NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

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

Dear [redacted]

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 16 June 2015 by Novartis Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **16 July 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Boglarka Mikudina, Technical Lead (Boglarka.Mikudina@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
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Encl. checklist for in confidence information

Section A: Literature searching, inclusion criteria, and study selection

A1. Priority Question.

Systematic review for clinical effectiveness studies:

- Please provide the full search strategy for each database that was used in the literature searches and populate the table in Appendix 3 of the company submission with the numbers of studies retrieved for each line.
- Please provide references of the 126 included randomised controlled trials, the other 147 included non-randomised controlled trials and the articles excluded at level II screening according to the PRISMA diagram (Figure 2, page 37 of the company submission).
- The eligibility criteria in Table 6 (page 35 of the company submission) suggests outcomes of adverse events and health-related quality of life were not included. If this is correct please provide references of the 238 articles excluded because of ineligible outcomes at level I screening (see PRISMA diagram, Figure 2, page 37 of the company submission).

Section B: Clarification on clinical effectiveness data

B1. Priority Question.

In Table 28, page 76 of the company submission what is the source of the data for the meta-analysis? Please provide further details of the pooling methods, including any caveats/limitations to this approach.

Please provide details / methods of the Blinded Independent Review Committee (BIRC).The company submission suggests that the BIRC was used for both progression-free survival and overall survival, however, BIRC data were not available for overall survival. Please clarify. Also, please clarify the methods used for meta-analysis of median overall survival.

B2. Priority Question.

Table 18, page 67 of the company submission notes the number of prior treatment regimens for participants in the 2 studies. Please provide details for what these prior treatments included and a breakdown of the number of patients that received each prior treatment.

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B3. Please clarify how many patients in each centre (please provide the country) took part in ASCEND-1 and ASCEND-2. Please provide data for adverse events suspected to be study drug related by “race” (categorised as Asian, Caucasian and “other”).

B4. The company submission states that the RECIST criteria have recently been updated. Please outline the differences between RECIST v1 (ASCEND-2) and RECIST v1.1 (ASCEND-1) criteria and the impact that this might have on objective response rate assessment (see page 64, Table 17 of the company submission).

B6. In the company submission, Figure 5 (page 59) and Figure 7 (page 61), the numbers and reasons for withdrawals after receiving treatment for the ASCEND 2 and ASCEND 1 studies are provided. Please provide further details on when withdrawals occurred from these 2 studies if possible. Please also provide details of how withdrawals from the study are accounted for in the analyses.

B7. On page 72 of the company submission the results for objective response rate from the 13th August cut-off in ASCEND 2 are stated to be 'consistent with those seen at the 26th February cut off'' – please provide the 26th February cut off data.

B8. On page 86 of the company submission it is stated that the adverse event results were 'suspected to be study drug related'. Please clarify how this was defined.

B9. Please provide numbers of patients in ASCEND1 and 2 who received other treatments post progression and details of these treatments, if possible.

B10. The company submission states that some patients don't tolerate crizotinib. Please provide the definition used for not tolerating crizotinib and the numbers of participants in the ASCEND studies who did not tolerate crizotinib.

B11. The adverse events for ASCEND 3 and the treatment naive subgroup of ASCEND 1 are presented in the company submission in Appendices 5 and 6, respectively. Please provide a pooled analysis of the treatment emergent adverse events for ceritinib from all studies (including from other ongoing trials such as ASCEND 4 & 5 if available).

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Section C: Clarification on cost-effectiveness data

Literature searches, inclusion criteria, and study selection:

C1. Priority Questions.

Systematic review for economic evaluations:

- Please provide the full search strategy for each database that was used in the literature searches and also provide the numbers of studies retrieved for each line (Appendix 9 of the company submission).
- Please provide the references for the 16 studies excluded at full text review and the other 82 studies selected for extraction (Figure 15, page 87).

Systematic review for health-related quality of life studies:

- Please provide a search strategy for each database with the numbers of studies retrieved for each line (Appendix 10 of the company submission).
- Please provide the references for the 148 studies excluded along with reasons for exclusion of each study at level II (Figure 22, page 103 of the company submission).

Systematic review for costs and resource use – update of systematic review for crizotinib NICE submission:

- Please provide a search strategy for each database with numbers of studies retrieved for each line (Appendix 12 of the company submission).
- The company present a list and details of 18 studies meeting eligibility criteria. Please provide the references for the 14 articles excluded at full text screening (Figure 23, page 109 of the company submission).

C2. Priority Question.

Given that no progression-free survival data were available for ALK positive patients, please clarify why a decision was made to use data from EGFR positive patients, rather than any other NSCLC subgroup?

C3. Priority Question.

Please explain why an adjustment has not been made to account for the higher utility values one would expect for best supportive care, given its lower adverse event profile.

It is stated that adverse event disutilities were not applied to the pre-progressive health state in the ceritinib arm of the model, as these should already have been captured in the utility data collected in the trial. However, the same utility values are used for the best supportive

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care arm, indicating that adverse event disutilities have also been applied here. We consider that this may be inappropriate since elsewhere no adverse events resulting from best supportive care are assumed. Please clarify whether the best supportive care arm includes disutility from treatment and, if so, justify why this approach was taken.

C4. Priority Question.

It is recognised that an indirect comparison could not be made between ceritinib and best supportive care (after crizotinib). However, please clarify why the comparison presented was not adjusted for baseline characteristics that may affect overall survival or progression free survival?

C5. Priority Question.

The company state that, in the data informing the Ou study, assignment to the various treatment options was not randomised, but rather based on prognostic factors. Patients assigned to the best supportive care group are likely therefore to be those anticipated not to benefit from further treatment. This particular best supportive care group is therefore also likely to be a group with worse prognosis, potentially leading to underestimation of the overall survival with best supportive care. Please explain how this potential bias was taken into account and methods used to adjust for it.

C6. Priority Question.

The Weibull extrapolation was chosen for best supportive care overall survival, although it was statistically the worst fitting model. On page 96 of the company submission it is briefly stated that the other extrapolations were not considered as “reliable”. Please provide reasons for why the other extrapolations were considered unreliable.

C7. Priority Question.

Please provide tables similar to Table 48 on page 96 of the company submission for overall survival projections with ceritinib, and progression-free survival projections for ceritinib and best supportive care, using each of the different possible survival functions.

C8. Only adverse events which occurred in more than 5% of trial participants were included in the model. This potentially excluded rare but serious adverse events which could have very high costs or disutilities associated with them. Are there any rare but serious events that were not captured in the model? If so, please provide an estimate of the likely impact of including them.

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C9. An assumption was made that all adverse events would occur within the first month of treatment. Please provide the trial data to support this assumption.

C10. It is stated that lab abnormalities were assumed to have a cost of 0, as they would be managed by dose adjustments. Presumably, however, there would be a cost associated with the physician's time in managing such adjustments, and potentially additional tests to monitor the adjusted doses. Please estimate the effect of including these costs in the analyses.