shape (γ) parameters of a parametric survival function are estimable" Depending of the parametric function, 1 to 3 parameters are required. Text above is not correct for exponential and gamma. **Propose to remove**: Please remove the outlined sentence.	Accepted
73	1799	Roche	**Please correct Current text:** Figures # and # Propose text: Figures A2 and A3	Accepted
75	1842	Roche	**Please update** Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), => AIC and BIC	Partly accepted, sentence changed to: Parametric functions were assessed on the basis of model goodness of fit with the use of (AIC) and (BIC),….
75	1842	Roche	**Please correct Missing space: change** 'ofusing' to 'of using'	Accepted
75	1844	Roche	**Please change Current text:** the log-normal function had the optimal fit	Accepted

Page	Line	MAH	Comment	Reply from author
			Proposed text: the log-normal function had the best fit	
75	1848	Roche	**Please change Current text:** the optimal fit **Proposed text:** the best fit	Accepted
75	1849	Roche	**Please change Current text:** the optimal fit **Proposed text:** the best fit	Accepted
78	1900	Roche	**Please clarify current text** to indicate whether the data indicates a fluctuation or a shift. **Current text:** Whether they indicate radical fluctuations or shifts that require piecewise or more flexible models.	Not Accepted: the text explains that one needs to consider more parameters than the log-cumulative hazard plots when choosing parametric function when extrapolating the PFS survival curves. A summary made by the MAH also concludes that taking these parameters into account resulted in the exponential function being an appropriate method of extrapolating option for PFS, despite its limitations
87	2070	Roche	**Please modify** to state that "if mixed, at least 80% must be advanced (stage IIIB) and/or metastatic (stage IV)" **Current text:** if mixed stage, at least 80% had to have advanced NSCLC. **Proposed text:** if mixed, at least 80% must be advanced (stage IIIB) and/or metastatic (stage IV)	Accepted
89	2087	Roche	**Propose to add** a footnote so that individuals may be redirected based on individual licensing.	Accepted
164	2294	Roche	Roche agrees that the limitaions and differences between the trials included in the network should be highlighted. However, it is worth noting the specific network details as they relate to the outputs of the NMA. Additional text has been added to this statement which highlights the problem and provides some additional context.	Partly accepted

Page	Line	MAH	Comment	Reply from author
			Current text: Despite the availability of indirect evidence/NMA, it has to be noted, that in ASCEND-4, four cycles of chemotherapy followed by maintenance therapy were used as a comparator. In contrast, in PROFILE 2295 1014, up to six cycles of the same chemotherapy were allowed, but without maintenance therapy. **Proposed text:** Given that there was a lack of direct evidence in the comparison of alectinib to ceritinib, a connected network of three trials (ALEX, PROFILE 1014, and ASCEND-4) were used to use indirect evidence to estimate the difference in treatment effect. As with all indirect comparison, there were differences within the three studies that should be noted as the differences may have affected the results of the NMA. Firstly, it has to be noted, that in ASCEND-4, four cycles of chemotherapy followed by maintenance therapy were used as a comparator. In contrast, in PROFILE 2295 1014, up to six cycles of the same chemotherapy were allowed, but without maintenance therapy. The difference between studies in time on treatment was 1.9 months (4.1 months on CHEMO in PROFILE 1014; 6 months on CHEMO in ASCEND-4) and the difference between median PFS in the trials was 1.1 months (median PFS was 7·0 months for CHEMO in PROFILE 1014; median PFS of 8·1 months for CHEMO in ASCEND-4). It is not known whether the difference of 1.1 months in median PFS is due to the maintenance or falls within the range of uncertainty due to other factors or sources of heterogeneity. It is assumed that there is no impact on response endpoints since response should be observed during induction phase (median time to response in CHEMO arm for PROFILE 1014 was 2.8 months compared to 3.1 months in ASCEND-4). There may be an impact on the safety endpoints assuming that more adverse events would occur with longer treatment.	
164	2298	Roche	The current text suggests caution in interpreting the results of the NMA because of heterogeneity between studies with respect to chemotherapy regimens and baseline prognostic factors (CNS metastases at baseline). The feasibility analysis submitted with the file acknowledges this heterogeneity and nonetheless concludes that the studies are similar enough to allow meaningful comparison. The difference in PFS in the	Not accepted: see comment to page 12 / line 324, page 17, line 476 and page 23, line 630.

Page	Line	MAH	Comment	Reply from author
			chemotherapy arms between the PROFILE 1014 and ASCEND-4 studies is of a magnitude (median 7 months vs 8.1 months) that would be unlikely to impact the overall outcome, given the magnitude of PFS benefit seen for alectinib in the results of the NMA. The proportion of patients with CNS metastases was reported to be higher in ALEX (40%) than the other studies (approx. 30%). However, please note that the ALEX study design required CNS imaging at baseline whereas the other studies did not. This could lead to greater detection and reporting of CNS metastases in the ALEX study and overestimate the true differences at baseline. **Current text:** Because of the uncertainties involved and possible dependencies regarding the heterogeneity, assumptions on the results in the NMA, these results are considered with caution. **Proposed text:** While there is a degree of uncertainty around indirect treatment comparisons, given the magnitude of benefit (statistically significant benefit is shown across all scenarios with HR of 0.4 and upper limit of credible intervals no higher than 0.7) the results can be considered robust.	
165	2334	Roche	**Request for** completeness to add the additional NMA table of PFS by IRC on the subgroup of CNS metastases to appendix 6.	
166	2338	Roche	PFS Table - **Please change** CrL = credible limit to CrI=credible interval	Accepted
167	2346	Roche	OS Table - **Please change** CrL = credible limit to CrI=credible interval	Accepted
168	2352	Roche	Table A.19, Item A2.2 - Roche suggests the item is **changed** to "satisfactory". The **Rationale** for this change has been provided below: **Rationale**: In order to have a connected network, chemotherapy was included. The inclusion of this treatment complies with the defined study questions (PICOS) and the NICE DSU TSD 1 which states that "If it is not possible to form a connected network of comparison of these treatments based on randomized data, it maybe possible to introduce further treatments so that a connected network can be formed". Additionally, chemotherapy was raised during the initial review by EUnetHTA as a comparator of	Accepted

Page	Line	MAH	Comment	Reply from author
			interest within this target population. For these reasons, Roche considers the inclusion of chemotherapy to be relevant.	
168	2352	Roche	Table A.19, Item A4.1 - Roche suggests the item is **changed** to "satisfactory" given that a **Justification** was provided. This **Justification** has also been provided: **Rationale**: Chemo arms: The difference between studies in time on treatment was 1.9 months (4.1 months on CHEMO in PROFILE 1014; 6 months on CHEMO in ASCEND-4) and the difference between median PFS in the trials was 1.1 months (median PFS was 7·0 months for CHEMO in PROFILE 1014; median PFS of 8·1 months for CHEMO in ASCEND-4). It is not known whether the difference of 1.1 months in median PFS is due to the maintenance or falls within the range of uncertainty due to other factors or sources of heterogeneity.Therefore, it was assumed that studies were "similar enough" to be connected in the evidence network. OS **Rationale**: Only PROFILE 1014 report OS data adjusted for treatment cross-over. However, patients could cross over from the CHEMO arm to the ALKi arm in three trials (PROFILE 1014, PROFILE 1029 and ASCEND-4); crossover from CRZ to ALEC was not allowed in the ALEX study. Only available for PROFILE1014 study but not available for the ASCEND-4 study therefore, an unadjusted OS was used within the base case analysis. This should be clarified in the comment box.	Accepted. ("Satisfactory"). While the uncertainties remain, they are considered adequately addressed by the MAH. Text in table has been updated with MaH's rationale.
169	2352	Roche	Table A.19, Item A5.1 - Roche suggests the item is **changed** to "satisfactory" given **Justification** was provided. Please see the **Justification** below: **Justification**: A feasibility assessment of the available evidence was conducted which included a review of all endpoints (both clinical and safety) within the trials, then evaluated for feasbility to connect to the network. Many of the endpoints not included in the trial were excluded since they were not reported in at least one trial within the network. Endpoint tables addressing the availability of data were provided in Section 6.3 of the feasibility assessment.	Accepted
169	2352	Roche	Table A.19, Item A5.2 - Roche suggests the item is **changed** to "Not Applicable" given **Justification** was provided.	Accepted. ("NA") The endpoints used are standard oncology endpoints.

Page	Line	MAH	Comment	Reply from author
			Justification: The definition of all endpoint definitions used in the NMA/ITC were evaluated prior to including the endpoint in the analysis. The scales and definitions of the endpoints were matched and differences were clarified. Further details on the selection and discussion of the endpoints was provided in section 6.3 and 6.4 of the feasibility assessment.	
169	2352	Roche	Table A.19, Section A7.2 - Roche suggests the item is **changed** to "satisfactory" given **Justification** was provided. Please see the **Justification** below: **Justification**: All differences in the trial populations were explored during the feasibility assessment and populations deamed to be similar were included in the base case. To understand the potential impact of such population differences on the outcome of the NMA, a sensitivity analysis was conducted using the PROFILE1029 study which included 100% Asian patients and the largest within trial disparity in CNS mets and lowest CNS mets in the experimental arm (~20%). The results of this sensitivity analysis were similar to those reported in the base case analysis therefore, this providing an understanding to the impact of these differences within the network.	Not accepted. The sensitivity analysis conducted by the MAH is not designed to identify the potential impact of differences in frequency and/or prior treatment of brain metastases across study populations (in ALEX, ASCEND-4, PROFILE1014) on the outcomes of the NMA.
170	2352	Roche	Table A.19, Item A8.2 - Roche suggests the item is **changed** to "satisfactory" given **Justification** was provided. Please see the **Justification** below: **Justifications**: Population heterogeneity: All differences in the trial populations were explored during the feasibility assessment and populations deamed to be similar were included in the base case. To understand the potential impact of such population differences on the outcome of the NMA, a sensitivity analysis was conducted using the PROFILE1029 study which included 100% Asian patients and the largest within trial disparity in CNS mets and lowest CNS mets in the experimental arm (~20%). The results of this sensitivity analysis were similar to those reported in the base case analysis therefore, this providing an understanding to the impact of these differences within the network. Open-label trials: Althought there are no adjustments that could be made for open-label	Not accepted while adjustment for this is not possible

Page	Line	MAH	Comment	Reply from author
			studies the open-label design could potentially impact on withdrawals as patients and investigators will be aware of their allocated treatment. Therefore, to understand if this may have potentially biased the results, reasons for treatment discontinuation/withdrawal were reviewed in detail. The findings showed that in the ALEX study (14), discontinuation from treatment (any reason) was higher in the CRZ control arm (105/151, 69.5%) than in the ALEC arm (68/152, 44.7%), as was withdrawal by subjects (11/151, 7.3% with CRZ vs. 3/152, 2% with ALEC). However, the main reason for withdrawal was PD (CRZ 39.7%; ALEC, 27.0%), and similar proportions of patients withdrew due to an AE (CRZ 12.6%; ALEC, 11.2%). Therefore, the potential for bias due to this study design is limited. Chemo differences: The difference between studies in time on treatment was 1.9 months (4.1 months on CHEMO in PROFILE 1014; 6 months on CHEMO in ASCEND-4) and the difference between median PFS in the trials was 1.1 months (median PFS was 7·0 months for CHEMO in PROFILE 1014; median PFS of 8·1 months for CHEMO in ASCEND-4). It is not known whether the difference of 1.1 months in median PFS is due to the maintenance or falls within the range of uncertainty due to other factors or sources of heterogeneity. It is assumed that there is no impact on response endpoints since response should be observed during induction phase (median time to response in CHEMO arm for PROFILE 1014 was 2.8 months compared to 3.1 months in ASCEND-4). There may be an impact on the safety endpoints assuming that more adverse events would occur with longer treatment.	
172	2352	Roche	Table Abbreviations - **Please add** 'NA=not applicable'	Accepted
172	2352	Roche	Item B2.2 in table Table A19 pg.170; line 2354: Suggestion to clarify **Current text:** A decision rule based on the deviance information criteria and the average residual deviance was prespecified, but considering the limited amount of data that can validate heterogeneity assumptions (which constitute the main difference between the fixed effects model and the random effects model), the presentation of extensive sensitivity analyses seems more adequate than deciding between the two extreme cases of absolute	Not accepted - see comment to page 23, line 630

Page	Line	MAH	Comment	Reply from author
			certainty about zero heterogeneity (fixed effects model) and high uncertainty regarding heterogeneity (random effects model with vague prior distribution). **Propose adding the following text:** Roche conducted a random effects analysis for the sensitivity analysis including PROFILE 1029 only. It has to be noted that there were only two studies for the contrast crizotinib vs chemotherapy and one study for all other contrasts. Roche used a vague prior for the between-studies standard deviation in the random effects models, assuming study heterogeneity has the same effect across all comparisons. There are insufficient data to relax this assumption. The vague prior seems appropriate given the lack of data. While a more informative prior could result in smaller 95% credible intervals this would imply more precision than can be justified by the data.	
82	2012	Roche	**Current text:** "Another aspect that needs to be considered when one is discussing OS benefit it is important to consider the follow-up therapy options available for patients. Clinicians will have three first-line options to choose from (alectinib, crizotinib and ceritinib), and it is hard to predict what the optimal treatment sequence will be. Therefore it is hard to predict long-term survival outcomes." Comment: The foundation of the OS benefit discussed in this submission, is the ALEX trial. The purpose of the ALEX trial was to test whether Alectinb is a better treatment than Crizotinb. The data is still immature since as a significant proportion of patients are still alive. However, there is a merit to try and extrapolate the full potenital OS benefit within this trial setting. However, taking the discussion beyond the trial objective can only be of a speculative nature and of little value in comparison to the randomised evidence provided.	Noted
83	2036	Roche	**Please change** the following sentence **Current text:** "Thereafter the MAH calculated the hazard ratio (HR) between treatment arms with the total duration (for the crizotinib arm, time to first dose of alectinib positive multiplied observed time until censoring or death, and for the alectinib arm, time to event without any adjustments)" to the new sentence **Proposed text:** "Thereafter the MAH calculated the hazard ratio (HR) between treatment	Accepted

Page	Line	MAH	Comment	Reply from author
			arms with the total duration (for the crizotinib arm, time to first dose of alectinib plus the multiplied observed time from first dose of alectinib until censoring or death, and for the alectinib arm, time to event without any adjustments)."	
106	2135	Roche	Table 7 - Roche suggests adding a description of the Profile 1029 study similar to the ASCEND-4 and PROFILE 1014 study.	Not accepted since the results from this study are not included in the base case
105	2143	Roche	Table A12 - In results section, **please correct** OR to ORR for ASCEND-4 trial. **Please consider adding:** the table is missing other endpoints including: DOR, DCR, time to response (IRC or INV), C-ORR, C-DCR, C-DOR, C-CBR, PROs, safety,	Partly accepted ORR corrected The tables are taken from EPARs
111	2150	Roche	Table 9: **Please change formatting** from portrait to landscape and widen the final column to improve readability	Accepted
144	2204	Roche	Table A13. Profile 1014 allocation concealment should be **changed** from 'Low' to 'Unclear risk of bias' since methods of concealment were not described.	Not accepted; a centralized permuted block design is described, allowing to set the risk of bias "low"
144	2204	Roche	Table A13. **Please add** PROFILE 1029 to the Cochrane Risk of Bias Table. This data was provided in the MAH dossier.	Partly accepted: PROFILE 1029 was added to the risk of bias table on study level but since it is not fully published it seemed not feasible to include also the risk of bias table on outcome level
144	2204	Roche	Table A13. ASCEND-4 Selective Reporting should be **changed** from 'Low' to 'High Risk' due to grouping Serious Adverse Event data were not reported. Full paper does indicate that serious adverse drug reactions were similar in both treatment groups but no data are given.	Not accepted; the reported endpoints are according to those mentioned in the project plan of ASCEND-4 and are reported in ClinicalTrials.gov register. Therefore omission of less favourable outcomes is unlikely.
145	2211	Roche	Roche noticed changes had been made to the Table A14. Risk of Bias by outcome and **propose that the following changes be made:** PROFILE 1029 be **added back** into the table as it is part of the evidence base review and	Not accepted; the first two comments have already been addressed above; PRO of ASCEND-4 will not be added because only those outcomes which had been reported in

Page	Line	MAH	Comment	Reply from author
			sensitivity analysis. AE - ASCEND-4: Selective outcome reporting unlikely: Should be **changed** from Low to High since grouped Serious Adverse Event data were not reported. Full paper does indicate that serious adverse drug reactions were similar in both treatment groups but no data are given. Patient Reported Outcomes - ASCEND-4 Trial should be added to the list for their PRO outcome to be evaluated.	the NMA were included in the GRADE table for studies other than ALEX
151	2236	Roche	Appendix 3: Table A17 Row - Europe/Column -Type of Approval (full, conditional, exceptional): **Please update** from Conditional to Full. **Current text:** Conditional **Proposed text:** Full	Accepted
151	2236	Roche	Appendix 3: Table A17 Row - Europe/Column -Verbatim wording of the (anticipated) indication(s): Please remove "Proposed indication" and keep the text "Alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC" **Current text:** Proposed indication: Alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC **Proposed text:** Alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC	Accepted
151	2236	Roche	Appendix 3: Table A17 Row - Europe/Column -Date of approval: **Please add** the additional date of approval for Alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC as Full approval achieved on December 21, 2017. **Proposed text:** 21 December 2017	Accepted
151	2236	Roche	Appendix 3: Table A17 Row - United States/Column -Type of Approval (full, conditional, exceptional): **Please add** Full approval **Proposed text:** Full	Accepted
151	2236	Roche	Appendix 3: Table A17 Row - United States/Column -Verbatim wording of the (anticipated) indication(s): Please remove "Proposed indication" and keep the text "Alectinib as	Accepted

Page	Line	MAH	Comment	Reply from author
			monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC" **Current text:** Proposed indication: Alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC **Proposed text:** Alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC	
151	2236	Roche	Appendix 3: Table A17 Row - United States/Column -Date of approval: **Please add** the additional date of approval for Alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC as Full approval achieved on 3 November, 2017. **Proposed text:** 21 December 2017	Accepted
156	2241	Roche	Appendix 3: Table A18 Row - Austria –Hauptverband der österreichischen Sozialversicherungsträger (HVB/Column -Reimbursement status: **Please update** from Reimbursement status "no" to "ongoing" **Current text:** No **Proposed text:** Ongoing	Accepted
156	2241	Roche	Appendix 3: Table A18 Row - Belgium –Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV-INAMI)/Column -Reimbursement status: **Please update** from Reimbursement status "no" to "ongoing" **Current text:** No **Proposed text:** Ongoing	Accepted
156	2241	Roche	Appendix 3: Table A18 Row - Bulgaria National Council for Price and Reimbursement of Medicinal Product/Column -Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "Preparing submission" **Current text:** Not yet submitted **Proposed text:** Preparing submission	Accepted
156	2241	Roche	Appendix 3: Table A18 Row - Denmark - Danish Medicines Council (Laegemiddelstyrelsen)/Column -Reimbursement status: **Please update** from Reimbursement status "Yes" to "Reimbursed" **Current text:** Yes **Proposed text:** Reimbursed	Accepted
156	2241	Roche	Appendix 3: Table A18 Row -England – National Institute for Health and Care Excellence, NICE)/Column -Reimbursement status: **Please update** from "not yet submitted" to "Ongoing" **Current text:** Not yet Submitted **Proposed text:** Ongoing	Accepted
156	2241	Roche	Appendix 3: Table A18 Row -Estonia – Estonian Health Insurance Fund (Eesti	Accepted

Page	Line	MAH	Comment	Reply from author
			Haigekassa)/Column -Reimbursement status: **Please update** from "not yet submitted" to "Ongoing" **Current text:** Not yet Submitted **Proposed text:** Ongoing	
157	2241	Roche	Appendix 3: Table A18 Row -Germany - Gemeinsamer Bundesausschuss (G BA)/Column - Summary of (reimbursement) recommendations and restrictions: **Propose to add**: "Full reimbursement while the assessment is ongoing" in the column - Summary of (reimbursement) recommendations and restrictions	Accepted
157	2241	Roche	Appendix 3: Table A18 Row - Greece – National Organisation for Medicines/Column - Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "ongoing" **Current text:** Not yet submitted **Proposed text:** Ongoing	Accepted
157	2241	Roche	Appendix 3: Table A18 Row - Hungary – National Health Insurance Fund of Hungary (OEP)/Column -Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "ongoing" **Current text:** Not yet submitted **Proposed text:** Ongoing	Accepted
157	2241	Roche	Appendix 3: Table A18 Row - Latvia - State Agency of Medicines (SAM)/Column - Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "Preparing submission" **Current text:** Not yet submitted **Proposed text:** Preparing submission	Accepted
157	2241	Roche	Appendix 3: Table A18 Row - Lithuania - Compulsory Health Insurance Fund (CHIF)/Column -Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "Preparing submission" **Current text:** Not yet submitted **Proposed text:** Preparing submission	Accepted
157	2241	Roche	Appendix 3: Table A18 Row - Luxemburg - Ministère de la Sécurité Sociale/Column - Reimbursement status: **Please update** from Reimbursement status "Yes Level of reimbursement: 100%" to "Reimbursed" **Current text:** Yes Level of reimbursement: 100% **Proposed text:** Reimbursed	Accepted
157	2241	Roche	Appendix 3: Table A18 Row - Netherlands – ZorgInstituut/Column -Reimbursement status: **Please update** from Reimbursement status "Yes Level of reimbursement: 100%" to "Reimbursed" **Current text:** Yes Level of reimbursement: 100% **Proposed text:**	Accepted

Page	Line	MAH	Comment	Reply from author
			Reimbursed	
157	2241	Roche	Appendix 3: Table A18 Row - Norway – Norwegian Medicines Agency/Column - Reimbursement status: **Please update** from Reimbursement status "Submission ongoing for first-line indication and crizotinib-failure indication" to "ongoing" **Current text:** Submission ongoing for first-line indication and crizotinib-failure indication **Proposed text:** Ongoing	Accepted
157	2241	Roche	Appendix 3: Table A18 Row - Poland – Ministry of Health (Ministerstwo Zdrowia, MZ)/Column -Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "ongoing" **Current text:** Not yet submitted **Proposed text:** Ongoing	Accepted
158	2241	Roche	Appendix 3: Table A18 Row - Scotland (Scottish Medicines Consortium, SMC)/Column - Summary of reasons for recommendations, rejections and restrictions: Please remove that "The marketing authorisation holder has not made a submission to SMC regarding this product in this indication. As a result SMC cannot recommend its use within NHS Scotland" as it is ongoing **Please remove text:** The marketing authorisation holder has not made a submission to SMC regarding this product in this indication. As a result SMC cannot recommend its use within NHS Scotland	Accepted
158	2241	Roche	Appendix 3: Table A18 Row - Slovakia - Ministry of Health (Ministervo zdravotníctva)/Column -Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "Preparing submission" **Current text:** Not yet submitted **Proposed text:** Preparing submission	Accepted
158	2241	Roche	Appendix 3: Table A18 Row - Slovenia - Health Insurance Institute of Slovenia (Zavod za zdravstveno zavarovanje Slovenije, ZZZS)/Column -Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "ongoing" **Current text:** Not yet submitted **Proposed text:** Ongoing	Accepted
158	2241	Roche	Appendix 3: Table A18 Row - Sweden - The Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV)	Accepted

Page	Line	MAH	Comment	Reply from author
			/Column -Reimbursement status: **Please update** from Reimbursement status "Yes" to "Reimbursed" **Current text:** Yes **Proposed text:** Reimbursed	
158	2241	Roche	Appendix 3: Table A18 Row -Sweden - The Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV)/Column - Summary of (reimbursement) recommendations and restrictions: **Please remove text:** Reimbursement restricted to approved indication	Accepted Reimbursement restricted to adult patients with ALK-positive advanced NSCLC previously treated with crizotinib
158	2241	Roche	Appendix 3: Table A18 Row - Switzerland - Federal Office of public health (Bundesamt für Gesundheit, BAG)/Column -Reimbursement status: **Please update** from Reimbursement status "Yes Level of reimbursement: 100%" to "Reimbursed" **Current text:** Yes Level of reimbursement: 100% **Proposed text:** Reimbursed	Accepted
158	2241	Roche	Appendix 3: Table A18 Row - Wales – All Wales Medicines Strategy Group, AWMSG))/Column -Reimbursement status: **Please update** from Reimbursement status "Not yet submitted" to "ongoing" **Current text:** Not yet submitted **Proposed text:** Ongoing	Accepted
158	2241	Roche	Appendix 3: Table A18 Row - Wales – All Wales Medicines Strategy Group, AWMSG))/Column - Summary of (reimbursement) recommendations and restrictions: **Please remove text:** In the absence of a submission from the holder of the marketing authorisation, alectinib (Alecensa®) cannot be endorsed for use within NHS Wales	Accepted
164	2302 corrected to+C26 2297	Roche	The higher frequency of CNS mets at baseline observed in the ALEX study compared with PROFILE 1014 and ASCEND-4 may be due to the requirement for all patients to have CNS imaging at baseline in the ALEX study. We suggest to mention this information. **Current Text**: Differences in the proportion of patients with CNS metastasis, an important prognostic factor, also exist between the studies included in the NMA. **Proposed text**: There were higher frequencies in the ALEX study (approximately 40%) compared with less than 30% in PROFILE 1014 and approximately 30% in ASCEND-4. The higher frequency of CNS metastases at baseline observed in the ALEX study may be explained by the requirement for all patients to have CNS imaging at baseline.	Accepted

Page	Line	MAH	Comment	Reply from author
173	2637		**Please update** reference to SmPC **Current text**: 4. EMA. SmPC Alecensa 2017 2017. Available from: 2367 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/0023684164/human_med_002068.jsp&mid=WC0b01ac058001d124. **Proposed text**: 4. EMA. SmPC Alecensa Jan 2018. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004164/WC500225707.pdf	Accepted