NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to consultees and commentators:

1. **Summary of changes made to CE ceritinib model following FAD** from Warwick Evidence

2. **Response from Novartis:**
   - Response to the Final Appraisal Determination
   - Patient access scheme submission

3. **Warwick Evidence Critique of Final Ceritinib Model Changes and PAS**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Summary of changes made to CE ceritinib model following FAD

ERG changes to base-case in CE model

The following changes have been implemented to the CE model, in line with the ERG's recommendations that the Appraisal Committee also agreed with:

- Set BSC overall survival to log-normal. (Replace "Weibull" with "Log-normal" in cell K19 of the effectiveness tab.)
- Assume 1.6 months of ceritinib treatment post-progression. (Set cell D12 in the Base case tab to yes.)
- Include costs for blood tests and outpatient visits for managing lab abnormalities. (Set cells I14, I15 and I17 in the Safety tab to £292.10
- Set utilities for both ceritinib and BSC to 0.713 (Cells E16 and E17 of the utility tab).
- To include all grade 3 and 4 AEs: cell D8 of the safety tab is set to yes then do the following additional steps:
  a) In the PSA setup tab, column G (deterministic mean) for the two sets of adverse events (ceritinib and docetaxel), change >=5% to >=0%, which should mean all adverse events are now included.
  b) Safety table, in total AE disutility for ceritinib and docetaxel, we need to take out the conditional statement for the utility set used.
  Hence, for ceritinib "=IF(utility_source_post_ALK="ASCEND-2",0,IF($D8=$AL7,IFERROR(SUMPRODUCT('PSA Setup'!F20:F27,$J$11:$J$18),0),0))" becomes just "=IF($D8=$AL7,IFERROR(SUMPRODUCT('PSA Setup'!F20:F27,$J$11:$J$18),0),0)".
  For docetaxel, "=IF(utility_source_post_ALK="ASCEND-2",0,IF($D8=$AL7,IFERROR(SUMPRODUCT('PSA Setup'!F29:F36,$J$11:$J$18),0),0))" becomes "=IF($D8=$AL7,IFERROR(SUMPRODUCT('PSA Setup'!F29:F36,$J$11:$J$18),0),0)"
  c) Finally, we need to recalculate AE costs for ceritinib, as changing the above means we are now double counting some events that were included both in the clarification response total and are now included in the model with change A. I think the simplest way to do this is to add the £145.46 from clarification response C8 (which is the total cost of all adverse events other than lab abnormalities) to that for the three lab abnormalities (£292.10 * (0.198+0.0726+0.0528)) = £94.47. Adding those together gives a total of £239.93. We therefore set ceritinib adverse event costs to £239.93

Additional changes implemented by Novartis to the CE model following the FAD:

Corrected relative dose intensity

Original dose intensity was 82.8% and this was criticised in both the FAD; the Committee noted that it would be between 82.8% and 100%. This has been amended to 90%.

- Cell K9 of the worksheet "Drug cost input", the command "=IF($I$9="Yes",82.8%,1)" has been replaced with "=IF($I$9="Yes",(82.8%+M13),1)"
- Cell M13 has "0.072" entered, bringing cell K9 to 90%.

Dispensation costs for ceritinib

The FAD noted that dispensation costs for ceritinib should be included in the basecase. These have now been incorporated in the CE model as follows:

- Worksheet "Drug Cost Input"

- Cells D54 includes the dispensing costs and put in £13.60
- This cost is then picked up by cells E39-E40, and the model will roll the change out from there.

All the above changes, alongside those also listed in table 1 of the "Patient access scheme submission template" document, generate a base case ICER of £86,364 per QALY.

Implementation of PAS

- The discount is captured in cell D13 of the "Drug cost input" worksheet.

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Mr M Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
1st Floor, 10 Spring Gardens
London SW12 2BU

4th March 2016

Dear Mr Boysen,

Re: Lung cancer (non-small-cell, anaplastic lymphoma kinase positive, previously treated) - ceritinib [ID729] – Final Appraisal Determination

Novartis appreciates that the National Institute for Health and Care Excellence (NICE) has withdrawn the Final Appraisal Determination (FAD) of the above appraisal in order to address issues in the estimates on the cost-effectiveness of ceritinib provided by the Evidence Review Group.

We would hope, however, that the Appraisal Committee could still find the document we are submitting of some use, as it captures some factual inaccuracies that we have identified in the version of the FAD that was distributed to us, aside from the issues around the ICERs presented by the ERG and then stated in the FAD by the Appraisal Committee.

For this purpose, we have provided you with a series of tabulated responses for each specific point that we raise regarding the FAD, indicating our proposed changes and the associated justification for making these.

[redacted]

I hope that our comments are of value. If you require clarification on any aspects of this, please do not hesitate to contact me.

Yours sincerely,

[redacted]

[redacted]

Issue 1 Inaccurate description and interpretation of treatment benefits from economic model (section 4.14 and 4.18) of FAD

Description of problem	Description of proposed amendment	Justification of amendment
Section 4.14 states that: "The Committee discussed the assumptions about the duration of treatment benefit. It noted that the company's model assumed that the benefits of treatment with ceritinib persist beyond the study period and after stopping treatment. […] The Committee heard from the clinical experts at the meeting that it was unlikely that ceritinib would offer a benefit beyond the end of treatment, and if it did, it would not be as long as 2 years. The Committee was not given evidence that the treatment benefit from ceritinib would continue after the end of treatment, and concluded that it was not appropriate to model any benefit beyond stopping treatment with ceritinib." Section 4.18 of the FAD states that "[…] the Committee was aware that both the company's and the ERG's base case included an indefinite treatment benefit from ceritinib after treatment with ceritinib had stopped, an assumption with which the Committee did not agree (see section 4.14)"	These statements should be removed from the FAD	These statements are not accurate as they do not correctly reflect the modelling of treatment benefits in the cost-effectiveness model submitted to NICE as part of this appraisal. Under all scenarios presented in the model (base case and scenario analysis) the clinical benefits and costs of ceritinib are always modelled on the basis of the PFS and OS curves. These, in turn, have been fitted to Kaplan-Meier (hence, trial-based) data, which have then been extrapolated over a time-horizon of 10 years. Trial-based, PFS data clearly reflect patients who are still on treatment and responding to it. At no point did the economic model submitted by Novartis, nor the ERG analyses, "*include an indefinite treatment benefit from ceritinib after treatment with ceritinib had stopped*". By definition, a PFS curve reflects patients who are on treatment and which are also considered to be progression-free (hence, receiving and responding to treatment) on the basis of the RECIST criteria. The extrapolation of the K-M curves over a time horizon of 10 years the model does not imply that the benefits from ceritinib continue indefinetively after treatment discontinuation. Rather, what the model does (as common to other CE models of oncology treatments) is to project in time the PFS gains and costs of ceritinib, assuming that the number of

		patients experiencing disease-free survival (and thus, benefit from ceritinib while on treatment) follows a certain pattern, guided by a given, best-fitted survival curve. The scenario which included the costs of maintaining patients on ceritinib for an additional 1.6 months after disease progression clearly reflect the case in which patients, no longer experiencing progression-free survival, are still receiving treatment. This, which is a case advocated by the Appraisal Committee (see section 4.13 of the FAD) is actually the opposite case of the one where treatment benefits of ceritinb are supposed to continue beyond treatment discontinuation. In addition, the scenario analyses explored by the ERG, where the duration of treatment benefit on ceritinib was assumed to stop at a given point in time, only reflected the assumption that, at that specific point, there were no more patients experiencing a response to treatment, and therefore the ERG has modelled this by assuming that the PFS curve (with associated benefits and costs) for the ceritinib arm “switch” to the BSC arm of the model. Again, these scenarios should not be seen as an indication of the issue that the manufacturer or the ERG had assumed that the “treatment benefit from ceritinib [continued] after treatment with ceritinib had stopped”, but, rather, as exploratory analyses where the benefits from and treatment costs associated with ceritinib (as modelled in the PFS curve) are assumed to (arbitrarily) stop at, say, 18 or 24 months from time 0 in the K-M curve.

Issue 2 Lack of clarity regarding methodology of outcome measurement

Description of problem	Description of proposed amendment	Justification for amendment
Section 3.3 states: *"The secondary outcomes included overall response rate assessed by a blinded independent review committee rather than by the investigator, overall survival, progression-free survival (defined as the time from starting treatment to the time of disease progression or death), and adverse events."*	We would suggest amending the text to state: "The secondary outcomes included overall response rate assessed by a blinded independent review committee rather than by the investigator, overall survival, progression-free survival (defined as the time from starting treatment to the time of disease progression or death), and adverse events. **Progression free survival was assessed by the investigator and by a blinded independent review committee to off-set any potential investigator-led bias.** "	Clarification is required to state that progression free survival is assessed using both methodologies.

Issue 3 Lack of clarity regarding methodology of outcome measurement

Description of problem	Description of proposed amendment	Justification for amendment
Section 3.5 states: "*Secondary outcomes included overall-response rate assessed by a blinded independent review committee, progression free survival, overall survival and safety*"	We would suggest amending the text to state: "Secondary outcomes included overall-response rate assessed by a blinded independent review committee, progression free survival, overall survival and safety. **Progression free survival was assessed by the investigator and by a blinded independent review committee to off-set any potential investigator-led bias.** "	Clarification is required to state that progression free survival is assessed using both methodologies.

Issue 4 Data reporting errors in Table 1

Description of problem	Description of proposed amendment	Justification for amendment
Table 1 incorrectly reports the ASCEND-1 BIRC assessed PFS (95% CI) as 7.0 (5.7 to 8.6).	The correct value should be 7.0 (5.7 to 8.7).	Correct data reporting error.
For consistency, ASCEND-1 investigator assessed OS (95% CI) should be reported to 1 d.p.	The correct values should be 16.7 (14.8, NE).	Correct data reporting error.

Issue 5 Lack of clarity regarding availability of data

Description of problem	Description of proposed amendment	Justification for amendment
Section 3.23 states: *"The ERG also noted that the company's submission gave baseline patient characteristics only for the combined BSC and chemotherapy subgroups in Ou et al. (2014), so the characteristics of the BSC group (which in the ERG's opinion is the relevant subgroup for the appraisal) were not presented to the Committee".*	We would suggest amending the text to state: "The ERG also noted that the company's submission gave baseline patient characteristics only for the combined BSC and chemotherapy subgroups in Ou et al. (2014), so the characteristics of the BSC group (which in the ERG's opinion is the relevant subgroup for the appraisal) were not presented to the Committee. **However, baseline characteristics for the specific subgroup of interest were not available which was a limitation acknowledged in the company's submission.** "	It should be noted that the reason why specific baseline characteristics were not reported was due to the fact that these were not available.

Issue 6 Data reporting error in Section 4.5

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.5 incorrectly reports the trial population of ASCEND-2 as n=130.	This value should be updated to n=140.	Correct data reporting error.

Issue 7 Data reporting error in Section 4.6

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.6 incorrectly states that: *"median progression-free survival with ceritinib was 6.9 months in ASCEND-1 and 7.0 months in ASCEND-2".*	The statement should read: "median progression-free survival with ceritinib was 7.2 months in ASCEND-1 and 7.0 months in ASCEND-2 as reported by BIRC assessment".	Correct data reporting error.

Issue 8 Data reporting error in Section 4.18

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.18 presents ICERs rounded to the nearest hundred, rather than the more specific numbers reported in the company's submission and ERG report.	The ICERs should read: • Company's base case: £62,456 • ERG's preferred parameters: £79,528 • ERG 2-year treatment effect: £99,703	Correct data reporting error.

Issue 9 Data reporting error in the summary of Appraisal Committee's key conclusions section – *key conclusion*

Description of problem	Description of proposed amendment	Justification for amendment
The key conclusion section erroneously states that: *"The clinical effectiveness data were based on single-arm phase I and II studies for ceritinib and on 2 observational studies for best supportive care*." However, Shepherd *et al.* 2005 was a randomised, placebo controlled trial used for PFS estimate of BSC.	The statement should read: "The clinical effectiveness data were based on single-arm phase I and II studies for ceritinib and on a RCT and an observational study for best supportive care."	Shepherd *et* al. 2005 should be listed as a randomised controlled trial as opposed to an observational study.

Issue 10 Data reporting error in the summary of Appraisal Committee's key conclusions section – *key conclusion*

Description of problem	Description of proposed amendment	Justification for amendment
The key conclusion section presents ICERs rounded to the nearest hundred, rather than the specific numbers reported in the company's submission and ERG report.	The ICERs should read: • Company's base case: £62,456 • ERG's preferred parameters: £79,528 • ERG 2-year treatment effect: £99,703	Correct data reporting error.

Issue 11 Wording amendment in the summary of Appraisal Committee's key conclusions section – *uncertainties generated by the evidence*

Description of problem	Description of proposed amendment	Justification for amendment
The 'uncertainties generated by the evidence' section states that: *"Regarding overall survival, the data for ceritinib were immature and the data for best supportive care came*	We would suggest that either 19% is stated explicitly or 'approximately 20%' is written.	Present data point more accurately.

from only 20% of patients from Ou et al. (2014).” However, 19% is a more accurate figure for the number of patients from Ou *et al.* relevant to the decision problem.		

Issue 12 Data reporting error in the summary of Appraisal Committee’s key conclusions section – *Estimate of the size of the clinical effectiveness including strength of supporting evidence*

Description of problem	Description of proposed amendment	Justification for amendment
This section incorrectly states that: *“median progression-free survival with ceritinib was 6.9 months in ASCEND-1 and 7.0 months in ASCEND-2”*	The statement should read: “median progression-free survival with ceritinib was 7.2 months in ASCEND-1 and 7.0 months in ASCEND-2 as reported by BIRC assessment”.	Correct data reporting error.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

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

March 2016

File name	Version	Contains confidential information	Date submitted
		YES	4 March 2016

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Ceritinib (Zykadia ®) for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer.

3.2 Please outline the rationale for developing the patient access scheme.

The simple discount PAS is a mechanism through which the NHS will be able to procure ceritinib at net prices lower than the current list prices. This discount results in a price for the combination that is cost-effective versus current treatment alternatives.

The proposed patient access scheme is a simple discount to the ceritinib list price. The discounts will apply at the point of invoicing ceritinib. The scheme for ceritinib will only be implemented upon publication of positive NICE guidance.

Should the list price for ceritinib change, the percentage discount will change accordingly to maintain a fixed net price

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Financially-based scheme: simple discount to list price. The amount of discount and net price will remain commercial in confidence.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The scheme applies to the entire population for whom ceritinib has been licensed, namely ALK+ NSCLC patients who have progressed on crizotinib.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Following positive NICE guidance for ceritinib under the current NICE appraisal, the PAS will apply to all supplies and preparations of ceritinib and is applicable to all current and future indications. No additional criteria will need to be met.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The scheme is applicable to 100% of the population treated with ceritinib in the NHS in England and Wales.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

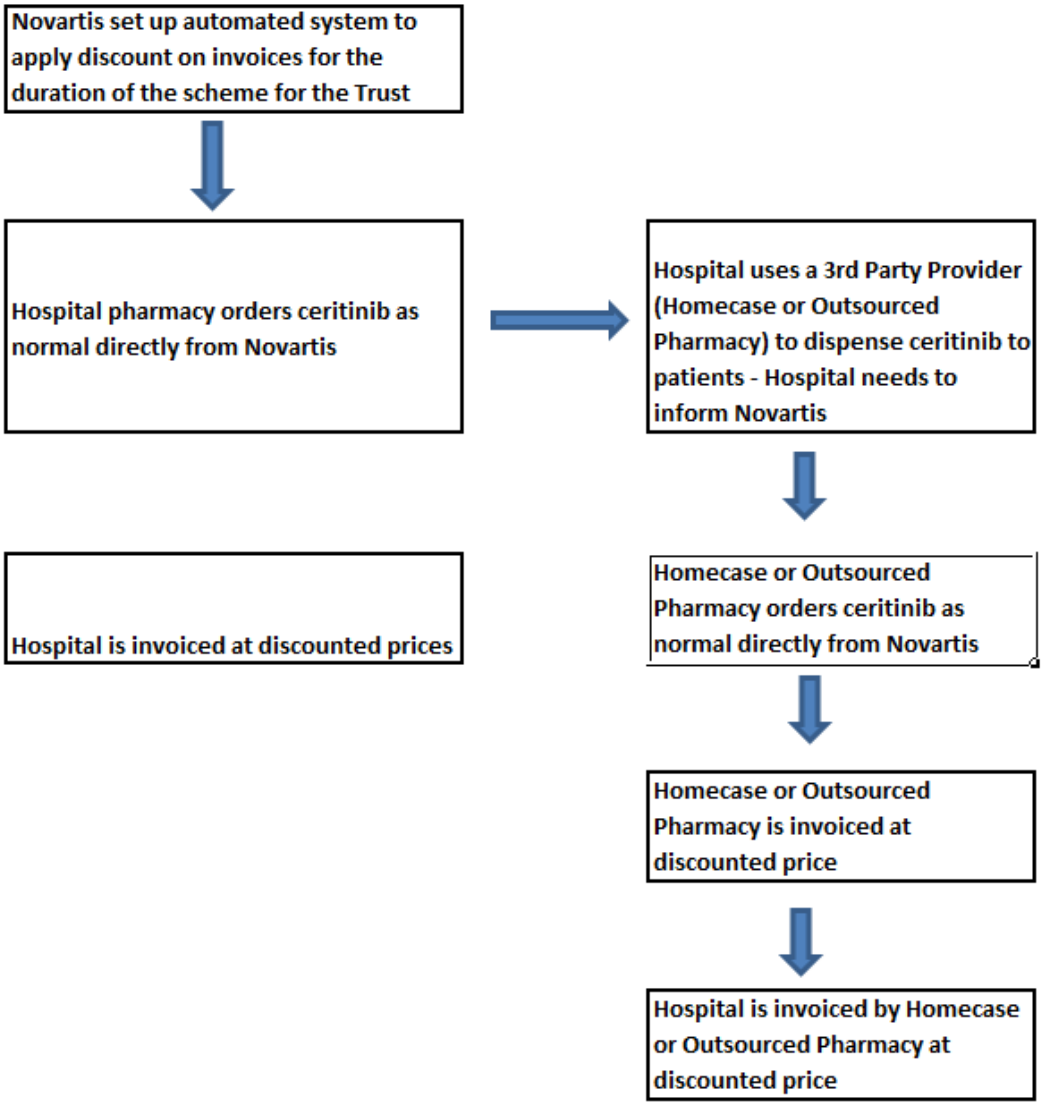
The discount will be applied at the point of invoicing for purchases of ceritinib packs made by NHS Providers on behalf of NHS patients. The proposed discount will be reflected in the invoice. The amount of discount and net price will remain commercial in confidence.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

There will be no need to collect any additional information.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The scheme will not require any additional NHS resource to access the PAS net price as hospital pharmacy will operate the standard NHS pharmacy procurement procedure to order ceritinib directly from Novartis.



3.10 Please provide details of the duration of the scheme.

Subject to positive NICE guidance for ceritinib under the current NICE appraisal, the proposed scheme will be in place until NICE review of the guidance, subject to the usual NICE review process

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to this scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The discount will apply automatically and will not require any additional documentation.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

N/A, the scheme proposed is a financial scheme (simple discount at the point of invoice).

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The population to whom the scheme applies has been presented in the main submission of evidence

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The economic model has been updated to reflect the following assumptions, which the Appraisal Committee has stated to consider the most plausible, both in the ACD and in the FAD. Table 1 below summarises the changes implemented to the base case.

Table 1: Changes implemented to the base case following ACD and FAD

Changes implemented to the base case	**Relevant section in retracted FAD**	**Implementation in Excel model**
Extrapolated OS curve for BSC	4.12	In line with the Committee conclusions, both the case when the Weibull curve and the log-normal curve is used for BSC are explored (the new base case uses log-normal as the OS curve for BSC; the Weibull is explored in a sensitivity analysis).
Time on treatment	4.13	In line with the Committee conclusions, the treatment duration is modelled taking into account the median time on treatment from ASCEND-2, with an extra 1.6 months on treatment after disease progression
Duration of treatment benefits	4.14	In the base case, treatment benefits for ceritinib are assumed to persist (for PFS and OS) until patients discontinute the treatment. In two scenario analyses, treatment benefits (in terms of PFS and

		OS) are assumed to no longer follow the extrapolated PFS and OS ceritinib curves, but switch to the respective PFS and OS curve of the BSC arm of the model. Please see also section 4.2.1 below for an extensive discussion on the rationale behind this approach.
Utility values	4.15	Use of the same utility values for the same health states, in both the BSC and ceritinib arm of the model, as suggested by the ERG. This value corresponds to 0.713 (Cells E16 and E17 of the utility tab). In addition, utility decrements due to possible AEs are not applied to the BSC arm of the model, resulting in an increase in the utility value for patients receiving BSC for the progression-free health state since patients on BSC would not experience the AEs associated with ceritinib.
Increase the Relative dose intensity in the economic model	4.16	A 90% relative dose intensity is applied in the model, to take into account of the view expressed by the Committee that the RDI "should be lower than 100% but higher than the estimate of 82.8% used by the company".
Administration costs for ceritinib	4.17	Administration costs have now been included in the model, a dispensing cost of £13.60 is assumed to be associated with each prescription. This is based on the cost of 12 minutes of hospital pharmacists time (hourly rate of a hospital pharmacist

		£68.00÷5=£13.60; source: PSSRU – Unit costs of health and Social Care 2014; available at: http://www.pssru.ac.uk/project-pages/unit-costs/2014/; accessed 1 February 2016). Ceritinib is assumed to be prescribed once monthly.
Costs for blood tests and for managing lab abnormalities		Following the ERG's report, these costs have now been included in the base case, which takes the relevant cost (in cells I14, I15 and I17 in the Safety tab) to £292.10
Inclusion of all grade 3 and 4 AEs for ceritinib		The total costs for AEs for the ceritinib arm of the model becomes equal to £239.93

Please refer to the Word document "ID729 Ceritinib model corrections after FAD 25012016 with NVS change.doc"(attached to this submission) received from ERG through NICE on 27 January for references on how these changes have been implemented in the CE model in Excel.

4.2.1 Duration of treatment benefit

In section 4.14 of the retracted FAD, the Committee discussed the assumptions about the duration of treatment benefit. The comments expressed by the Committee are reported below:

4.14: The Committee discussed the assumptions about the duration of treatment benefit. It noted that the company's model assumed that the benefits of treatment with ceritinib persist beyond the study period and after stopping treatment. It also noted that the exploratory analysis by the ERG, which reduced the duration of treatment benefit with ceritinib to 2 years, substantially raised the incremental cost-effectiveness ratio (ICER). The Committee heard from the clinical experts at the meeting that it was unlikely that ceritinib would offer a benefit beyond the end of treatment, and if it did, it would not be as long as 2 years. The Committee was not given evidence that the treatment benefit from ceritinib would continue after the end of treatment, and concluded that it was not appropriate to model any benefit beyond stopping treatment with ceritinib.

These statements are not accurate as they do not correctly reflect the modelling of treatment benefits in the cost-effectiveness model submitted to NICE as part of this appraisal.

Under all scenarios presented in the model (base case and scenario analysis) the clinical benefits and costs of ceritinib are always modelled on the basis of the PFS and OS curves. These, in turn, have been fitted to Kaplan-Meier (hence, trial-based) data, which have then been extrapolated over a time-horizon of 10 years. Trial-based, PFS data clearly reflect patients who are still on treatment and responding to it.

At no point did the economic model submitted by Novartis, nor the ERG analyses, "*include an indefinite treatment benefit from ceritinib after treatment with ceritinib had stopped*". By definition, a PFS curve reflects patients who are on treatment and which are also considered to be progression-free (hence, receiving and responding to treatment) on the basis of the RECIST criteria. The extrapolation of the K-M curves over a time horizon of 10 years the model does not imply that the benefits from ceritinib continue indefinitely after treatment discontinuation. Rather, what the model does (as common to other CE models of oncology treatments) is to project in time the PFS gains and costs of ceritinib, assuming that the number of patients experiencing disease-free survival (and thus, benefit from ceritinib while on treatment) follows a certain pattern, guided by a given, best-fitted survival curve.

In addition, the scenario which included the costs of maintaining patients on ceritinib for an additional 1.6 months after disease progression clearly reflect the case in which patients, no longer experiencing progression-free survival, are still receiving treatment. This, which is a case advocated by the Appraisal Committee (see section 4.13 of the FAD) is actually the opposite case of the one where treatment benefits of ceritinb are supposed to continue beyond treatment discontinuation.

The scenario analyses explored by the ERG, where the duration of treatment benefit on ceritinib was assumed to stop at a given point in time, only reflected the assumption that, at that specific point, there were no more patients experiencing a response to treatment, and therefore the ERG has modelled this by assuming that the PFS curve (with associated benefits and costs) and

the OS curve for the ceritinib arm "switch" to the respective PFS and OS curves in the BSC arm of the model. Again, these scenarios should not be seen as an indication of the issue that the manufacturer or the ERG had assumed that the "treatment benefit from ceritinib [continued] after treatment with ceritinib had stopped", but, rather, as exploratory analyses where the benefits from and treatment costs associated with ceritinib (as modelled in the PFS and OS curve) are assumed to (arbitrarily) stop at, say, 18 months or 2 years from time 0 in the model.

In light of the above rationale, Novartis has modelled the following additional scenarios in the CE model:

Table 2: Scenarios on duration of treatment benefits for patients treated with ceritinib

Scenarios	**Time at which changes in PFS and OS curves are applied:**
Reduce treatment benefits for ceritinib arm of the model (by switching PFS and OS curves of ceritinib to PFS and OS BSC curves)	- 18 months from time zero; - 24 months from time zero

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the economic model (resubmitted to NICE as part of this appraisal process) the simple discount has been incorporated by decreasing the list price per package of ceritinib by the percentage equivalent to the PAS figure. In the sheet "Drug cost inputs", cell D13 reports the level of discount; cell D9 reports the cost per package of ceritinib (at current list price net of the percentage discount from cell D13). The simple PAS offered has been captured in the manner just described across all scenario analysis conducted.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data submitted for the current NICE appraisal of ceritinib are not affected by the simple PAS offered on the ceritinib list price.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The proposed scheme consists of a simple discount, and therefore there will be no additional costs associated with its implementation and operation in NHS England and Wales.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Implementation of this scheme will not incur additional treatment-related costs. Treatment costs for the NHS in England and Wales will in fact be reduced whilst all other elements of the treatment pathway will remain unchanged.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

Table 3: Base-case cost-effectiveness results without PAS

	Ceritinib	**BSC**
Drug and administration costs (£)	64,985	0
Treatment associated adverse events costs (£)	234	0
Medical costs (£)	10,781	7,339
Total costs (£)	76,000	7,339
Difference in total costs (£)	N/A	68,661
LYG	1.77	0.46
LYG difference	N/A	1.31
QALYs	1.06	0.27
QALY difference	N/A	0.80
ICER (£)	N/A	86,364

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 4: Base-case cost-effectiveness results with PAS [redacted]

	Ceritinib	BSC
Drug and administration costs (£)	[redacted]	0
Treatment associated adverse events costs (£)	234	0
Medical costs (£)	10,781	7,339
Total costs (£)	[redacted]	7,339
Difference in total costs (£)	N/A	[redacted]
LYG	1.77	0.46
LYG difference	N/A	1.31
QALYs	1.06	0.27
QALY difference	N/A	0.80
ICER (£)	N/A	XXXXXX

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 5: Base-case incremental results without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BSC	7,339	0.46	0.27	-	-	-		
Ceritinib	76,000	1.77	0.46	68,661	1.31	0.80	86,364	86,364

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 6: Base-case incremental results with PAS [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BSC	7,339	0.46	0.27	-	-	-		
Ceritinib	[redacted]	1.77	0.46	[redacted]	1.31	0.80	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

In order to test the robustness of the model results, deterministic sensitivity analyses (DSA) were conducted by varying key variables on the model outcomes. All costs were varied in the range by ±25% from the base-case value. Utilities were varied by ±10% from the base-case value. Alternative discount rates for cost and outcomes were also explored (0%, 6%). The following variables and lower/upper ranges were used in the deterministic sensitivity analyses (DSA).

The results of the deterministic sensitivity analyses on the ICERs are presented in [redacted] and in [redacted] incorporating the simple discount on the ceritinib list price.

[redacted]

[redacted]

[redacted]

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The mean ICER at the discounted price for ceritinib are summarised in below.

Table 7: Mean ICER, mean incremental costs and mean incremental QALYs [redacted]

	Mean ICER	Mean incremental costs	Mean incremental QALYs
Ceritinib XXXXX [redacted] vs. BSC	[redacted]	[redacted]	0.79

The scatter plot linked to the PSA is presented in [redacted] below.

[redacted]

The cost-effectiveness acceptability curve (in [redacted] below) shows a probability of [redacted] that ceritinib is cost-effective versus BSC at a willingness-to-pay of £50,000 per QALY, which is the relevant threshold in light of the fact that ceritinib was acknowledged to have met the end-of-life criteria in the FAD issued by the Appraisal Committee.

[redacted]

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

The structural assumptions of the model were tested in scenario analyses. The scenario analyses covered:

- Treatment continuation with active drug therapies after disease progression (BSC + systemic therapy)
- Time horizons (5 and 20 years)
- Use of alternative survival distributions to model PFS and OS for ceritinib
- Use of Weibull curve for BSC OS
- Use of different sources of HSUVs
- Assumption around PFS for patients on BSC
- Assumptions around ceritinib dose intensity, administration costs and systemic therapy acquisition cost
- Assumption that treatment benefits (with associated costs and PFS, OS benefits) stop at 18 months or at 24 months from start of treatment

The scenario where the treatment continuation with ceritinib post-progression continued for an additional 1.6 months is now part of the base case analysis and is therefore no longer considered as a scenario analysis.

Table 8: Scenario Analyses – ceritinib vs. best supportive care [redacted]

Parameter	Base case choice	Scenario analysis	ICER (£/QALY)	% change from base case ICER
Base case			XXXXX	
Use systemic therapy treatment following progression on crizotinib	No	Yes (assume 30% of patients receive docetaxel and 70% BSC)	XXXXX	[redacted]
Time horizon	10 years	5 years	XXXXX	[redacted]
		20 years	XXXXX	[redacted]
PFS function: ceritinib	log logistic	Exponential	XXXXX	[redacted]
		Weibull	XXXXX	[redacted]
		log-normal	XXXXX	[redacted]
		Gompertz	XXXXX	[redacted]
OS function: ceritinib	Weibull	Exponential	XXXXX	[redacted]
		Gompertz	XXXXX	[redacted]
		log-logistic	XXXXX	[redacted]
		log-normal	XXXXX	[redacted]
Health state utility values	Health state utility value for progression free from ASCEND-2 trial for both ceritinib and BSC (0.713)	Nafees *et al.* for PFS for both ceritinib and BSC (0.653) with no response-adjustment	XXXXX	[redacted]
		Chouaid *et al.* for both ceritinib and BSC (0.620)	XXXXX	[redacted]

		with no response-adjustment		
OS function for BSC	Distribution used for OS: Log-normal	Weibull	XXXXX	[redacted]
PFS for patients on BSC	Assume patients on BSC experience PFS	Assume no PFS for patients on BSC	XXXXX	[redacted]
Administration cost for ceritinib	Since ceritinib is an oral treatment, no administration costs are included in the base case	Assign administration costs of £156.68 per cycle for ceritinib until disease progression	XXXXX	[redacted]
Relative drug intensity - Ceritinib	Set equal to 90%, following FAD	Assumed to be 100% for ceritinib	XXXXX	[redacted]
Docetaxel acquisition cost	eMIT	Use BNF cost and assume 30% of patients receive docetaxel and 70% BSC	XXXXX	[redacted]
Treatment benefits from ceritinib	Assumed to be extrapolated over 10 years time horizon	At 18 months from start of treatment, switch PFS and OS benefits to BSC arm of model	XXXXX	[redacted]
Treatment benefits from ceritinib	Assumed to be extrapolated over 10 years time horizon	At 24 months from start of treatment, switch PFS and OS benefits to BSC arm of model	XXXXX	[redacted]

Abbreviations: BSC, best supportive care; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 9: Results showing the impact of patient access scheme on ICERs

	ICER for ceritinib vs. BSC	
	Without PAS	**With PAS** [redacted]
Base case	86,364	[redacted]
Use systemic therapy treatment following progression on crizotinib	90,049	XXXXXX
Time horizon: 5 years	86,333	XXXXXX
Time horizon: 10 years	86,514	XXXXXX
PFS function for ceritinib: exponential	80,653	XXXXX
PFS function for ceritinib: Weibull	78,181	XXXXXX
PFS function for ceritinib: log-normal	86,523	XXXXXX
PFS function for ceritinib: Gompertz	78,496	XXXXXX

OS function for ceritinib: exponential	77,894	XXXXX
OS function for ceritinib: Gompertz	95,292	XXXXXX
OS function for ceritinib: log-logistic	65,335	XXXXXX
OS function for ceritinib: log-normal	58,984	XXXXXX
Health state utility values - Nafees *et al.*[38] for PFS for both ceritinib and BSC (0.653) with no response-adjustment	90,774	XXXXX
Health state utility values - Chouaid *et al.* for both ceritinib and BSC (0.620) with no response-adjustment	94,821	XXXXXX
Use Weibull OS distribution for BSC	84,497	XXXXXX
PFS for patients on BSC: Assume no PFS for patients on BSC	80,593	XXXXXX
Include cost for ceritinib administration until disease progression	91,839	XXXXX
Relative drug intensity, assumed to be 100% for ceritinib	95,418	XXXXXX
Docetaxel acquisition cost (Use BNF cost and assume 30% of patients receive docetaxel and 70% BSC)	87,672	XXXXXX
Treatment benefits from ceritinib (I): At 18 months from start of treatment, switch PFS and OS benefits to BSC arm of model	85,421	XXXXXX
Treatment benefits from ceritinib (II): At 24 months from start of treatment, switch PFS and OS benefits to BSC arm of model	82,494	XXXXX

PAS: patient access scheme.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

These documents are currently being finalised with PASLU and DH. Novartis will share them with NICE as soon as they become available.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

N/A

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

N/A

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

N/A

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

N/A

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

N/A

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

N/A

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

N/A

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Warwick Evidence Critique of Final Ceritinib Model Changes and PAS

Novartis and ERG changes to the base-case

All changes identified by the Appraisal Committee [1] have been implemented correctly in the ERG and Novartis modified model [2], with one exception (see below)

Changes together generate a new base case ICER of £86,364/QALY [3]. The final iteration from the previous base case (£79,595/QALY) is mainly driven by increasing dose intensity of ceritinib from 83% to 90%.

PAS use of the new base-case

The PAS reports the new base case analysis [4], corrected for a discount reduction of [redacted]. Applying [redacted] in the drug cost the ICER reduces from £86,364/QALY to [redacted]

Adjusting the base case model [3] input drug cost [redacted] replicates the value in the PAS (i.e. D13 of the "Drug cost input" worksheet [2]).

Changes not matching the Committee's preferred analysis

For the previous FAD [1], ERG model estimates were offered assuming treatment benefits truncated at 2 years and 18 months, substantially raising the ICER. There is a modelling error in these scenario analyses and they should be discounted.

Modelling the limitation of duration of benefit (and ceritinib drug costs) leads to 2-year and 18-month scenario estimates of £82,494/QALY and £85,421/QALY respectively [5,6]. Setting a limited time for treatment benefit does not significantly alter the ICER estimated, because [1] most QALY benefits and costs accrue in the first years of treatment [2] setting longer term cerinitib benefits to zero also an offsetting reduction in drug and administration costs.

We agree partially with Novartis' challenge to the interpretation of ongoing ceretinib benefits [3; (4.2.1)]. It can be argued Progression Free Survival (PFS) should not be arbitrarily truncated as it is the best estimate of ongoing progression-free survival in a diminishing group who haven't progressed and may still benefit from treatment. However this assumes no selection effects

differentiate between subjects remaining progression free for different lengths of time. The overall ceritinib parametric survival curve is conditioned predominantly by time on treatment, to extrapolate this without modification would appear to make a strong assumption about maintenance of benefit and future survival post-treatment, thus exploration of truncated survival is appropriate. The impact upon estimated ICERs is marginal as seen from the scenarios presented, because of the small changes arising in incremental QALYs and costs in the survival tails.

In this instance, and in the absence of compelling evidence one way or the other, the ERG agrees with the use of the base case analysis as a reasonable modelled representation of the evidence available. Our reservations about the quality and comparability of the observational data remain, particularly informing the survival curves.

Description and critique of any further company changes

There are no further changes to discuss.

Sensitivity/scenario analyses helpful at the previous meeting

The impact of assumptions of long-term benefit has been summarised (above).

The committee expressed an interest in seeing survival benefit stopped for cerinitib (above BSC) after treatment has stopped. The model is not constructed in a way that facilitates such a calculation and substantial model rebuilding would be required. The two scenarios provide a proxy for this more involved analysis.

References

[1] [ID729] ceritinib - Final Appraisal Determination.pdf

[2] ID729 Ceritinib model corrections after FAD - ERG and Novartis changes - 040316 JP [ACIC] (6).docx

[3] (ID729) ceritinib - Novartis Ceritinib NICE CE model_basecase_post FAD - 040316 JP (ACIC).xlsm

[4] Addendum to NICE submission for PAS inclusion ceritinib.docx

[5] (ID729) ceritinib - Novartis Ceritinib NICE CE model_2 years treatment benefits_post FAD - 040316 JP (ACIC).xlsm

[6] (ID729) ceritinib - Novartis Ceritinib NICE CE model_18 months treatment benefits_post FAD - 040316 JP (ACIC).xlsm