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 the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Novartis
   - Royal College of Physicians on behalf of the NCRI/RCP/ACP/RCR

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Novartis	Novartis would like to thank the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal and to provide further clarifications for consideration. Our comments are provided in response to the standard four questions on which NICE have stated they are interested in receiving comments, as detailed on Page 1 of the ACD. There are four primary comments that we have on the ACD, which have been outlined below: i. Novartis welcomes NICE's proposal that the guidance on this technology is considered for review by the Guidance Executive when the results of the ASCEND-5 trial are reported (expected to be in the second quarter of 2016). In order to enable a timely review, Novartis will update NICE as soon as possible upon any development on the availability of the ASCEND-5 clinical trial data. ii. Based on the available evidence, we strongly believe that it is reasonable to conclude that ceritinib **meets the requirements for an end-of-life therapy.** iii. We believe that ceritinib is an innovative technology, as indicated by its Promising Innovative Medicine (PIM) designation, and offers benefits beyond those captured in the quality adjusted life year (QALY) outcome. iv. The comparator selected in the scope was limited to BSC, due to the absence of other third-line treatment options and understanding of the management of ALK+ NSCLC at the time of the scope decision. Clinical practice, however, clearly demonstrates that fitter patients and patients who have not yet received chemotherapy in previous lines of treatment, are likely to undergo treatment with systemic anticancer therapy (SACT) rather than BSC upon disease progression on crizotinib. SACT should therefore be considered as the relevant comparator to ceritinib for those patients that are considered eligible to receive this type of treatment.	Comments noted.

Consultee	Comment [sic]	Response
Novartis	In addition to these comments, we have also presented a summary of factual inaccuracies and further clarifications for consideration. Overall, we believe that the ACD represents a fair summary of the evidence presented by Novartis and the subsequent Evidence Review Group (ERG) review. We are highly disappointed, however, to see that the NICE Committee has not acknowledged the end of life status for ceritinib, with the ACD citing a lack of sufficient certainty in the evidence. We believe that the NICE Committee has made this judgement without fully taking into account the nature of this indication. We firmly believe that, taking account of the various sources of information on which a decision can be based (presented in this response), it is clear that ceritinib merits end-of-life status. For conditions such as this, where there is an extensive unmet need and a highly innovative therapy that represents a step-change in the management of the condition, we ask that NICE takes a balanced, considered approach in its assessment of the end-of-life criteria, rather than seeking objective confirmation that, given the comparator identified in the scope (best supportive care), would not be feasible. In fact, clinical experts have advised Novartis that it would be ethically challenging to design a randomised controlled study where patients could be allocated to either BSC or active treatment with ceritinib. This will always result in unavoidable uncertainty in estimates, and an inevitable difficulty in measuring the extension to life "objectively and robustly".	
Novartis	I. Has all of the relevant evidence been taken into account? There are several pieces of evidence that Novartis does not believe the Committee has adequately considered, mainly the determination of whether ceritinib meets the criteria for an end of life treatment and the innovative nature of the technology. Additional comments as well as factual inaccuracies and clarification questions have also been provided in this section. a. End of Life Criteria With regards to the end of life criteria, the ACD concluded that the life expectancy for people with anaplastic lymphoma kinase positive (ALK+) NSCLC on current standard of care and the size of the population eligible to receive ceritinib were within a suitable range to meet the pre-specified criteria. However, it also noted that "while it was possible that ceritinib offers an average extension to life of at least 3 months, the data were too uncertain to consider that this criterion had been met	Thank you for your comment. After further discussion, the Committee considered that it was reasonable to conclude that ceritinib offers an average extension to life of at least 3 months and therefore meets the end of life criteria. See section 4.21 and 4.22 of the FAD.

Consultee	Comment [sic]	Response
	objectively and robustly". As discussed above, as an oncology treatment for patients near to the end of their life, it is unreasonable to expect direct evidence versus a best supportive care comparator in this indication due to the ethical implications of such a trial design. In addition, the uncontrolled nature of the evidence presented for ceritinib is a direct reflection of the early licensing of this therapy based on phase I and phase II single-arm studies in recognition of ceritinib's innovative value and the unmet need faced by this patient population. Therefore, the only possible approach to approximating extension to life with ceritinib is to estimate the survival benefit of ceritinib using a naïve indirect comparison with the best available evidence as determined by a systematic literature review. This is the approach that was taken in our submission. In the phase II clinical trial (ASCEND-2), median overall survival (OS) amongst 140 patients treated with ceritinib was 14.9 months (95% CI: 13.5, NE). Survival estimates were similar in a phase I trial of ceritinib (ASCEND-1) in which 163 patients treated with ceritinib experienced a median OS of 16.7 months (95% CI: 14.8, NE). The pooled estimate of median OS across the ASCEND-2 and ASCEND-1 clinical trials was 15.64 months (95% CI: 14.66, NE). A retrospective analysis by Ou et al. was the only available, relevant evidence source in the population under consideration, as identified by a systematic literature review. There are acknowledged limitations in this naïve indirect comparison in relation to the small sample size of the Ou et al. study, the lack of stratification of baseline characteristics by BSC vs chemotherapy groups in the publication and the limited information on potential confounding factors, as noted by the ERG report. However, the ERG also noted that there is no other data to use; this paucity of available data must be seen as a reflection of the high unmet need in this indication and will inevitably give rise to considerable limitations in an attempted comparison. The median overall survival for treatment with BSC (no active treatment) in the Ou et al. study was approximately 2.2 months; 8.9 months when considering the entire patient cohort, including patients who continued on crizotinib following disease progression. Taking the estimate for OS pooled across patients who received BSC or chemotherapy the median OS is 3.9 months and for the patients receiving chemotherapy alone the estimate of OS was 5.4 months. Considering a pooled median OS of 15.64 months reported across the ASCEND-2 and ASCEND-1 trials, these results suggests an extension to overall survival of approximately 10 months, well above the 3 month requirement for the end of life criteria. Furthermore, even if the OS of the entire cohort considered in the Ou et al. study is considered, 8.9	

Consultee	Comment [sic]	Response
	months, the extension to overall survival would still be approximately 6 months, again much greater than the 3 month limit specified by the end of life criteria. Although we acknowledge the caveats that must be associated with such naïve comparisons, in the face of the limitations imposed by the available data the only reasonable method to explore uncertainty is to compare ceritinib against this available data. Such a comparison suggests that even if BSC was associated with the treatment benefit in terms of extension to life that resulted from use of chemotherapy in this study (a conservative assumption), ceritinib offers an extension to life over BSC of well above 3 months. A clinical advisor consulted by the company prior to the submission confirmed that the BSC results from the Ou et al. studies could be generalised to all patients who have progressed on crizotinib, and is not specific to those that are considered less fit. Thus, the statement in the ACD response that "the BSC group in Ou et al may therefore have been sicker than patients in the ASCEND studies" is not supported, suggesting that the results from the Ou et al. study do not underestimate the effectiveness of BSC for the population of interest, and therefore supports the estimate of an extension to overall survival of approximately 10 months for patients on ceritinib. This would be consistent with correspondence with the author of the Ou et al. study who confirmed that "BSC will not perform better against novel ALK inhibitors for patients who continue CBPD as ALK is such a strong oncogenic driver that continual ALK suppression with an ALK inhibitor is important". Furthermore, during the NICE Committee meeting expert clinicians confirmed that an OS estimate of 3–6 months was reasonable for patients receiving BSC in the indication under review. By taking the upper bound estimate here (6 months), in order for ceritinib to not meet the necessary criteria of resulting in an extension to life of at least 3 months following BSC, the OS of patients receiving ceritinib would need to be less than 9 months, which would assume that each of the ASCEND clinical trials individually overestimates OS by a minimum of 5 months (~one-third of the absolute estimate) in order for this criteria to not be met. Taken another way, given that PFS was 6.9 months and 7.0 months in the ASCEND-1 and ASCEND-2 trials, respectively, in order for the extension to life offered by ceritinib to be less than 3 months following BSC, this would require an assumption that post-progression survival following ceritinib treatment is less than 2 months. Given that the Committee agreed that the ASCEND-1 and ASCEND-2 trials could be considered generalisable to the relevant population in England, it seems highly unreasonable to implicitly suggest that the trial estimates observed represent such considerable overestimates of the actual overall survival on ceritinib for the relevant	

Consultee	Comment [sic]	Response
	population in England. A retrospective analysis of 73 patients treated with sequential crizotinib and ceritinib provides further support of the benefit of ceritinib in terms of overall survival. A subgroup of patients in this study (n=32; 44%) received their crizotinib treatment in a second-line setting which represents a similar patient population to the PROFILE 1007 study of crizotinib. The combined median OS from the time of crizotinib initiation for sequential treatment with crizotinib and ceritinib for this patient subgroup was 30.3 months. Given that median overall survival in the PROFILE 1007 study was 20.3 months, this again indicates an approximate 10 month extension to life for the post-crizotinib population when treated with ceritinib. In conclusion, we accept that it is not possible to generate an objective quantitative estimate for extension to life, but attest that it is not a reasonable expectation in this indication. We believe that, in accordance with the NICE guidance, estimates of the extension to life can be shown or reasonably inferred from the available data, and that this is strongly indicative of a survival benefit >3 months. The patient expert at the Committee meeting highlighted the "immeasurable value" of a therapy that has the potential to extend life at the end of life, and consideration of the NICE end of life criteria should take into account this value alongside the inevitable uncertainty. Based on the balance of evidence presented above and in the submission document itself, we believe that the only reasonable conclusion is to consider ceritinib as an end of life therapy. *References were provided but not reproduced here.*	
Novartis	b. Innovative Nature of Ceritinib The ACD notes that "the Committee concluded that ceritinib may be innovative". We believe that there is considerable evidence of the innovative value of ceritinib that has been formally recognised by various regulatory bodies and that there is little doubt that ceritinib is an innovative therapy. Firstly, the innovative value of ceritinib has been formally recognised through the granting of a Promising Innovative Medicines (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA). Ceritinib is one of only 9 therapies currently to have been awarded this designation, which is awarded based on consideration of the benefit/risk balance of the medicine based on available data	Thank you for your comment. The Committee noted that ceritinib has received a Promising Innovative Medicines designation by the MHRA. However it noted that it had not been presented with any additional evidence of benefits that were not captured in the measurement of QALYs. Please see section 4.23 of the FAD.

Consultee	Comment [sic]	Response
	and forms part of the Early Access to Medicines Scheme (EAMS). In the United States of America, the Food and Drug Administration (FDA) have similarly formally recognised the innovative value of ceritinib, granting both Accelerated Approval and Breakthrough Therapy Designation to ceritinib for the treatment of ALK+ NSCLC in patients with disease progression on, or who are intolerant to, crizotinib. Accelerated Approval recognises medicines that fulfil an unmet medical need for serious conditions whilst Breakthrough Therapy Designation is awarded to those therapies that may demonstrate substantial improvement over available therapy. These therefore act as recognition of the potential for ceritinib to provide a step-change in the management of a condition for which there are currently highly limited options. The ACD commented on a lack of evidence regarding the benefit of ceritinib with respect to controlling brain metastases and improving patient quality of life. However, in its licensed population, ceritinib has demonstrated efficacy in treating patients who reported brain metastases at baseline, while data from non-clinical models has shown that ceritinib is able to effectively penetrate the blood-brain barrier. In contrast, crizotinib has demonstrated poor penetration of the blood-brain barrier; ceritinib has a 20-fold greater potency than crizotinib in enzymatic assays, and, as noted by the ERG, the effects of crizotinib on brain metastases remain less certain. Furthermore, a recent presentation by Crino et al. highlighted that the ASCEND-2 trial found no deterioration in patient's lung cancer symptoms and QoL while receiving ceritinib treatment, regardless of the presence or absence of baseline brain metastases. *References were provided but not reproduced here.*	
Novartis	c. Systemic Anticancer Chemotherapy (SACT) as relevant comparator for ceritinib The comparator for the current appraisal of ceritinib was restricted to best supportive care (BSC) in the NICE scope. The National Chemotherapy Algorithm for the treatment of NSCLC, however, reports that chemotherapy is also used for patients who have progressed on crizotinib at second-line. In addition, clinical experts consulted by Novartis have confirmed that fitter patients	Thank you for your comment. The Committee concluded that it was not presented with additional evidence that suggests that systemic chemotherapy should be considered as a comparator for ceritinib. Please see section 4.2 in the FAD.

Consultee	Comment [sic]	Response
	and patients who have not yet received such treatment in previous lines of treatment, undergo treatment with systemic anticancer therapy (SACT), rather than receiving BSC. This is supported by a recent international survey of physicians, which found 77% of physicians in the EU (n=30) would prescribe chemotherapy for patients who have progressed on crizotinib, while only 30% would recommend BSC. Novartis is conducting a multi-centre retrospective study following ALK+ NSCLC patients who have progressed on crizotinib on the NHS in the UK. The primary objective of the study is to describe treatment pathways for ALK+ NSCLC patients in the UK from initiation of first-line treatment. It is expected that this study will present in Q1 2016 and its finding will inform understanding of the relevant comparators for ceritinib in future NICE reappraisals. Restricting the relevant comparator of ceritinib to BSC alone has important methodological implications in that clinical experts have confirmed that it would not be ethical to randomise patients to BSC in a clinical trial. As a consequence, the possibility to generate clinical evidence that fulfils the NICE reference case (in terms of randomised, comparative data) would be highly improbable. Furthermore, with crizotinib recently gaining positive CHMP opinion as 1st line treatment for ALK+ NSCL patients, it is highly likely that a larger number of patients would be considered eligible for chemotherapy upon disease progression on crizotinib. *References were provided but not reproduced here.*	
Novartis	d. Eligible Patient Population The Appraisal Consultation Document notes that the estimated eligible patient population is 120 patients. However, Novartis would like to take the opportunity to correct this value, which we acknowledge was an error in our own submission that has subsequently been taken forward into the NICE materials. Within our submission, we presented the calculation of the eligible patient population via two alternative methods: 1. Table 5 of our submission presented an estimation based on CDF notifications for crizotinib in a second-line setting and then subsequent rates of survival and progression to receive ceritinib following this. This gave rise to an estimated eligible patient population of 66 patients.	Comment noted. The FAD has been updated to reflect this, please see section 4.21.

Consultee	Comment [sic]	Response
	2. Appendix 2 of our submission presented an estimation based on a similar approach for calculation to that taken in the second-line appraisal of crizotinib by NICE (TA296) and this gave rise to an estimated eligible patient population of 98 patients. We fully acknowledge that we quote an eligible patient population of 120 patients within the Executive Summary and the section considering the end of life criteria within our submission. However, as highlighted above, this value has no basis in an attempt to use evidence to derive an estimation; it simply represents a "placeholder" value from before the calculations were completed and that was not subsequently updated. We have no doubt that the preference of NICE and all stakeholders would be for the estimates of the eligible patient population to be those that are evidence-based, and therefore we ask that the Committee acknowledges the values of 66 and 98 patients, rather than the value of 120 patients, as the estimated size of the eligible patient population in their Final Appraisal Determination document. We would be very happy to publish an erratum on this point if this would be helpful as we feel that this is an important point to clarify; given that various parties will no doubt be referring back to these publically available documents in the future we do not wish for this inaccuracy to carry forwards any further.	
Novartis	e. Factual Inaccuracies The ACD states that in using the Ou et al. (2014) study to estimate survival for patients undergoing best supportive care (BSC), "the company deemed that the appropriate comparison included both BSC and chemotherapy". This is not an accurate representation of the way in which the Ou et al. data was considered within our submission. We specified that the study "evaluated patients receiving BSC (no active treatment), of relevance to the decision problem outlined in this submission. In addition, this study also evaluated patients receiving systemic chemotherapy, of relevance to a scenario analysis". To clarify, we considered the appropriate comparison to be with the BSC group only (hence why this was selected as the base case) and the comparison to BSC and chemotherapy was considered only as an exploratory scenario analysis. Where available, results of the two treatment arms BSC (n=37) and systemic chemotherapy (n=37) were presented separately in order to make the distinction clear. For example, the mean overall survival for patients in the BSC arm was presented as 2.2 months (95% CI: 1.1, 3.8) and 5.4 months (95%	Thank you for your comment. Section 2.3 of the FAD has been amended.

Consultee	Comment [sic]	Response
	CI: 3.8, 12.3) in the systemic therapy arm. The estimate of 2.2 months was carried forward as the main comparison. Where the value of the pooled estimate of all patients who did not continue crizotinib (BSC and systemic therapy) 3.9 months (95% CI: 2.7, 5.1), was considered, this was in the context of simply exploring uncertainty in the BSC estimate presented in the Ou et al. paper and demonstrating how the estimate altered when also considering those patients who received chemotherapy. This pooled estimate was not used in the naïve indirect comparison with the ASCEND-2 and ASCEND-1 trials.	
Novartis	f. Additional Clarifications • Our submission presents the mean change from baseline in EORTC QLQ-C30 global health status as assessed in ASCEND-2 in Figure 21 of the submission. The ACD noted that the company submission did not provide the actual scores from the European Organisation for Research and Treatment of Cancer's core quality-of-life questionnaire (EORT-QLQ-C30) in ASCEND-2, nor did it state the time point at which the summary of results was calculated. As such, please find the additional data presented in Table 1 below. *Table was provided but not reproduced here.*	Comment noted, Section 3.7 of the FAD has been amended to reflect this.
Novartis	• The ACD response concludes that the application of a reduced dose intensity of 82.8% in the economic model was likely to underestimate the dosage paid for by the NHS due to unused tablets that would be wasted as a consequence of short term dose reductions. The dose intensity of 82.8% was based on a weighted average of the mean relative dose intesitises from the ASCEND-1 and ASCEND-2 trials, and therefore consistent with the clinical data presented in the submission. As noted in the committee meeting itself, it can be considered appropriate to apply the trial dose intensity when calculating the ICER because the effectiveness side of the equation was based on results from these clinical trials and therefore reflective of effectiveness estimates at this average dose intensity. An increase to a 100% dose intensity, as presented in a scenario analysis in the company submission, resulted in a 19% increase in the ICER (from £62,456/QALY to £74,519/QALY). This is likely an overestimate due to not accounting for increased effectiveness that may be associated with patients who are in fact taking a higher dose, and does not allow for patients who experience a long-term dose reduction,	Thank you for your comment. The Committee concluded that on average in clinical practice the NHS would not pay for the full dose, but it was likely to pay for more than 82.8% because of wastage. So, the Committee concluded that the dose intensity in the model should be lower than 100% but higher than the estimate of 82.8% used by the company. Please see section 4.17.

Consultee	Comment [sic]	Response
	which as noted in the ACD response is unlikely to result in wasted tablets.	
Novartis	• Considering that there is no available evidence on the efficacy of BSC in patients with ALK+ NSCLC, an older study by Shepherd et al. was presented to provide data on NSCLC patients randomised to receive erlotinib or palliative care. It is acknowledged that the patient population in the Shepherd et al. study is broader than the population of interest, ALK+ NSCLC, in part because the ALK mutation had not yet been identified at the time of this study. However, in the absence of alternative data, the value of a median PFS of 1.8 months for patients receiving palliative care was considered in the cost-effectiveness model presented in the company submission. Novartis would like to stress that clinical experts contacted by the company stated that upon discontinuation on crizotinib and without any suitable active treatment, patients would experience a very rapid progression of their disease. Thus, it should be noted that the inclusion of a period of PFS for the BSC arm in the economic model presented in the company submission represents a very conservative approach to the cost-effectiveness analysis.	Thank you for your comment. The Committee was not presented with data on whether the disease in patients with ALK positive NSCLC progresses faster or slower than in patients whose tumours are not ALK positive, but heard from the clinical experts that ALK positive NSCLC may have a natural history that differs from other types of NSCLC. The Committee also heard that the Shepherd et al. trial did not limit the study to people receiving third line treatment and that patients in Shepherd et al. had lower (that is, better) scores for ECOG performance status than patients in the ASCEND trials, so they might have been fitter and their disease less likely to progress. The Committee concluded that the size of the difference in progression-free survival is likely to be confounded. Please see section 4.6 of the FAD.
Novartis	II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? With the exception of the comments noted in Part I of this response, Novartis considers that the summaries of clinical and cost-effectiveness represent reasonable interpretations of the evidence.	Comment noted.
Novartis	III. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Novartis firmly believe that ceritinib represents a step-change in the management of ALK+ NSCLC in patients previously treated with crizotinib, by providing a targeted therapy with demonstrable benefits in terms of progression-free survival and overall survival. The value of such an option for patients who are currently faced with treatment options limited to either chemotherapy or best supportive care, is immeasurable.	Thank you for your comments. Please see section 4.21, 4.21 and 4.23 in the FAD.

Consultee	Comment [sic]	Response
	Novartis also strongly believes that ceritinib meets the end-of-life criteria for patients previously treated with crizotinib, and that therefore the NICE guidance should be reviewed in order to incorporate this fundamental finding. Finally, Novartis welcomes the recommendation included in section 7 of the ACD to proceed to review this guidance "when the results of the ASCEND-5 trail are reported (expected to be in the second quarter of 2016)" (page 38 of ACD) and urges NICE to consider re-evaluation of ceritinib as a priority upon availability of this data.	
Novartis	IV. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Novartis does not consider that there are any aspects of the recommendations that require particular consideration in this regard.	Comment noted.
National Cancer Research Institute, Royal College of Physicians, Association of Cancer Physicians Royal College of Radiologists (NCRI/RCP/ACP/RCR)	The NCRI/RCP/ACP/RCR are grateful for the opportunity to respond to the above Appraisal Consultation Document. We would like to make the following comments: • Our experts note that the initial QALY was above the threshold for NICE approval and that the QALY increased following review by the committee.	Comment noted.
NCRI/RCP/ACP/RCR	• We note that the increase to the QALY followed comparison of other second line studies versus BSC (Shepherd et al. and Ou et al.). This gave OS of 2.2 months and was open to bias as the patients with ALK positive lung cancer were deemed fitter. Our experts do not believe this necessarily follows as ALK activated patients can present very late, often with brain metastases. There is also difficulty in getting patients on ASCEND 5 related to the fitness of patients and rapidity with which they progress after crizotinib.	Thank you for your comment, the Committee discussed the differences in the study populations for the ASCEND, Ou et al. and Shepherd et al. studies. It noted the high risk of bias because of confounding and concluded that the results of the naive indirect comparison were uncertain. Please see section 4.5, 4.6 and 4.7 of the FAD.
NCRI/RCP/ACP/RCR	We note that the committee concluded that as ASCEND2 allowed treatment of ceritinib beyond radiological progression, this would be replicated in real life. In the	Thank you for your comment. The Committee discussed whether the duration of treatment

Consultee	Comment [sic]	Response
	study this was 1.6months but this is likely to be longer. Our expert believe that this is likely as chemotherapy with docetaxel would be next or BSC.	with ceritinib is likely to be longer than 1.6 months, as it was presented in the ASCEND-2 study. It concluded that, in clinical practice, treatment with ceritinib could plausibly continue after disease progression and the best estimate of the duration of treatment came from ASCEND-2. Please see section 4.9 of the FAD.

Comments received from clinical experts and patient experts

None

Comments received from commentators

None

Comments received from members of the public

None

Summary of comments received from members of the public

None

Comment received internally from NICE

Comment [sic]	Response
From the pre-meeting briefing document. Quote: 'The company assumed there were no administration costs for ceritinib'. However pharmacy costs for a specialist cancer centre may be of relevance here particularly since the comparator 'best supportive care' would encompass	Thank you for your comment. The Committee heard from the ERG that compared with the high costs of ceritinib treatment, which is one of the key drivers of cost effectiveness, the impact of administration costs on the ICER is likely to be small. The Committee acknowledged this, but concluded that administration costs for ceritinib should have been

administration costs via a different service provision (such as primary care supply of standard therapies). It is not clear if these costs are factored into the economic model elsewhere?	included in the modelling. Please see FAD section 4.18.

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Mr M Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
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London SW12 2BU

27th October 2015

Dear Mr Boysen,

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

Novartis would like to thank the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal and to provide further clarifications for consideration.

Our comments are provided in response to the standard four questions on which NICE have stated they are interested in receiving comments, as detailed on Page 1 of the ACD.

There are four primary comments that we have on the ACD, which have been outlined below:

i. Novartis welcomes NICE's proposal that the guidance on this technology is considered for review by the Guidance Executive when the results of the ASCEND-5 trial are reported (expected to be in the second quarter of 2016). In order to enable a timely review, Novartis will update NICE as soon as possible upon any development on the availability of the ASCEND-5 clinical trial data.
ii. Based on the available evidence, we strongly believe that it is reasonable to conclude that ceritinib **meets the requirements for an end-of-life therapy.**
iii. We believe that ceritinib is an innovative technology, as indicated by its Promising Innovative Medicine (PIM) designation, and offers benefits beyond those captured in the quality adjusted life year (QALY) outcome.
iv. The comparator selected in the scope was limited to BSC, due to the absence of other third-line treatment options and understanding of the management of ALK+ NSCLC at the time of the scope decision. Clinical practice, however, clearly demonstrates that fitter patients and patients who have not yet received chemotherapy in previous lines of treatment, are likely to undergo treatment with

systemic anticancer therapy (SACT) rather than BSC upon disease progression on crizotinib. SACT should therefore be considered as the relevant comparator to ceritinib for those patients that are considered eligible to receive this type of treatment.

In addition to these comments, we have also presented a summary of factual inaccuracies and further clarifications for consideration.

Overall, we believe that the ACD represents a fair summary of the evidence presented by Novartis and the subsequent Evidence Review Group (ERG) review. We are highly disappointed, however, to see that the NICE Committee has not acknowledged the end of life status for ceritinib, with the ACD citing a lack of sufficient certainty in the evidence. We believe that the NICE Committee has made this judgement without fully taking into account the nature of this indication.

We firmly believe that, taking account of the various sources of information on which a decision can be based (presented in this response), it is clear that ceritinib merits end-of-life status. For conditions such as this, where there is an extensive unmet need and a highly innovative therapy that represents a step-change in the management of the condition, we ask that NICE takes a balanced, considered approach in its assessment of the end-of-life criteria, rather than seeking objective confirmation that, given the comparator identified in the scope (best supportive care), would not be feasible. In fact, clinical experts have advised Novartis that it would be ethically challenging to design a randomised controlled study where patients could be allocated to either BSC or active treatment with ceritinib. This will always result in unavoidable uncertainty in estimates, and an inevitable difficulty in measuring the extension to life “objectively and robustly”.

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

Yours sincerely,

[redacted]

[redacted]

Novartis Pharmaceuticals UK Ltd

Table of Contents

I. Has all of the relevant evidence been taken into account?

There are several pieces of evidence that Novartis does not believe the Committee has adequately considered, mainly the determination of whether ceritinib meets the criteria for an end of life treatment and the innovative nature of the technology. Additional comments as well as factual inaccuracies and clarification questions have also been provided in this section.

a. End of Life Criteria

With regards to the end of life criteria, the ACD concluded that the life expectancy for people with anaplastic lymphoma kinase positive (ALK+) NSCLC on current standard of care and the size of the population eligible to receive ceritinib were within a suitable range to meet the pre-specified criteria. However, it also noted that "*while it was possible that ceritinib offers an average extension to life of at least 3 months, the data were too uncertain to consider that this criterion had been met objectively and robustly*".

As discussed above, as an oncology treatment for patients near to the end of their life, it is unreasonable to expect direct evidence versus a best supportive care comparator in this indication due to the ethical implications of such a trial design. In addition, the uncontrolled nature of the evidence presented for ceritinib is a direct reflection of the early licensing of this therapy based on phase I and phase II single-arm studies in recognition of ceritinib's innovative value and the unmet need faced by this patient population. Therefore, the only possible approach to approximating extension to life with ceritinib is to estimate the survival benefit of ceritinib using a naïve indirect comparison with the best available evidence as determined by a systematic literature review. This is the approach that was taken in our submission.

In the phase II clinical trial (ASCEND-2), median overall survival (OS) amongst 140 patients treated with ceritinib was 14.9 months (95% CI: 13.5, NE).[1] Survival estimates were similar in a phase I trial of ceritinib (ASCEND-1) in which 163 patients treated with ceritinib experienced a median OS of 16.7 months (95% CI: 14.8, NE).[2] The pooled estimate of median OS across the ASCEND-2 and ASCEND-1 clinical trials was 15.64 months (95% CI: 14.66, NE).

A retrospective analysis by Ou *et al.* was the only available, relevant evidence source in the population under consideration, as identified by a systematic literature review. There are acknowledged limitations in this naïve indirect comparison in relation to the small sample size of the Ou *et al.* study, the lack of stratification of baseline characteristics by BSC vs chemotherapy groups in the publication and the limited information on potential confounding factors, as noted by the ERG report. However, the ERG also noted that there is no other data to use; this paucity of available data must be seen as a reflection of the high unmet need in this indication and will inevitably give rise to considerable limitations in an attempted comparison.

The median overall survival for treatment with BSC (no active treatment) in the Ou *et al.* study was approximately 2.2 months; 8.9 months when considering the entire patient cohort, including patients who continued on crizotinib following disease progression.[3] Taking the estimate for OS pooled across patients who received BSC or chemotherapy the median OS is 3.9 months and for the patients receiving chemotherapy alone the estimate of OS was 5.4

months.[3] Considering a pooled median OS of 15.64 months reported across the ASCEND-2 and ASCEND-1 trials, these results suggests an **extension to overall survival of approximately 10 months**, well above the 3 month requirement for the end of life criteria. Furthermore, even if the OS of the entire cohort considered in the Ou *et al.* study is considered, 8.9 months, the extension to overall survival would still be approximately 6 months, again much greater than the 3 month limit specified by the end of life criteria. Although we acknowledge the caveats that must be associated with such naïve comparisons, in the face of the limitations imposed by the available data the only reasonable method to explore uncertainty is to compare ceritinib against this available data. Such a comparison suggests that even if BSC was associated with the treatment benefit in terms of extension to life that resulted from use of chemotherapy in this study (a conservative assumption), ceritinib offers an extension to life over BSC of well above 3 months.

A clinical advisor consulted by the company prior to the submission confirmed that the BSC results from the Ou *et al.* studies could be generalised to all patients who have progressed on crizotinib, and is not specific to those that are considered less fit. Thus, the statement in the ACD response that "the BSC group in Ou *et al* may therefore have been sicker than patients in the ASCEND studies" is not supported, suggesting that the results from the Ou *et al.* study do not underestimate the effectiveness of BSC for the population of interest, and therefore supports the estimate of an extension to overall survival of approximately 10 months for patients on ceritinib. This would be consistent with correspondence with the author of the Ou *et al.* study who confirmed that "BSC will not perform better against novel ALK inhibitors for patients who continue CBPD as ALK is such a strong oncogenic driver that continual ALK suppression with an ALK inhibitor is important".

Furthermore, during the NICE Committee meeting expert clinicians confirmed that an OS estimate of 3–6 months was reasonable for patients receiving BSC in the indication under review. By taking the upper bound estimate here (6 months), in order for ceritinib to not meet the necessary criteria of resulting in an extension to life of at least 3 months following BSC, the OS of patients receiving ceritinib would need to be less than 9 months, which would assume that **each of the ASCEND clinical trials individually overestimates OS by a minimum of 5 months (~one-third of the absolute estimate)** in order for this criteria to not be met. Taken another way, given that PFS was 6.9 months and 7.0 months in the ASCEND-1 and ASCEND-2 trials, respectively, in order for the extension to life offered by ceritinib to be less than 3 months following BSC, this would require an assumption that post-progression survival following ceritinib treatment is less than 2 months. Given that the Committee agreed that the ASCEND-1 and ASCEND-2 trials could be considered generalisable to the relevant population in England, it seems highly unreasonable to implicitly suggest that the trial estimates observed represent such considerable overestimates of the actual overall survival on ceritinib for the relevant population in England.

A retrospective analysis of 73 patients treated with sequential crizotinib and ceritinib provides further support of the benefit of ceritinib in terms of overall survival. A subgroup of patients in this study (n=32; 44%) received their crizotinib treatment in a second-line setting which represents a similar patient population to the PROFILE 1007 study of crizotinib. The combined median OS from the time of crizotinib initiation for sequential treatment with crizotinib and ceritinib for this patient subgroup was 30.3 months.[4] Given that median overall

survival in the PROFILE 1007 study was 20.3 months, this again indicates **an approximate 10 month extension to life** for the post-crizotinib population when treated with ceritinib.[5]

In conclusion, we accept that it is not possible to generate an objective quantitative estimate for extension to life, but attest that it is not a reasonable expectation in this indication. We believe that, in accordance with the NICE guidance, estimates of the extension to life can **be shown or reasonably inferred** from the available data, and that this is strongly indicative of a survival benefit **>3 months**. The patient expert at the Committee meeting highlighted the "immeasurable value" of a therapy that has the potential to extend life at the end of life, and consideration of the NICE end of life criteria should take into account this value alongside the inevitable uncertainty. Based on the balance of evidence presented above and in the submission document itself, we believe that the only reasonable conclusion is to consider ceritinib as an end of life therapy.

b. Innovative Nature of Ceritinib

The ACD notes that "the Committee concluded that ceritinib **may be innovative**". We believe that there is considerable evidence of the innovative value of ceritinib that has been formally recognised by various regulatory bodies and that there is little doubt that ceritinib is an innovative therapy.

Firstly, the innovative value of ceritinib has been formally recognised through the granting of a Promising Innovative Medicines (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA). Ceritinib is one of only 9 therapies currently to have been awarded this designation, which is awarded based on consideration of the benefit/risk balance of the medicine based on available data and forms part of the Early Access to Medicines Scheme (EAMS).[6]

In the United States of America, the Food and Drug Administration (FDA) have similarly formally recognised the innovative value of ceritinib, granting both Accelerated Approval and Breakthrough Therapy Designation to ceritinib for the treatment of ALK+ NSCLC in patients with disease progression on, or who are intolerant to, crizotinib.[7] Accelerated Approval recognises medicines that fulfil an unmet medical need for serious conditions whilst Breakthrough Therapy Designation is awarded to those therapies that may demonstrate substantial improvement over available therapy. These therefore act as recognition of the potential for ceritinib to provide a step-change in the management of a condition for which there are currently highly limited options.

The ACD commented on a lack of evidence regarding the benefit of ceritinib with respect to controlling brain metastases and improving patient quality of life. However, in its licensed population, ceritinib has demonstrated efficacy in treating patients who reported brain metastases at baseline, while data from non-clinical models has shown that ceritinib is able to effectively penetrate the blood-brain barrier.[8-11] In contrast, crizotinib has demonstrated poor penetration of the blood-brain barrier; ceritinib has a 20-fold greater potency than crizotinib in enzymatic assays, and, as noted by the ERG, the effects of crizotinib on brain metastases remain less certain.[12, 13] Furthermore, a recent presentation by Crino *et al.* highlighted that the ASCEND-2 trial found no deterioration in patient's lung cancer symptoms and QoL while receiving ceritinib treatment, regardless of the presence or absence of baseline brain metastases.[14]

c. Systemic Anticancer Chemotherapy (SACT) as relevant comparator for ceritinib

The comparator for the current appraisal of ceritinib was restricted to best supportive care (BSC) in the NICE scope.

The National Chemotherapy Algorithm for the treatment of NSCLC, however, reports that chemotherapy is also used for patients who have progressed on crizotinib at second-line.[15]

In addition, clinical experts consulted by Novartis have confirmed that fitter patients and patients who have not yet received such treatment in previous lines of treatment, undergo treatment with systemic anticancer therapy (SACT), rather than receiving BSC. This is supported by a recent international survey of physicians, which found 77% of physicians in the EU (n=30) would prescribe chemotherapy for patients who have progressed on crizotinib, while only 30% would recommend BSC.[16]

Novartis is conducting a multi-centre retrospective study following ALK+ NSCLC patients who have progressed on crizotinib on the NHS in the UK. The primary objective of the study is to describe treatment pathways for ALK+ NSCLC patients in the UK from initiation of first-line treatment. It is expected that this study will present in Q1 2016 and its finding will inform understanding of the relevant comparators for ceritinib in future NICE reappraisals.

Restricting the relevant comparator of ceritinib to BSC alone has important methodological implications in that clinical experts have confirmed that it would not be ethical to randomise patients to BSC in a clinical trial. As a consequence, the possibility to generate clinical evidence that fulfils the NICE reference case (in terms of randomised, comparative data) would be highly improbable. Furthermore, with crizotinib recently gaining positive CHMP opinion as 1st line treatment for ALK+ NSCL patients, it is highly likely that a larger number of patients would be considered eligible for chemotherapy upon disease progression on crizotinib.[17]

d. Eligible Patient Population

The Appraisal Consultation Document notes that the estimated eligible patient population is **120 patients**. However, Novartis would like to take the opportunity to correct this value, which we acknowledge was an error in our own submission that has subsequently been taken forward into the NICE materials.

Within our submission, we presented the calculation of the eligible patient population via two alternative methods:

1. Table 5 of our submission presented an estimation based on CDF notifications for crizotinib in a second-line setting and then subsequent rates of survival and progression to receive ceritinib following this. This gave rise to an estimated eligible patient population of **66 patients**.

2. Appendix 2 of our submission presented an estimation based on a similar approach for calculation to that taken in the second-line appraisal of crizotinib by NICE (TA296) and this gave rise to an estimated eligible patient population of **98 patients**.

We fully acknowledge that we quote an eligible patient population of **120 patients** within the Executive Summary and the section considering the end of life criteria within our submission.

However, as highlighted above, this value has no basis in an attempt to use evidence to derive an estimation; it simply represents a "placeholder" value from before the calculations were completed and that was not subsequently updated.

We have no doubt that the preference of NICE and all stakeholders would be for the estimates of the eligible patient population to be those that are evidence-based, and therefore we ask that the Committee acknowledges the values of **66** and **98** patients, rather than the value of 120 patients, as the estimated size of the eligible patient population in their Final Appraisal Determination document. We would be very happy to publish an erratum on this point if this would be helpful as we feel that this is an important point to clarify; given that various parties will no doubt be referring back to these publically available documents in the future we do not wish for this inaccuracy to carry forwards any further.

e. Factual Inaccuracies

The ACD states that in using the Ou *et al.* (2014) study to estimate survival for patients undergoing best supportive care (BSC), "the company deemed that the appropriate comparison included both BSC and chemotherapy". This is not an accurate representation of the way in which the Ou *et al*. data was considered within our submission. We specified that the study "evaluated patients receiving BSC (no active treatment), of relevance to the decision problem outlined in this submission. In addition, this study also evaluated patients receiving systemic chemotherapy, of relevance to a scenario analysis". To clarify, we considered the appropriate comparison to be with the BSC group only (hence why this was selected as the base case) and the comparison to BSC and chemotherapy was considered only as an exploratory scenario analysis. Where available, results of the two treatment arms BSC (n=37) and systemic chemotherapy (n=37) were presented separately in order to make the distinction clear. For example, the mean overall survival for patients in the BSC arm was presented as 2.2 months (95% CI: 1.1, 3.8) and 5.4 months (95% CI: 3.8, 12.3) in the systemic therapy arm. The estimate of 2.2 months was carried forward as the main comparison. Where the value of the pooled estimate of all patients who did not continue crizotinib (BSC and systemic therapy) 3.9 months (95% CI: 2.7, 5.1), was considered, this was in the context of simply exploring uncertainty in the BSC estimate presented in the Ou *et al.* paper and demonstrating how the estimate altered when also considering those patients who received chemotherapy. This pooled estimate was not used in the naïve indirect comparison with the ASCEND-2 and ASCEND-1 trials.

f. Additional Clarifications

- Our submission presents the mean change from baseline in EORTC QLQ-C30 global health status as assessed in ASCEND-2 in Figure 21 of the submission. The ACD noted that the company submission did not provide the actual scores from the European Organisation for Research and Treatment of Cancer's core quality-of-life questionnaire (EORT-QLQ-C30) in ASCEND-2, nor did it state the time point at which the summary of results was calculated. As such, please find the additional data presented in Table 1 below.

Table 1: Summary of EORTC QLQ-C30 scores by time point (Fully analysis set)

Time point, n	Statistic	Baseline	Post Baseline	Change[a]
C1 D1, n=134	Mean (SD)	55.16 (25.747)	NA	NA
	Median, (Min, Max)	58.33 (0.0, 100.0)	NA	NA
C2 D1, n=122	Mean (SD)	55.60 (25.989)	54.44 (21.592)	-1.16 (22.095)
	Median, (Min, Max)	58.33 (0.0, 100.0)	50.00 (0.0, 100.0)	0.00 (-58.3, 75.0)
C3 D1, n=114	Mean (SD)	57.68 (26.286)	56.21 (23.144)	-1.46 (25.792)
	Median, (Min, Max)	66.67 (0.0, 100.0)	58.33 (0.0, 100.0)	0.00 (-58.3, 83.3)
C5 D1, n=98	Mean (SD)	60.46 (25.645)	63.18 (21.066)	2.72 (25.293)
	Median, (Min, Max)	66.67 (0.0, 100.0)	66.67 (0.0, 100.0)	0.00 (-58.3, 83.3)
C7 D1, n=82	Mean (SD)	62.70 (24.541)	67.58 (21.397)	4.88 (26.930)
	Median, (Min, Max)	66.67 (0.0, 100.0)	66.67 (0.0, 100.0)	0.00 (-100.0, 83.3)
C9 D1, n=47	Mean (SD)	61.17 (25.137)	59.57 (21.632)	-1.60 (28.533)
	Median, (Min, Max)	66.67 (0.0, 100.0)	58.33 (0.0, 100.0)	0.00 (-91.7, 83.3)
C11 D1, n=29	Mean (SD)	62.07 (25.838)	64.37 (21.810)	2.30 (22.919)
	Median, (Min, Max)	66.67 (0.0, 91.7)	66.67 (16.7, 100.0)	0.00 (-66.7, 58.3)
C13 D1, n=18	Mean (SD)	57.41 (25.226)	61.11 (22.506)	3.70 (20.457)
	Median, (Min, Max)	66.67 (8.3, 83.3)	58.33 (16.7, 91.7)	4.17 (-50.0, 41.7)
C15 D1, n=2	Mean (SD)	58.33 (11.785)	58.33 (11.785)	0.00 (0.000)
	Median, (Min, Max)	58.33 (50.0, 66.7)	58.33 (50.0, 66.7)	0.00 (0.0, 0.0)
EOT, n=28	Mean (SD)	51.79 (24.360)	39.58 (20.864)	-12.20 (19.176)
	Median, (Min, Max)	54.17 (0.0, 91.7)	45.83 (0.0, 83.3)	-16.67 (-41.7, 33.3)

[a]Change = Post Baseline – Baseline
Abbreviations: C, cycle; D, day; EOT, end of treatment; SD, standard deviation

- The ACD response concludes that the application of a reduced dose intensity of 82.8% in the economic model was likely to underestimate the dosage paid for by the NHS due to unused tablets that would be wasted as a consequence of short term dose reductions. The dose intensity of 82.8% was based on a weighted average of the mean relative dose intesitises from the ASCEND-1 and ASCEND-2 trials, and therefore consistent with the clinical data presented in the submission. As noted in the committee meeting itself, it can be considered appropriate to apply the trial dose intensity when calculating the ICER because the effectiveness side of the equation was based on results from these clinical trials and therefore reflective of effectiveness estimates at this average dose intensity.

  An increase to a 100% dose intensity, as presented in a scenario analysis in the company submission, resulted in a 19% increase in the ICER (from £62,456/QALY to £74,519/QALY). This is likely an overestimate due to not accounting for increased effectiveness that may be associated with patients who are in fact taking a higher dose, and does not allow for patients who experience a long-term dose reduction, which as noted in the ACD response is unlikely to result in wasted tablets.

- Considering that there is no available evidence on the efficacy of BSC in patients with ALK+ NSCLC, an older study by Shepherd *et al.* was presented to provide data on NSCLC patients randomised to receive erlotinib or palliative care.[18] It is acknowledged that the patient population in the Shepherd *et al.* study is broader than the population of interest, ALK+ NSCLC, in part because the ALK mutation had not yet been identified at the time of this study. However, in the absence of alternative data, the value of a median PFS of 1.8 months for patients receiving palliative care was considered in the cost-effectiveness model presented in the company submission. Novartis would like to stress that clinical experts contacted by the company stated that upon discontinuation on crizotinib and without any suitable active treatment, patients would experience a very rapid progression of their disease. Thus, it should be noted that the inclusion of a period of PFS for the BSC arm in the economic model presented in the company submission represents a very conservative approach to the cost-effectiveness analysis.

II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

With the exception of the comments noted in Part I of this response, Novartis considers that the summaries of clinical and cost-effectiveness represent reasonable interpretations of the evidence.

III. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Novartis firmly believe that ceritinib represents a step-change in the management of ALK+ NSCLC in patients previously treated with crizotinib, by providing a targeted therapy with demonstrable benefits in terms of progression-free survival and overall survival. The value of such an option for patients who are currently faced with treatment options limited to either chemotherapy or best supportive care, is immeasurable.

Novartis also strongly believes that ceritinib meets the end-of-life criteria for patients previously treated with crizotinib, and that therefore the NICE guidance should be reviewed in order to incorporate this fundamental finding.

Finally, Novartis welcomes the recommendation included in section 7 of the ACD to proceed to review this guidance "*when the results of the ASCEND-5 trail are reported (expected to be in the second quarter of 2016)*" (page 38 of ACD) and urges NICE to consider re-evaluation of ceritinib as a priority upon availability of this data.

IV. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Novartis does not consider that there are any aspects of the recommendations that require particular consideration in this regard.

V. References

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Mr Jeremy Powell
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From The Registrar
[redacted]

30 October 2015

Dear Mr Powell

Re: ACD - non company consultees & commentators: (Lung cancer (non-small-cell, anaplastic lymphoma kinase positive, previously treated) - ceritinib) [729]

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 31,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI/RCP/ACP/RCR are grateful for the opportunity to respond to the above Appraisal Consultation Document. We would like to make the following comments:

- Our experts note that the initial QALY was above the threshold for NICE approval and that the QALY increased following review by the committee.
- We note that the increase to the QALY followed comparison of other second line studies versus BSC (Shepherd et al. and Ou et al.). This gave OS of 2.2 months and was open to bias as the patients with ALK positive lung cancer were deemed fitter. Our experts do not believe this necessarily follows as ALK activated patients can present very late, often with brain metastases. There is also difficulty in getting patients on ASCEND 5 related to the fitness of patients and rapidity with which they progress after crizotinib.

We note that the committee concluded that as ASCEND2 allowed treatment of ceritinib beyond radiological progression, this would be replicated in real life. In the study this was 1.6months but this is likely to be longer. Our expert believe that this is likely as chemotherapy with docetaxel would be next or BSC.

Yours sincerely

[redacted]
Registrar