National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ceritinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer [ID729]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by the end of **21 August 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Confidentiality highlighting from page 12 – page 30

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The confidentiality status of the following pieces of data on these pages can change to academic in confidence: [redacted] The following pieces of information on these pages can have their confidentiality highlighting removed entirely: • 46.0% (95% CI 38.2, 54.0) • [redacted] – see comment on alteration in "Description of proposed amendment" • 1.6 months • Q3 2015	Amendment of confidentiality highlighting as described. For the data point [redacted], this should be altered to read 8.8 [6.0, 13.1] before removing the confidentiality highlighting	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted. The data change appears to be simply a change in rounding, so the ERG is unclear why this would need to change.

Issue 2 Lack of clarity regarding patient population of Gainor study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2 Summary of clinical effectiveness evidence submitted by the Company (page 11) states that "A further study, which is a retrospective review of participants who were included in one centre of the ASCEND-1 and -2 studies was also identified in	We would suggest amending the text to state "a retrospective review of participants who were included in the ASCEND-1 study".	This would clarify the patient population included in the Gainor et al. study.	Text changed to: a retrospective review of participants who were included in one centre of the ASCEND-1 study".

the CS." On the assumption that the reference in question is the Gainor et al. 2015 study, we would suggest rewording to clarify that the patients were included in the ASCEND-1 study, not the ASCEND-2 study.			

Issue 3 Clarification over inclusion of patients failing to respond to crizotinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 of the ERG report notes that it is unclear if the estimates of the patient population account for patients failing to respond to crizotinib.	To clarify, these patients are not accounted for in the calculation. This statement may therefore be amended.	Clarification provided for the ERG.	A helpful clarification, but not a factual inaccuracy, so no change to the ERG report is required.

Issue 4 Information on outcomes from the EMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 20 of the ERG report, it was noted that the CS provides little information on outcomes from the EMA.	Please note that the details on outcomes from the EMA are available in the European Public Assessment Report, which has been provided along with this response.	To provide the relevant information that was felt to be missing from the CS.	Not a factual inaccuracy; no change to ERG report required

Issue 5 Ambiguous reporting of quality assessment responses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.4. Quality assessment (Page 26) of ERG report states that 'blinding of care providers, participant and outcome assessors', 'selective reporting of outcomes' and 'intention to treat analysis' "were all rated positively by the CS". In this case the term "positively" is ambiguous and does not clearly represent the responses report in the CS. In both ASCEND-2 and ASCEND-1 the CS submission states "no" in response to "is there any evidence to suggest that the authors measured more outcomes than they reported?"	We would suggest amending the text to state "were all rated favourably by the CS".	This would avoid any ambiguity with respect to the selective reporting of outcomes in the ASCEND-2 and ASCEND-1 trials.	Not a factual inaccuracy; no change to ERG report required

Issue 6 Ambiguous reporting of eligibility criteria for the clinical systematic review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.2.3. Outcomes (page 25) states that "The CS sets out in its eligibility criteria… to include studies that included at least one of the outcomes of response rate (ORR)". We would suggest amending the abbreviation ORR to RR in line with the criteria specified in the CS.	We would suggest amending the text to state "outcomes of response rate (RR)".	This would represent a more direct reporting of the inclusion criteria of the systematic review.	The suggested wording is a slight improvement, but we do not believe the initial sentence is unclear or represents an error.

Issue 7 Factual inaccuracy in description of the Gainor study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2. Critique of trials of the technology of interest, their analysis and interpretation (page 28) states that "a retrospective analysis (Gainor et al., 2015) from which the majority of participants had been enrolled in the ASCEND-1 or ASCEND-2 studies)".	Suggest amending text to state "from which the majority of participants had been enrolled in the ASCEND-1 study."	No patients were enrolled from the ASCEND-2 study in the Gainor et al. study, hence text should be amended for factual accuracy.	Text amended as suggested

Issue 8 Lack of clarity in description of receipt of ceritinib dosing after prior ALK inhibitors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2 Critique of trials of the technology of interest, their analysis and interpretation (page 29) states that "the first dose of ceritinib was expected to be within 60 days since the last dose of the initial ALK inhibitor". The term "initial" implies the first ALK inhibitor that was ever received by the patient, rather than "prior" which is specific to the ALK inhibitor received before the study drug.	We would suggest amending the text to state "the first dose of ceritinib was expected to be within 60 days since the last dose of the prior ALK inhibitor", in line with the wording in the CS submission and CSR.	The error should be amended for clarity.	Text amended as suggested

Issue 9 Lack of clarity in wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2. Critique of trials of the technology of interest, their analysis and interpretation (page 29) states that "Prior treatment with a prior ALK inhibitor was required, and the first dose of ceritinib was expected to be within 60 days since the last dose of the initial ALK inhibitor. Inclusion criteria for the subset of ASCEND-1 which is of relevance to the decision problem NSCLC patients with advanced tumours who were required to have at least one prior regimen including crizotinib and have received ceritinib at a dose of 750mg." The wording of these two sentences is currently unclear and we suggest rewording for clarity.	We would suggest that these two sentences are reworded to clarify their intended meaning. One possibility is to amend the text to state "inclusion criteria for the subset of ASCEND-1 which is of relevance to the decision problem includes prior treatment with a prior ALK inhibitor, and the first dose of ceritinib expected to be within 60 days since the last dose of the prior ALK inhibitor". (Please see comment above)	The text should be amended for clarity.	Text amended as suggested

Issue 10 Small error in reported percentage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2 Critique of trials of the technology of interest, their analysis and interpretation (page 30) states that "56.3% of participants had received 3rd line therapy or beyond". The percentage should be 56.4% (92/163).	The percentage should be amended to 56.4%.	The error should be amended for accuracy.	Text amended as suggested

Issue 11 Error in reporting of baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 3: Baseline characteristics of the ceritinib studies (page 31): ECOG – Performance status grade at baseline, N (%), ASCEND-1 ERG report incorrectly states 0=383 (23.3).	Data correction to 0=38 (23.3).	The error should be amended for accuracy.	Text amended as suggested

Issue 12 Small error in reported percentage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 3: Baseline characteristics of the ceritinib studies (page 31): Number of prior regimens (for advanced / metastatic disease), ASCEND-2 ERG report states >3=29 (20.6), instead of 20.7.	Suggest percentage amended to 20.7%.	The error should be amended for accuracy.	Text amended as suggested

Issue 13 Confidentiality highlighting of baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 3: Baseline characteristics of the ceritinib studies (page 31): data highlighting is not consistent with the revised CS. For example, disease	Highlighted data in this table should be amended in line with the revised submission provided to NICE.	The error should be amended for consistency with the revised submission.	Changes in CIC status noted.

burden based on BIRC assessment has been highlighted as commercial in confidence, in line with the original CS submission, however, this has subsequently been revised and is classified as academic in confidence.			

Issue 14 Page number inconsistencies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the ERG report there are page number inconsistencies when referencing the CS. We appreciate there has been discrepancies between page numbers when the documents have been viewed, and it is likely a number of such errors are a consequence of this.	For example: 1. Section 4.1.2. Inclusion criteria (ERG report page 24) states that the inclusion criteria for the systematic review were clearly stated on page 41-2 of the CS. However, these criteria are shown on page 39-40 of the CS. 2. Section 4.1.3. Critique of data extraction (ERG report page 26) states that statistical analyses are presented on pages 64-66, however, this is presented on page 64 only of the CS.	The error should be amended for accuracy.	We agree there are a small number of inaccurate page number references, but we don't believe they lead to a lack of clarity at any point.

Issue 15 Ambiguous reporting of Guerin study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.1. Generalisability of the study populations to the UK population (page 37) states that "A recent epidemiological study of patients in routine clinical settings…found the median age on diagnosis of ALK+ NSCLC was 67 years". The Guerin et al. study states "Patient's median age was 67 years upon NSCLC diagnosis", and does not refer to ALK diagnosis at this stage. Therefore we suggest amending the text to make clear that the diagnosis referred to is for NSCLC not necessarily ALK+.	We would suggest that the texts is amended to "found the median age on diagnosis of NSCLC was 67 years".	The description should be amended in line with the original reference.	Text amended as suggested (although ERG notes that the Guerin et al study only included those with ALK+ and therefore the age of participants at ALK+ diagnosis is likely to be higher than 67).

Issue 16 Incorrect trial identification in discussion on outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.4: Critique of the indirect comparison and/or multiple treatment comparison (page 39) states "less favourable …DCR (for ASCEND-1)". This should read ASCEND-2 instead of	Suggest text amended to "less favourable...(DCR) (for ASCEND-2)".	The error should be amended for accuracy.	Text amended as suggested

ASCEND-1.			

Issue 17 Amendment to description of confidentiality status

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.4: Critique of the indirect comparison and/or multiple treatment comparison (page 39) states "it should be noted that the BIRC assessments for ORR, DOR, and PFS in ASCEND-1 and TTR in ASCEND-2 are identified as CiC", which is no longer the case following revision of the CS.	Suggest sentence removed or replaced by "it should be noted that the BIRC assessment of TTR in ASCEND-2 is identified as AiC".	The error should be amended for consistency with the revised submission.	Changes in CIC status noted.

Issue 18 Confidentiality highlighting amendments to align with revised submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On **page 40** of the report, the following data can have their confidentiality status altered as described in the next column: 1. ORR for ASCEND-1 via BIRC of 46.0% (95% CI	1. The highlighting of this data can be removed. 2. This can be altered to 8.8 (6.0, 13.1) and, once this change is made, the confidentiality highlighting can be removed, in line with the revised submission. 3. The highlighting of this should be changed to	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted. The data change appears to be simply a change in rounding, so the ERG is unclear why this would need to

38.2, 54.0) 2. DOR for ASCEND-1 via BIRC of [redacted]. 3. Median TTR from ASCEND-2 via BIRC of [redacted]	academic in confidence.		change.
The confidentiality status of some data on page 41 can be altered: 1. 59 [redacted] 2. 100 (61.3%) 3. [redacted] 4. [redacted] 5. 67.2 (95% CI 58.9, 74.1).	1. These can be changed to academic in confidence, and indeed the highlighting can be removed entirely from the number 59 (though not from the accompanying [redacted]) in line with the revised submission. 2. This can have the highlighting removed entirely 3. This can be changed to 16.7 (95% CI 14.8, NE). If this change is made, the confidentiality highlighting can be removed 4. This can be changed to academic in confidence 5. This can have the highlighting removed entirely	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted. The data change appears to be simply a change in rounding, so the ERG is unclear why this would need to change.
The confidentiality status of some data on page 42 can be altered: 1. 59 [redacted] 2. 100 (61.3%) 3. [redacted]	1. These can be changed to academic in confidence, and indeed the highlighting can be removed entirely from the number 59 (though not from the accompanying [redacted], in line with the revised submission. 2. This can have the highlighting removed entirely	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted. The data change appears to be simply a change in rounding, so the ERG is unclear why this would need to

4. [redacted] 5. [redacted] 6. 67.2 (58.9, 74.1) 7. [redacted]	3. This can be changed to 16.7 (95% CI 14.8, NE). If this change is made, the confidentiality highlighting can be removed 4. This can be changed to academic in confidence 5. This can be changed to academic in confidence 6. This can have the highlighting removed entirely 7. This can be changed to academic in confidence		change.
The confidentiality status of some data on page 43 can be altered: 1. [redacted] 2. 93 [redacted] 3. [redacted] 4. [redacted] 5. [redacted] 6. [redacted]	1. This can be changed to 7.0 [5.7, 8.6]. If this change is made, the confidentiality highlighting can be removed. The word "similar" therefore will no longer need to be marked as confidential 2. The value 93 no longer needs to be marked as confidential, though the [redacted] needs to remain as academic in confidence 3. This can be changed to academic in confidence 4. These can be changed to academic in confidence 5. This can be changed to academic in confidence 6. These can be changed to academic in confidence	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted. The data change appears to be simply a change in rounding, so the ERG is unclear why this would need to change.
The confidentiality status of some data on page 44 can be	1. This can have the highlighting removed	The confidentiality status has been revised in light of the confidentiality	Changes in CIC status

altered: 1. 75 (46.0%) (38.2, 54.0) 2. [redacted]	entirely 2. These can be changed to academic in confidence	queries from NICE on the main submission.	noted.
The confidentiality status of some data on page 45 can be altered: 1. [redacted] 2. [redacted] 3. [redacted] 4. [redacted]	1. This can be changed to academic in confidence 2. This can be changed to 8.8 months (95% CI 6.0, 13.1). If this change is made, the confidentiality highlighting can be removed 3. This can be changed to academic in confidence 4. This can be changed to academic in confidence	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted.
The confidentiality status of some data on page 46 can be altered: 1. Table 12 of the ERG report 2. [redacted]	1. All confidentiality highlighting in Table 12 of the ERG report can be altered to academic in confidence. In addition, the value of [redacted] can be changed to 8.8 (6.0, 13.1) – if this change is made then the confidentiality highlighting can be removed from this data point 2. These can be changed to academic in confidence	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted.

Issue 19 Unclear statement on page 40 regarding outcomes presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40 of the ERG report makes the following statement: “The CS	We suggest this is reworded to “The CS presents the outcomes of ORR, DCR, DOR, TTR, PFS, OS and	This amendment will aid clarity of understanding of the evidence	The ERG does not believe the original

presents the outcomes of ORR, DCR, DOR, TTR, PFS, OS and adverse events as numbers, proportions, medians and 95% CIs, with the outcomes of PFS and OS for the ASCEND-1 and ASCEND–2 studies pooled." This sentence is perhaps a little misleading as it implies that OS and PFS outcomes were not presented separately for each trial.	adverse events as numbers, proportions, medians and 95% Cis. The outcomes of PFS and OS are presented for the ASCEND-1 and ASCEND–2 studies individually and for these two studies pooled."	presented.	statements, combined with the data presented, are likely to lead to misinterpretations.

Issue 20 Incorrect description of RECIST criteria on page 43

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 43, the description of the differences in RECIST v1.0 and RECIST v1.1 contains some errors.	The ERG report states that for RECIST v1.0 the minimum measurable lesion size is 20mm for spiral computed tomography; this is incorrect as the minimum measurable lesion size under RECIST v1.0 is ≥10mm with for spiral computed tomography and ≥20mm for conventional (non-spiral computed tomography) techniques. For RECIST v1.1 the minimum measurable lesion size is 10mm via CT scan but 20mm via chest x-ray.	The RECIST criteria should be reported accurately for anyone attempting to understand the potential impact of differences in RECIST criteria between the ASCEND-1 and ASCEND-2 trials.	Text amended as suggested

Issue 21 Small correction required to description of adverse event data presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47, the ERG report states that adverse events presented in Table 32 of the company submission included "….events leading to dose adjustments". The correct definition of these adverse events is "adverse events leading to dose adjustments or interruptions"	The wording should be amended to "…events leading to dose adjustments or interruptions"	To ensure accurate classification of adverse events	A useful clarification, but not one likely to lead to any misinterpretations.

Issue 22 Incorrect table number referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47, the ERG report states that "…a summary of grade 3/4 adverse events suspected to be drug related is presented in CS Table 86"	Change wording to "…a summary of grade 3/4 adverse events suspected to be drug related is presented in CS Table 35"	Incorrect table reference has been reported.	Text amended as suggested

The summary of grade 3/4 adverse events suspected to be drug related for ASCEND-2 study is presented in Table 35 of the submission.			

Issue 23 Revision to description of confidentiality status on page 47

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47, the ERG report states that "…CS presents data from the ASCEND-3 study (CS Appendix 5) and the treatment naïve subgroup of ASCEND-1 in Appendix 6. Much of these data are marked CIC". In light of the revision to the confidentiality status of some information in the submission, the information referred to here is now AiC.	Change wording to ""…CS presents data from the ASCEND-3 study (CS Appendix 5) and the treatment naïve subgroup of ASCEND-1 in Appendix 6. Much of these data are marked **AIC**.	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted.

Issue 24 Revision to confidentiality status of data in Table 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The confidentiality status of the information in Table 13 (page 47) of the ERG report can be adjusted. This information is now	Alter highlighting of data in Table 13 from commercial in confidence highlighting to academic in confidence highlighting	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted.

academic in confidence.			

Issue 25 Inaccurate reporting in the footnotes of Table 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The footnotes of Table 13 state that: [a] All deaths including those > 30 days after the last dose of study drug. [b] Deaths occurring more than 30 days after the last dose of study drug are not included. Whilst this description is accurate for ASCEND-2 study, for the ASCEND-1 study a time frame of 28 days (rather than 30) was used, as reported in our original submission.	The footnotes should be amended to reflect the differing reporting time frames for ASCEND-1 versus ASCEND-2.	The current reporting is factually inaccurate.	Text amended as suggested

Issue 26 Amendment to confidentiality highlighting in Table 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The pooled adverse event data in Table 14 (page 48) is currently marked as commercial in	Alter highlighting of data in Table 14 from commercial in confidence highlighting to	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main	Changes in CIC status noted.

confidence. In light of the revision to the confidentiality status of some information in the submission, the information referred to here is now AiC.	academic in confidence highlighting	submission.	

Issue 27 Amendment to data reported on Page 51

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.5.2. Brain metastases and treatment with ceritinib and crizotinib (page 51) states that "33 were considered through BIRC assessment to have confirmed active target lesions at baseline". However, the Mok et al. poster states "By BIRC, 33 patients had brain lesions selected as target lesions at baseline" and does not specify that these are active target lesions. Therefore, we would suggest amending in line with the original reference.	We would suggest amending the text to state "33 were considered through BIRC assessment to have confirmed target lesions at baseline".	The data shown should be amended in line with the original reference.	Text amended as suggested

Issue 28 Slight amendment to reported percentage of patients with brain metastases at baseline

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 of the ERG report states that in the ASCEND-2	Amend percentage to 71.4%, or 71%	The percentage report should be	Text amended as suggested

study, 72% (n=100) had brain metastases at baseline. This percentage should read 71.4% or 71%.		correct.	

Issue 29 Unclear sentence on Page 52

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 of the ERG report states "As noted above, the inclusion criteria in the PROFILE studies (population in Ou et al., 20141) were excluded in they had symptomatic brain lesions." This sentence does not read very clearly and we suggest it is reworded.	We suggest this sentence is reworded, along the lines of: "As noted above, the inclusion criteria in the PROFILE studies (population in Ou et al., 20141) **dictated that patients** were excluded in they had symptomatic brain lesions."	Lack of clarity in this sentence precludes full understanding of the relevant eligibility criteria.	Text amended as suggested

Issue 30 Lack of preciseness in reporting the inclusion criteria of PROFILE 1005 and 1001 with regards to brain metastases

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 of the ERG report states "An analysis of the patients with brain metastases in the PROFILE 1005 and 1007[23] studies with crizotinib showed…. The intercranial DCR for the two groups was 56% and 62% respectively. As noted above, the inclusion criteria in the PROFILE	We suggest that "As noted above, the inclusion criteria in the PROFILE studies (population in Ou et al. 2014[1])…" is altered to "As noted above, the inclusion criteria in the PROFILE 1001 and PROFILE 1005 studies (population in Ou et al. 2014[1]).	Lack of preciseness may lead to false understanding of the populations in the Ou et al. study and the nature of the eligibility criteria regarding brain metastases.	Text amended to: As noted above, the inclusion criteria in the PROFILE 1001 and PROFILE 1005 studies (population in Ou et al. 2014) dictated that patients were excluded if they had symptomatic brain metastases.

studies (population in Ou et al., 2014[1]) were excluded in they had symptomatic brain lesions." The Ou et al. 2014 study considered patients from PROFILE **1001** and 1005. We believe that the way the ERG report is currently phrased might lead a reader to assume that the Ou *et al.* 2014 study is based on PROFILE 1005 and 1007 and suggest that this is clarified. Furthermore, the description of the exclusion criteria of the PROFILE studies as "symptomatic brain lesions" is not aligned to the wording of the actual eligibility criteria of these trials. For avoidance of doubt we believe that this should be adjusted.	Furthermore, we suggest that "were excluded in they had symptomatic brain lesions" is reworded to "were excluded if they had brain metastases that were not treated and neurologically stable". This comment should be taken alongside our comment in Issue 21.		

Issue 31 Confidentiality status of data on page 53

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The confidentiality status of data on page 53 can be altered: 1. [redacted]	2. This can be changed to be marked as academic in confidence	The confidentiality status has been revised in light of the confidentiality queries from NICE on the main submission.	Changes in CIC status noted.

Issue 32 Typographical error in Section 5.2.4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There is a typo in Section 5.2.4 relating to interventions and comparators (page 58). Sentence reads: "Ceritinib treatment is assumed to continue until disease progression, with treatment terminated immediately terminated until disease progression."	Sentence should read along the lines of: "Ceritinib treatment is assumed to continue until disease progression, with treatment terminated immediately **on disease progression**."	Correction required to clarify meaning of statement	Text amended as suggested

Issue 33 Error in reporting of AIC and BIC criteria for progression-free survival models

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There is an error in the reported values in Table 21 of the ERG report. Instead of reporting PFS for ceritinib, the PFS for BSC has been duplicated and incorrectly labelled.	The correct table should be reported as follows:	Incorrect data has been presented.	Table amended as suggested

Parametric model	PFS for ceritinib		PFS for BSC	
	AIC	BIC	AIC	BIC
Exponential	757.66	761.38	605.60	609.08
Weibull	751.57	759.02	585.21	592.17
Gompertz	758.46	765.91	607.35	614.31
Log-logistic	743.96	751.42	530.50	537.46
Log-normal	749.78	757.23	551.92	558.88

Issue 34 Incorrect figure for KM PFS data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Figure 4 in the ERG presents the incorrect plot for KM PFS data with log-logistic parametric curves. Note: this is taken from Figure 19 in the Manufacturers submission document which, as noted by the ERG, is incorrect.	The correct plot for KM PFS data with log-logistic parametric curves is presented in Appendix 15 of the Manufacturers Submission (Figure 33). Figure 4 in the ERG report should be replaced with this figure.	Incorrect data has presented.	Figure amended as suggested

Issue 35 Incorrect reporting og incremental QALYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 34 in the ERG report is incorrect. Specifically, the column presented the Incremental QALYs has duplicated the QALY for the BSC treatment arm. Note: We acknowledge that this was an error copied over from the	The correct table should be as follows: **Health state** / **QALY ceritinib** / **QALY BSC (no active treatment)** / **Increment** / **Absolute increment** / **% absolute increment** "Progression free" survival / 0.72 / 0.16 / 0.56 / 0.56 / 67.5%	Incorrect data has been presented.	Table amended as suggested

Manufacturer's Submission document.	"Progressed disease" survival	0.36	0.09	0.27	0.27	32.5%		
	Total	1.08	0.25	0.83	0.83	100.0%		