NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

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:
   - Roche
   - Pfizer

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Additional evidence** provided by the company, Roche

5. **ERG review of the additional evidence**, provided by BMJ Group
   - Addendum to the review of additional evidence

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

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Single Technology Appraisal

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

Type of stakeholder:

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 Social Care 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 document (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 and Social Care, 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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Roche	Roche are disappointed with the provisional negative recommendation. Alectinib is an innovative treatment, as demonstrated by the Promising Innovative Medicine (PIM) designation, and Early Access to Medicines Scheme (EAMS), that would provide a significant improvement over currently available therapies for ALK-positive NSCLC. NICE have acknowledged the benefit alectinib brings, in terms of Progression Free Survival (PFS) and CNS Progression Free Survival, and Roche will endeavour to work with NICE to turn this preliminary decision around to a positive Final Appraisal Determination. Based on our reading of the ACD, the key concerns underpinning the draft recommendation are uncertainty around a number of assumptions in the economic model: • Appropriate Overall Survival (OS) distribution • Appropriate RECIST measurement • Subsequent therapy distributions • Management of CNS metastases • Appropriate progressed disease utility value Our full response is provided below and addresses in turn, each of the above mentioned key points underpinning the draft negative recommendation, and any additional analyses to support a reversal of this preliminary negative recommendation. In addition, as part of this response, we have: • Included the latest data cut of the ALEX trial, as supportive evidence • Submitted a new PAS proposal to Department of Health to support committee decision making in determining alectinib to be a cost-effective option for untreated ALK-positive NSCLC Please note: NICE preferred assumptions regarding wastage and oncologist visits have been updated for all analyses.	Thank you for your comment. The FAD recommends alectinib for adults with untreated ALK-positive advanced NSCLC.
2	Company	Roche	Overall Survival distribution:	Thank you for your comment. During the appraisal the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The ACD states: "The company used an exponential extrapolation of overall survival for alectinib and crizotinib for their base case, because this was the second best fit to the PROFILE 1014 data and judged by the company to be clinically plausible based on their discussions with clinical experts … for consistency with the company's modelling of progression-free survival, the ERG preferred to use Kaplan–Meier data for the first 18 months, and then switch to an exponential tail. The committee agreed with the ERG's comments and concluded that the ERG's approach for modelling overall survival was the most reasonable." Given the committee preference for KM for the first 18 months, then switching to exponential tail, the company base case has been updated with this assumption.	committee considered the overall survival extrapolation function (see section 3.20 of the FAD).
3	Company	Roche	Appropriate RECIST analysis: The ACD states: "The clinical experts confirmed that CNS RECIST is not routinely used in UK clinical practice. The committee concluded that assessing events using only RECIST criteria was more appropriate than assessments based on CNS RECIST and RECIST criteria." Given the committee preference for the RECIST-only analysis, the company base case has been updated with this assumption. Nevertheless, as described in our clarification question response, the RECIST+CNS-RECIST analysis was chosen as the base case analysis as it is the most robust option available: incorporating all identified CNS progressions from the ALEX trial (in line with the competing risks analysis secondary endpoint). Whilst Roche understands, and highlighted ourselves that CNS RECIST is not conducted in clinical practice, there are two main limitations with the RECIST-only analysis: 1. A number of CNS events are likely missing: clinicians were not required to capture progression location; therefore any event without further information was classified as a "non-CNS progression" potentially underestimating the analysis. 2. Extrapolation under-captures anticipated long term CNS progressions: CNS progressions that are captured by CNS RECIST+RECIST will ultimately become symptomatic CNS progressions, they are just captured earlier	Thank you for your comment. During the appraisal the committee considered whether progression events should be measured using CNS-RECIST and RECIST, or RECIST only (see section 3.16 of the FAD). The committee concluded that analyses based on RECIST only are more clinically relevant.
4	Company	Roche	Subsequent therapy distributions: The ACD states: "The clinical experts advised that in routine practice they would expect around 70% to 80% of people on crizotinib to have treatment with ceritinib after progression … The clinical experts also explained that people having alectinib would not have subsequent treatment with a tyrosine kinase inhibitor. They estimated that 50% of people who progressed while taking alectinib would have subsequent	Thank you for your comment. During the appraisal the committee considered the subsequent treatment distributions (see section 3.22 of the FAD). The committee also considered the role of subsequent treatments on quality of life (see section 3.25-3.28 of the FAD). It concluded that the distribution of subsequent treatments in the company's model

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>chemotherapy, and that the remaining 50% would have best supportive care … The committee preferred to assume a distribution that more closely reflects UK clinical practice.”

Roche agrees subsequent therapies should reflect clinical practice: Roche tried to be reflective of UK clinical practice in the submitted base case (original submission ahead of ERG clarification questions). Therefore we are happy to update our base case in line with what was advised during the committee meeting.

Based on the conclusion in the ACD, there are three approaches we could undertake. Based on the conclusion in the ACD, we are presenting only the 2 more conservative scenarios regarding subsequent treatment distributions: a middle ground scenario, or a lower ceritinib usage (decreasing the costs associated with crizotinib). Both options are highlighted below.

For simplicity, and to again reflect a more conservative ICER for alectinib, only one line of subsequent therapy is included for crizotinib (therefore not accounting for the 40% to 50% anticipated to receive third line chemotherapy); and it is assumed the remaining proportion of patients in the second line setting who do not receive ceritinib after crizotinib only receive best supportive care (BSC) as opposed to chemotherapy.

<table>
<tr><td rowspan="2">Scenario</td><td colspan="2">Post-alectinib</td><td colspan="2">Post-crizotinib</td></tr>
<tr><td>Chemotherapy</td><td>BSC</td><td>Ceritinib</td><td>BSC</td></tr>
<tr><td>“Middle ground”</td><td>50%</td><td>50%</td><td>75%</td><td>25%</td></tr>
<tr><td>“Conservative”</td><td>50%</td><td>50%</td><td>70%</td><td>30%</td></tr>
</table>

Our updated base case includes the low ceritinib usage assumptions, with the middle ground option being presented as a scenario analysis.</td><td>reflected clinical practice, but considered that it was preferable to also model the role of subsequent treatments on quality of life.</td></tr>
<tr><td>5</td><td>Company</td><td>Roche</td><td>Management of CNS metastases:

The ACD states: “The clinical experts explained that treatment of CNS metastases is highly complex. They agreed that steroids would be offered to most people with CNS metastases. The clinical experts estimated that 20% to 25% of people with CNS metastases would have stereotactic radiotherapy, and 25% would have whole-brain radiotherapy, but that these treatments are not mutually exclusive. The clinical experts also suggested that surgical resection is sometimes used to manage CNS metastases. Although the committee recognised that treatment of CNS metastases is a complex area with variation in practice, it considered that the estimates that more closely reflect UK clinical practice (that is, 20% to 25% having stereotactic radiosurgery, 25% having whole brain radiotherapy) were the best assumptions to use in the model.”</td><td>Thank you for your comment. During the appraisal the committee considered the management of CNS metastases (see section 3.24 of the FAD). It concluded that the company’s model adequately captures the management of CNS progression events.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Roche agrees management of CNS metastases should reflect clinical practice. Therefore we have updated our base case in line with what was advised during the committee meeting.

Similarly to above, based on the conclusion in the ACD, there are three approaches we could undertake. Based on the conclusion in the ACD, we are presenting only the 2 more conservative scenarios regarding CNS metastases management costs: a middle ground scenario, or a scenario assuming less use of SRS and surgical resection, reducing overall costs of CNS progression. Both options are highlighted below.

<table>
<tr><td>Scenario</td><td>SRS</td><td>WBRT</td><td>Surgical resection</td><td>Steroids</td></tr>
<tr><td>“Middle ground”</td><td>22.5%</td><td>25%</td><td>5%</td><td>100%</td></tr>
<tr><td>“Conservative”</td><td>20%</td><td>25%</td><td>0%</td><td>100%</td></tr>
</table>

Our updated base case includes the lower costs associated with CNS progression, with the middle ground option being presented as a scenario analysis. Either scenario is still deemed conservative however, based on clinical expert feedback that these treatments are not mutually exclusive.</td><td></td></tr>
<tr><td>6</td><td>Company</td><td>Roche</td><td>Progressed disease utility value:

The ACD states: “The clinical experts stated that the company’s utility of 0.52 for the CNS progressed-disease state was reasonable, but the utility for the non-CNS progressed disease state may be an overestimate. The committee recalled that the utility estimates accepted for the recent appraisal of ceritinib were lower than the values derived from ALEX. The clinical experts highlighted that the utility estimates in ALEX may be affected by the inclusion of people with asymptomatic CNS progressed disease, and by those who were too ill to complete quality-of-life questionnaires. Because of this, the committee accepted the company’s chosen health state utility values, but considered that the value for non-CNS progressed disease may be too high.”

Roche appreciates the committee consideration and acceptance of the ALEX trial utilities. However, to provide further certainty in committee decision making, a scenario has been incorporated utilising the Roughley et al utility values, as described by the ERG.

It should be highlighted these utilities are associated with a different population to the ALEX trial population, therefore should not be considered as a base case. However, we hope this scenario analysis also demonstrates alectinib to be a cost effective option for untreated ALK-positive NSCLC, when accounting for the updated PAS.</td><td>Thank you for your comment. During the appraisal the committee considered the post-progression utility values and the role of subsequent treatments on quality of life (see section 3.25-3.28 of the FAD). It concluded that the distribution of subsequent treatments in the company’s model reflected clinical practice, but considered that it was preferable to also model the role of subsequent treatments on quality of life. The committee also concluded that it was acceptable for post-progression utilities to reflect the site of disease progression.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
7	Company	Roche	Updated data cut of ALEX: An updated data cut of ALEX was undertaken in [redacted], when [redacted]. Full results have been provided in Appendix 1, however a summary has been provided here. To highlight: upon completion of primary analysis, the two independent review committee's (IRCs) were disbanded. As such, the only update to PFS available is by INV. The economic model has been updated with the new data (including updated distributions – see Appendix 1), however given the committee preference for PFS by IRC, and the committee preference to capture the costs and quality of life decrements associated with CNS progression (only possible with IRC measurement), only the OS updated result has been implemented as an economic analysis, and only as a scenario analysis. **[This comment makes reference to additional evidence from the ALEX trial submitted by the company. Details of this evidence can be found in Appendix 1.]**	Thank you for your comment. During the appraisal the committee considered data from the updated data-cut from ALEX (see section 3.19 of the FAD). It concluded that the most recent data on overall survival was the best available for estimating cost-effectiveness.
8	Company	Roche	Conclusions, and updated results: **[This comment makes reference to updated cost-effectiveness analyses submitted by the company. Details of this evidence can be found in Appendices 2 and 3.]**	Thank you for your comment. During the appraisal the committee considered the cost-effectiveness results from the company's update analyses (see sections 3.29 to 3.31 of the FAD). The committee concluded that alectinib is a cost-effective use of NHS resources for adults with untreated ALK-positive advanced NSCLC.
9	Commentator	Pfizer	The dosing for crizotinib is factually incorrect (pages 40 & 126 of Committee papers). It should be 250 mg administered orally twice daily.	Thank you for your comment. This factual inaccuracy has been explored and was found to have no impact on the most plausible ICER. For transparency, the committee were presented with details of this comment during the appraisal.
10	Commentator	Pfizer	The administration cost used in TA406 and TA422 is factually incorrect (page 163 of Committee papers). The administration cost accepted by the Committee at the time was £14.40	Thank you for your comment. This factual inaccuracy has been explored and was found to have no material impact on the most plausible ICER. For transparency, the committee were presented with details of this comment during the appraisal.
11	Commentator	Pfizer	The cost of ALK testing is factually incorrect (page 173 of Committee papers). In TA406 the Committee accepted a cost of £75 per IHC test and £120 per test for confirmatory FISH (for those who tested positive following IHC testing)	Thank you for your comment. This factual inaccuracy has been explored and was found to have no impact on the most plausible ICER. For transparency, the committee were presented with details of this

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				comment during the appraisal.
12	Commentator	Pfizer	The outcomes following real-world adjustment of PROFILE1014 data are factually incorrect (pages 394, 490 & 539 of Committee papers). The outcomes accepted by the Committee were 24.6 months median OS and 33.9 months mean OS (exponential curve in table B2, page 17, Company response to ACD TA406)	Thank you for your comment. PROFILE 1014 was considered as supplementary information, for validation only. This factual inaccuracy therefore had no impact on the most plausible ICER. For transparency, the committee were presented with details of this comment during the appraisal.
13	Commentator	Pfizer	The reference supporting treatment duration for crizotinib is incorrect (page 504 of Committee papers). While it states PROFILE1007 on page 504, the reference 75 is for PROIFILE1014	Thank you for your comment. This factual inaccuracy has been explored and was found to have no material impact on the most plausible ICER.
14	Commentator	Pfizer	Solomon 2014 (PROFILE1014) does not report utility values (row 2, Table 70, page 572 Committee papers). Utility values were reported in Felip 2015 (PROFILE1014), as noted in row 3 of Table 70)	Thank you for your comment. This factual inaccuracy has been explored and was found to have no material impact on the most plausible ICER.
15	Web comment		Hi there, I am writing with regard to the approval of Alectinib as a therapy for for ALK+ NSCLC patients and other aspects of the management of this disease within the NHS. I am a caregiver to my mother who was diagnosed with ALK+ NSCLC last year. I am also a member of the ALK+ Facebook group of which there are now over 1000 members. This gives members easy access to a lot of the research/information available regarding ALK+ lung cancer. Through keeping abreast of this information, it has become apparent that (at present) NHS ALK+ patients are receiving a distinct difference in treatment pathways and in some cases sub-standard care compared to other developed countries in the world. Here are some examples: 1) Alectinib is not currently available for use on the NHS as first line therapy. Many UK ALK+ patients are eagerly awaiting your decision on this approval. It will be very interesting to see what NICE's rational is for whatever decision they make and how it compares to the rationale of leading researchers and healthcare providers across the world. 2) Alectinib not currently being available or use on the NHS as a treatment option after first line treatment. One of NICE's concerns is that whilst Alectinib is more effective in the first line setting at delaying disease progression, it is not yet clear to them that it is superior in prolonging overall survival. If you are using lack of evidence for prolonged survival as a reason not to approve Alectinib first line. Then how do you justify not approving Alectinib for patients who progress on Crizotinib/and or Ceretinib when there is clear evidence that it can work in second line settings to "prolong survival"?	Thank you for your comment. The committee agreed that additional treatment options for delaying disease progression, particularly CNS disease progression, would benefit people with untreated ALK-positive advanced NSCLC. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for alectinib. The FAD recommends alectinib for adults with untreated ALK-positive advanced NSCLC.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			3) Not being offered routine brain MRI's as standard protocol at diagnosis or on an on-going basis unless symptomatic of brain metastases. This is despite current 1st line treatment of Crizotinib having poor CNS penetration. This is despite research which shows that patients without brain metastasis at diagnosis who start on Crizotinib, 1 in 3 will develop brain metastases within 12 months. This figure continues to rise after 12 months. This is despite the fact brain metastases are not always symptomatic, especially when they are in a more treatable stage. 4) Not offering re-biopsy after disease progression on 2 more lines of treatment to establish the sub-mutations driving cancer growth. This is despite the fact that research shows re-biopsy enables a more precise prediction of which treatment would offer the most benefit and which ones won't. This is despite the cost of millions of £'s worth of wasted medications that is inevitable if you choose a trial and error approach to treatment pathways over using an evidence based approach that is fast becoming standard practice in other countries. The above mentioned ALK+ Facebook group has collectively raised enough money to fund 2 research grants and proposals are currently in the process of being selected. It is fair to say that many ALK+ patients are hugely involved in trying to ensure they have a longer, brighter future whilst battling this disease. It is not fair that many of these patients are also being denied life prolonging care that seems to be well established in the rest of the world. I would really appreciate a response to this E-mail with your views on points 1-4 above and I hope that at least some of these points are also being discussed as part of your consultation process for the approval of Alectinib. If you cannot respond, please direct me to somebody who can. Thank you in advance.	
16	Web comment		Dear Admin Team at NICE, Hope all well from your end. I`m writing to you with regards to the ongoing process of licencing the Drug Alectinib for metastasis Non-small cell Lung Cancer.	Thank you for your comment. The committee agreed that additional treatment options for delaying disease progression, particularly CNS disease progression, would benefit people with untreated ALK-positive

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			As we all know statistically this is the most deadly and a lethal cancer which kills people not only in UK but also in other countries. The decease kills more people than prostate, colon and breast cancers altogether. After more than four decades the very poor outcome /prognosis stays the same and there`s lot to do to make things better for those affected. These new target therapy drugs and immunotherapy drugs have shown very positive outcomes through years of clinical trials in both quality of life and progression free survival. Most of the countries have understood the need and have approved or fast tracked access to these new drugs to combat this deadly decease. It is widely understood by now the stigma that Lung cancer is a smoker's decease is not the case for all. More & more evidence out there to say if you have lungs you can get lung cancer. My husband (47 Years old) recently diagnosed with lung cancer stage 4 after he suffered a PE (Pulmonary Emboli- bilateral) His history goes back to 2010 and he was asking for help throughout only to diagnosed in Nov-2017. He was a life-long non-smoker and was only 40 when the symptoms appeared. He was clearly at a disadvantage of being a non-smoker as none of the medical professionals were suspicious along the way and he has been treated for many misdiagnosis. I wish we could get back those years where his treatments would have been curative other than palliative but sadly now the only option is to manage its spreading and try to get him a good quality of life so he can be around his two young daughters bit longer(16yrs & 12yrs) He has ALK positive EML4 mutation and started off with Crizotinib. Now he is on Brigatinib under compassionate use. The newer TKI`s (tyrosine kinase inhibitors) for ALK mutations ( Eg; Alectinib, Brigatinib, Lorlatinib..) proven to give more broader coverage for resistance mutations and more protection in CNS system . All in all the more chances and hope to live longer with the loved one`s which they deserve. I understand the prospective of cost effectiveness in delivering new drugs under NHS but at the same time only 2%-5% patients represent ALK mutation and require these drugs to prolong life and most of them are young non-smokers. Any Cancer diagnosis is a horrible news to a family let along a Stage 4 Lung cancer. This changed almost everything in our life it is uncertainty, fear, financial difficulty and trauma we experience on a daily basis I am kindly requesting on behalf of every family affected by Lung Cancer who are having the ALK mutation in United Kingdom, to approve / Licence this new life saving drug which will surely make a huge difference to many patients & families. Thank you very much and looking forward for a favourable outcome. Yours Faithfully,	advanced NSCLC. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved commercial arrangement for alectinib. The FAD recommends alectinib for adults with untreated ALK-positive advanced NSCLC.
17	Web comment		Dear Team You will no doubt have received a few emails from ALK patients regarding alectinib, which is currently going through a NICE consultation process.	Thank you for your comment. The committee agreed that additional treatment options for delaying disease progression, particularly CNS disease progression, would benefit people with untreated ALK-positive

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			I am both a medical doctor (GP) and a patient, diagnosed with stage 4 ALK positive NSCLC in Oct 17. I am, however, in the fortunate position to have taken out private health insurance a few years ago, in part, to gain better access to cancer drugs. I did not seriously think I would be using my health insurance before the age of 50 and learning of my diagnosis has been a shock. I have been a healthy, non-smoker taking part in fitness activities most of my life. I have only had a handful of days off sick from work. A similar profile applies to other ALK patients. We are a cohort of lung cancer patients who are young, fit and 'healthy'. With the right targeted treatment, we all aspire to continue our working lives, paying our taxes etc. Due to my private insurance, I am very lucky to have had access to alectinib as a first line ALK inhibitor. Recent studies all support superiority over crizotinib relating to the Progression Free Survival (PFS) and its ability to cross the blood brain barrier - very important as a third of stage 4 NSCL patients will have brain metastases at diagnosis. Within five days of taking this medication, my symptoms of shortness of breath climbing up a flight of stairs and cough all improved. My CT scan result at 3 months reported a 50% reduction in tumour size. I am currently training for a 10K run, raising money for charity. Side effects from treatment have been manageable and I am hoping to return to work in the next couple of months. Alectinib has quite literally changed my life. Although I am not curable, I am currently living well with my cancer. I don't know if my story will add any value to your final decision on alectinib availability on the NHS. I hope you consider what first line drug you would want a friend or relative to take if they were diagnosed. My professional choice after reading all available data, is for alectinib to be available first line. I would really like my fellow 'ALKies' to have access to this drug in the same way I do, without any more delay. Regards	advanced NSCLC. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for alectinib. The FAD recommends alectinib for adults with untreated ALK-positive advanced NSCLC.
18	Web comment		Good morning, As a mother of a daughter (Vicky) aged 30 diagnosed with nsclc stage 1V ALK+ August 2017, I feel that our families voice should be heard before any decisions are made regarding the approval of Alectinib 1st line. Please make sure my e-mail is shared with all parties involved in the debate and decision making. To cut a long story short a few weeks after diagnosis, Vicky's biopsy showed she was ALK+. A horrific diagnosis was now feeling less horrific and even hopeful. After much research especially on The ALK+ Facebook page which is a closed group of over	Thank you for your comment. The committee agreed that additional treatment options for delaying disease progression, particularly CNS disease progression, would benefit people with untreated ALK-positive advanced NSCLC. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for alectinib. The FAD recommends alectinib for adults with untreated ALK-positive advanced NSCLC.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			1000 members we read of people surviving and thriving on targeted therapy in the USA. 3 years, 5 years and 10+ . My daughter is one of the lucky ones whose diagnosis occurred when the EAMS 1st line Alectinib was available. Her wonderful Oncologist applied for the drug and Roche agreed that she was eligible (thank you Roche). After a few weeks of minor side effects Vicky has continued to work full time as a Personal Trainer and also training to do a half marathon in June.She ran 11.3 miles last week and averaged an 8.5 minute pace. My point here is that most people diagnosed ALK+ are below the age of 50. This drug has far fewer side effects than Crizotinib and allows for a relatively normal and fulfilled life and can contributin to society. As Im sure youre aware, the ALEX trial showed that progression free survival (PFS) with alectinib as your first line drug is 25.7 mos and 11.1 with crizotinib. In the NP28673 trial, which tested alectinib as the second line drug after criztotinib resistance, the median PFS was 8.9 months. So crizotinib plus alectinib = 20 mos compared to 25.7 with alectinib as first line. WORSE, the NP28673 study showed that only 48% (internationally) responded to alectinib in the second line, while 83% responded to the drug in ALEX as the first-line drug. Surely these statistics stand alone as a reason to make Alectinib 1st line. Vicky's oncologist obviously agrees with this (other wise he wouldn't have applied for Alectinib) as do all of the leading lung cancer specialists throughout the developed world. Another huge factor is that unfortunately Crizotinib is known to have very poor protection of the brain and most people on this medication will fail because of brain metastasis. This can often lead to a very complicated progression called LMD. Alectinib is far superior.at protecting the brain. This reduces the need for other costly therapies alongside Alectinib which invariably happens with Crizotinib. My daughter is so fortunate to have this fantastic drug and we are so grateful!. She has had 2 scans so far and they show large shrinkage and stability. I want everybody diagnosed with this senseless disease to have the same opportunity as Vicky. I therefore implore you to approve the use of Alectiilib 1st line. I attach my daughter's blog which shows you the real face of ALK+ .https://www.facebook.com/vickyvstrongerthancancer/ Kind regards	
19	Web		To whom it may concern,	Thank you for your comment. The committee agreed

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	comment		I'm writing to you to highlight my case for you to approve Alectinib to the NHS. My name is Merete Baksh, I'm 67 years old, I have lived a quite healthy and active life, when diagnosed with stage 4 lung cancer nearly a year ago, my family, friends and myself was in shock and disbelief as I have lived a health life). Being tested and found the ALK mutation present, I started taking Crizotinib nearly ten months ago, I'm living a full life with very little side effects, I am aware the drug will stop working and I will get progression sooner or later, I would feel more hopeful if I knew Alectinib will be an option for me in the future, just as is for my fellow ALK patients around the world. Thank you for taking your time to read this email and hope you will pass it on to whoever iwill be making the decision to release Alectinib. Yours sincerely	that additional treatment options for delaying disease progression, particularly CNS disease progression, would benefit people with untreated ALK-positive advanced NSCLC. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for alectinib. The FAD recommends alectinib for adults with untreated ALK-positive advanced NSCLC.
20	Web comment		Dear Sir or Madam, I wanted to register my disappointment at your provisional refusal to allow alectinib as first line treatment for alk positive NSCLC patients. I suffer from this disease, and Tyrosine Kinase Inhibitors such as alectinib have made a huge difference to my life. Like many people I am relatively young, in my forties, have dependent children, and have none of the normal risk factors for lung cahcer; I have never smoked. Taking these drugs allows me to continue to look after my children, to work, to pay taxes, and to make a contribution to society. It is too late for me to have alectinib as first line therapy; it was not available when I was first diagnosed. However I do see many other patients through social media, who do very well on it for a very long time, often longer than crizotinib and ceritinib combined. It seems to be the almost universal choice for oncologists when they are able to prescribe it, including oncologists in Britain during the period when it was briefly available on an expanded access scheme. Therefore I find it very difficult to understand how this decision not to approve alectinib can be made. It will undoubtedly lead to lives being shorter and more unpleasant than they otherwise would for many otherwise blameless people in the prime of their lives. Parents will be torn away from their children sooner. Which would seem to be against the principles of the NHS and any decent society. Yours faithfully,	Thank you for your comment. The committee agreed that additional treatment options for delaying disease progression, particularly CNS disease progression, would benefit people with untreated ALK-positive advanced NSCLC. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for alectinib. The FAD recommends alectinib for adults with untreated ALK-positive advanced NSCLC.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

NICE National Institute for Health and Care Excellence

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roche Products Ltd; hereinafter “Roche”
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return via NICE Docs

NICE National Institute for Health and Care Excellence

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Roche are disappointed with the provisional negative recommendation. Alectinib is an innovative treatment, as demonstrated by the Promising Innovative Medicine (PIM) designation, and Early Access to Medicines Scheme (EAMS), that would provide a significant improvement over currently available therapies for ALK-positive NSCLC. NICE have acknowledged the benefit alectinib brings, in terms of Progression Free Survival (PFS) and CNS Progression Free Survival, and Roche will endeavour to work with NICE to turn this preliminary decision around to a positive Final Appraisal Determination. Based on our reading of the ACD, the key concerns underpinning the draft recommendation are uncertainty around a number of assumptions in the economic model: • Appropriate Overall Survival (OS) distribution • Appropriate RECIST measurement • Subsequent therapy distributions • Management of CNS metastases • Appropriate progressed disease utility value Our full response is provided below and addresses in turn, each of the above mentioned key points underpinning the draft negative recommendation, and any additional analyses to support a reversal of this preliminary negative recommendation. In addition, as part of this response, we have: • Included the latest data cut of the ALEX trial, as supportive evidence • Submitted a new PAS proposal to Department of Health to support committee decision making in determining alectinib to be a cost-effective option for untreated ALK-positive NSCLC Please note: NICE preferred assumptions regarding wastage and oncologist visits have been updated for all analyses.
2	**<u>Overall Survival distribution</u>** The ACD states: *"The company used an exponential extrapolation of overall survival for alectinib and crizotinib for their base case, because this was the second best fit to the PROFILE 1014 data and judged by the company to be clinically plausible based on their discussions with clinical experts … for consistency with the company's modelling of progression-free survival, the ERG preferred to use Kaplan–Meier data for the first 18 months, and then switch to an exponential tail. The committee agreed with the ERG's comments and concluded that the ERG's approach for modelling overall survival was the most reasonable."* Given the committee preference for KM for the first 18 months, then switching to exponential tail, the company base case has been updated with this assumption.
3	**<u>Appropriate RECIST analysis</u>** The ACD states: *"The clinical experts confirmed that CNS RECIST is not routinely used in UK clinical practice. The committee concluded that assessing events using only RECIST criteria was more appropriate than assessments based on CNS RECIST and RECIST criteria."* Given the committee preference for the RECIST-only analysis, the company base case has been

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

<table>
<tr><td></td><td>updated with this assumption.

Nevertheless, as described in our clarification question response, the RECIST+CNS-RECIST analysis was chosen as the base case analysis as it is the most robust option available: incorporating all identified CNS progressions from the ALEX trial (in line with the competing risks analysis secondary endpoint).

Whilst Roche understands, and highlighted ourselves that CNS RECIST is not conducted in clinical practice, there are two main limitations with the RECIST-only analysis:
1. A number of CNS events are likely missing: clinicians were not required to capture progression location; therefore any event without further information was classified as a “non-CNS progression” potentially underestimating the analysis.

2. Extrapolation under-captures anticipated long term CNS progressions: CNS progressions that are captured by CNS RECIST+RECIST will ultimately become symptomatic CNS progressions, they are just captured earlier</td></tr>
<tr><td>4</td><td><u>Subsequent therapy distributions</u>

The ACD states: “The clinical experts advised that in routine practice they would expect around 70% to 80% of people on crizotinib to have treatment with ceritinib after progression … The clinical experts also explained that people having alectinib would not have subsequent treatment with a tyrosine kinase inhibitor. They estimated that 50% of people who progressed while taking alectinib would have subsequent chemotherapy, and that the remaining 50% would have best supportive care … The committee preferred to assume a distribution that more closely reflects UK clinical practice.”

Roche agrees subsequent therapies should reflect clinical practice: Roche tried to be reflective of UK clinical practice in the submitted base case (original submission ahead of ERG clarification questions). Therefore we are happy to update our base case in line with what was advised during the committee meeting.

Based on the conclusion in the ACD, there are three approaches we could undertake. Based on the conclusion in the ACD, we are presenting only the 2 more conservative scenarios regarding subsequent treatment distributions: a middle ground scenario, or a lower ceritinib usage (decreasing the costs associated with crizotinib). Both options are highlighted below.

For simplicity, and to again reflect a more conservative ICER for alectinib, only one line of subsequent therapy is included for crizotinib (therefore not accounting for the 40% to 50% anticipated to receive third line chemotherapy); and it is assumed the remaining proportion of patients in the second line setting who do not receive ceritinib after crizotinib only receive best supportive care (BSC) as opposed to chemotherapy.

<table>
<tr><td rowspan="2">Scenario</td><td colspan="2">Post-alectinib</td><td colspan="2">Post-crizotinib</td></tr>
<tr><td>Chemotherapy</td><td>BSC</td><td>Ceritinib</td><td>BSC</td></tr>
<tr><td>“Middle ground”</td><td>50%</td><td>50%</td><td>75%</td><td>25%</td></tr>
<tr><td>“Conservative”</td><td>50%</td><td>50%</td><td>70%</td><td>30%</td></tr>
</table>

Our updated base case includes the low ceritinib usage assumptions, with the middle ground option being presented as a scenario analysis.</td></tr>
<tr><td>5</td><td><u>Management of CNS metastases</u>

The ACD states: “The clinical experts explained that treatment of CNS metastases is highly complex. They agreed that steroids would be offered to most people with CNS metastases. The clinical experts</td></tr>
</table>

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

<table>
<tr><td></td><td>

estimated that 20% to 25% of people with CNS metastases would have stereotactic radiotherapy, and 25% would have whole-brain radiotherapy, but that these treatments are not mutually exclusive. The clinical experts also suggested that surgical resection is sometimes used to manage CNS metastases. Although the committee recognised that treatment of CNS metastases is a complex area with variation in practice, it considered that the estimates that more closely reflect UK clinical practice (that is, 20% to 25% having stereotactic radiosurgery, 25% having whole brain radiotherapy) were the best assumptions to use in the model."

Roche agrees management of CNS metastases should reflect clinical practice. Therefore we have updated our base case in line with what was advised during the committee meeting.

Similarly to above, based on the conclusion in the ACD, there are three approaches we could undertake. Based on the conclusion in the ACD, we are presenting only the 2 more conservative scenarios regarding CNS metastases management costs: a middle ground scenario, or a scenario assuming less use of SRS and surgical resection, reducing overall costs of CNS progression. Both options are highlighted below.

Scenario	SRS	WBRT	Surgical resection	Steroids
"Middle ground"	22.5%	25%	5%	100%
"Conservative"	20%	25%	0%	100%

Our updated base case includes the lower costs associated with CNS progression, with the middle ground option being presented as a scenario analysis. Either scenario is still deemed conservative however, based on clinical expert feedback that these treatments are not mutually exclusive.

</td></tr>
<tr><td>6</td><td>

Progressed disease utility value

The ACD states: *"The clinical experts stated that the company's utility of 0.52 for the CNS progressed-disease state was reasonable, but the utility for the non-CNS progressed disease state may be an overestimate. The committee recalled that the utility estimates accepted for the recent appraisal of ceritinib were lower than the values derived from ALEX. The clinical experts highlighted that the utility estimates in ALEX may be affected by the inclusion of people with asymptomatic CNS progressed disease, and by those who were too ill to complete quality-of-life questionnaires. Because of this, the committee accepted the company's chosen health state utility values, but considered that the value for non-CNS progressed disease may be too high."*

Roche appreciates the committee consideration and acceptance of the ALEX trial utilities. However, to provide further certainty in committee decision making, a scenario has been incorporated utilising the Roughley et al utility values, as described by the ERG.

It should be highlighted these utilities are associated with a different population to the ALEX trial population, therefore should not be considered as a base case. However, we hope this scenario analysis also demonstrates alectinib to be a cost effective option for untreated ALK-positive NSCLC, when accounting for the updated PAS.

</td></tr>
<tr><td>7</td><td>

Updated data cut of ALEX

An updated data cut of ALEX was undertaken in [redacted], when [redacted]. Full results have been provided in Appendix 1, however a summary has been provided here.

To highlight: upon completion of primary analysis, the two independent review committee's (IRCs) were disbanded. As such, the only update to PFS available is by INV.

The economic model has been updated with the new data (including updated distributions – see

</td></tr>
</table>

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

Appendix 1), however given the committee preference for PFS by IRC, and the committee preference to capture the costs and quality of life decrements associated with CNS progression (only possible with IRC measurement), only the OS updated result has been implemented as an economic analysis, and only as a scenario analysis.

PFS (INV) – [redacted]

	Crizotinib	Alectinib
Median PFS (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI), p-value	[redacted]	

[redacted]

OS – [redacted]

	Crizotinib	Alectinib
Median OS (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI), p-value	[redacted]	

Please return via NICE Docs

NICE National Institute for Health and Care Excellence

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

	
8	**Conclusions, and updated results** An updated base case has been provided, in response to this ACD, accounting for the assumptions, as discussed above. A summary is also provided below. Full details can be found in Appendix 2. In addition, a number of scenario analyses have been conducted as supportive evidence (as also discussed in earlier sections of this response). For full details, please see Appendix 3. A summary is also provided below. Finally, Roche has updated the discount of alectinib, from [redacted] to [redacted], equating to a pack price of [redacted]. All with-PAS results account for this new discount. Base case analysis The new base case accounts for the following updates: • No wastage – crizotinib dosing updated to account for 30 day pack • Oncologist visit every 4 weeks • KM+Exponential OS distribution • RECIST only PFS and CNS PFS • IRC PFS endpoint • Original utility values (PFS, non-CNS PD, CNS PD) • 50% chemotherapy usage post-alectinib; 70% ceritinib usage post-crizotinib; remaining patients receiving BSC • 20% SRS, 25% WBRT, 100% steroid usage for management of CNS metastases • February 2017 ALEX data cut The updated base case results in a QALY gain of 3.79, and a life-year gain of 5.14 for alectinib, opposed to a QALY gain of 2.84, and a life-year gain of 4.32 for crizotinib. The resulting ICER at list prices is £69,310. Accounting for the updated alectinib PAS, this ICER decreases to [redacted], reflecting the greater health benefit and reduced cost relative to crizotinib at list price. However, as crizotinib and ceritinib are also subject to confidential PAS discounts, this ICER should be interpreted with caution. Scenario analyses

Please return via NICE Docs

NICE National Institute for Health and Care Excellence

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

	Scenario 1: • 50% chemotherapy usage post-alectinib; 75% ceritinib usage post-crizotinib; remaining patients receiving BSC • 22.5% SRS, 25% WBRT, 5% surgery, 100% steroid usage for management of CNS metastases Scenario 2: • 50% chemotherapy usage post-alectinib; 70% ceritinib usage post-crizotinib; remaining patients receiving BSC • 20% SRS, 25% WBRT, 0% surgery, 100% steroid usage for management of CNS metastases • Updated overall survival ([redacted] data cut) Scenario 3: • 50% chemotherapy usage post-alectinib; 75% ceritinib usage post-crizotinib; remaining patients receiving BSC • 22.5% SRS, 25% WBRT, 5% surgery, 100% steroid usage for management of CNS metastases • Updated overall survival ([redacted] data cut) Scenario 4: • 50% chemotherapy usage post-alectinib; 70% ceritinib usage post-crizotinib; remaining patients receiving BSC • 20% SRS, 25% WBRT, 0% surgery, 100% steroid usage for management of CNS metastases • Roughley et al utility value for progressed disease (0.65) rather than ALEX data to reflect the non-CNS PD health state Three of four scenarios result in lower ICER estimates for alectinib, than the base case, ranging from £58,994 per QALY to £66,881 per QALY at list price, and [redacted] to [redacted] with the updated alectinib discount. Conversely, by adapting the PD utility value, the ICERs increase to £74,563 per `QALY at list price, and [redacted] with the updated alectinib discount. Whilst the crizotinib and ceritinib PAS are not known by Roche, we hope the committee are satisfied with the updated analyses to deem alectinib a cost effective option to treat ALK positive NSCLC and enable patients to access this innovative medicine.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more

NICE National Institute for Health and Care Excellence

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent	Pfizer Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The dosing for crizotinib is factually incorrect (pages 40 & 126 of Committee papers). It should be 250 mg administered orally twice daily
2	The administration cost used in TA406 and TA422 is factually incorrect (page 163 of Committee papers). The administration cost accepted by the Committee at the time was £14.40

Please return via NICE Docs

NICE National Institute for Health and Care Excellence

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Consultation on the appraisal consultation document – deadline for comments is **5pm on 26 April** via NICE Docs

3	The cost of ALK testing is factually incorrect (page 173 of Committee papers). In TA406 the Committee accepted a cost of £75 per IHC test and £120 per test for confirmatory FISH (for those who tested positive following IHC testing)
4	The outcomes following real-world adjustment of PROFILE1014 data are factually incorrect (pages 394, 490 & 539 of Committee papers). The outcomes accepted by the Committee were 24.6 months median OS and 33.9 months mean OS (exponential curve in table B2, page 17, Company response to ACD TA406)
5	The reference supporting treatment duration for crizotinib is incorrect (page 504 of Committee papers). While it states PROFILE1007 on page 504, the reference 75 is for PROIFILE1014
6	Solomon 2014 (PROFILE1014) does not report utility values (row 2, Table 70, page 572 Committee papers). Utility values were reported in Felip 2015 (PROFILE1014), as noted in row 3 of Table 70)

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return via NICE Docs

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Comments on the ACD:	

Hi there,

I am writing with regard to the approval of Alectinib as a therapy for for ALK+ NSCLC patients and other aspects of the management of this disease within the NHS.

I am a caregiver to my mother who was diagnosed with ALK+ NSCLC last year. I am also a member of the ALK+ Facebook group of which there are now over 1000 members. This gives members easy access to a lot of the research/information available regarding ALK+ lung cancer.

Through keeping abreast of this information, it has become apparent that (at present) NHS ALK+ patients are receiving a distinct difference in treatment pathways and in some cases sub-standard care compared to other developed countries in the world. Here are some examples:

1) **Alectinib is not currently available for use on the NHS as first line therapy.**

   Many UK ALK+ patients are eagerly awaiting your decision on this approval. It will be very interesting to see what NICE's rational is for whatever decision they make and how it compares to the rationale of leading researchers and healthcare providers across the world.

2) **Alectinib not currently being available or use on the NHS as a treatment option after first line treatment.**

   One of NICE's concerns is that whilst Alectinib is more effective in the first line setting at delaying disease progression, it is not yet clear to them that it is superior in prolonging overall survival. If you are using lack of evidence for prolonged survival as a reason not to approve Alectinib first line. Then how do you justify not approving Alectinib for patients who progress on Crizotinib/and or Ceretinib when there is clear evidence that it can work in second line settings to "prolong survival"?

3) **Not being offered routine brain MRI's as standard protocol at diagnosis or on an on-going basis unless symptomatic of brain metastases.**

   This is despite current 1st line treatment of Crizotinib having poor CNS penetration.

   This is despite research which shows that patients without brain metastasis at diagnosis who start on Crizotinib, 1 in 3 will develop brain metastases within 12 months.

   This figure continues to rise after 12 months.

This is despite the fact brain metastases are not always symptomatic, especially when they are in a more treatable stage.

4) Not offering re-biopsy after disease progression on 2 more lines of treatment to establish the sub-mutations driving cancer growth.

This is despite the fact that research shows re-biopsy enables a more precise prediction of which treatment would offer the most benefit and which ones won't.
This is despite the cost of millions of £'s worth of wasted medications that is inevitable if you choose a trial and error approach to treatment pathways over using an evidence based approach that is fast becoming standard practice in other countries.

The above mentioned ALK+ Facebook group has collectively raised enough money to fund 2 research grants and proposals are currently in the process of being selected. It is fair to say that many ALK+ patients are hugely involved in trying to ensure they have a longer, brighter future whilst battling this disease. It is not fair that many of these patients are also being denied life prolonging care that seems to be well established in the rest of the world.

I would really appreciate a response to this E-mail with your views on points 1-4 above and I hope that at least some of these points are also being discussed as part of your consultation process for the approval of Alectinib. If you cannot respond, please direct me to somebody who can.

Thank you in advance.

Name	[redacted]
Comments on the ACD:	

Dear Admin Team at NICE,

Hope all well from your end.

I`m writing to you with regards to the ongoing process of licencing the Drug Alectinib for metastasis Non-small cell Lung Cancer.

As we all know statistically this is the most deadly and a lethal cancer which kills people not only in UK but also in other countries. The decease kills more people than prostate, colon and breast cancers altogether.

After more than four decades the very poor outcome /prognosis stays the same and there`s lot to do to make things better for those affected.

These new target therapy drugs and immunotherapy drugs have shown very positive outcomes through years of clinical trials in both quality of life and progression free survival. Most of the countries have understood the need and have approved or fast tracked access to these new drugs to combat this deadly decease.

It is widely understood by now the stigma that Lung cancer is a smoker's decease is not the case for all. More & more evidence out there to say if you have lungs you can

get lung cancer.

My husband (47 Years old) recently diagnosed with lung cancer stage 4 after he suffered a PE (Pulmonary Emboli- bilateral)

His history goes back to 2010 and he was asking for help throughout only to diagnosed in Nov-2017.

He was a life-long non-smoker and was only 40 when the symptoms appeared.

He was clearly at a disadvantage of being a non-smoker as none of the medical professionals were suspicious along the way and he has been treated for many misdiagnosis.

I wish we could get back those years where his treatments would have been curative other than palliative but sadly now the only option is to manage its spreading and try to get him a good quality of life so he can be around his two young daughters bit longer(16yrs & 12yrs)

He has ALK positive EML4 mutation and started off with Crizotinib. Now he is on Brigatinib under compassionate use. The newer TKI`s (tyrosine kinase inhibitors) for ALK mutations ( Eg; Alectinib, Brigatinib, Lorlatinib..) proven to give more broader coverage for resistance mutations and more protection in CNS system . All in all the more chances and hope to live longer with the loved one`s which they deserve.

I understand the prospective of cost effectiveness in delivering new drugs under NHS but at the same time only 2%-5% patients represent ALK mutation and require these drugs to prolong life and most of them are young non-smokers.

Any Cancer diagnosis is a horrible news to a family let along a Stage 4 Lung cancer. This changed almost everything in our life it is uncertainty, fear, financial difficulty and trauma we experience on a daily basis

I am kindly requesting on behalf of every family affected by Lung Cancer who are having the ALK mutation in United Kingdom, to approve / Licence this new life saving drug which will surely make a huge difference to many patients & families.

Thank you very much and looking forward for a favourable outcome.

Yours Faithfully,

Name	[redacted]
Comments on the ACD:	

Dear Team

You will no doubt have received a few emails from ALK patients regarding alectinib, which is currently going through a NICE consultation process.

I am both a medical doctor (GP) and a patient, diagnosed with stage 4 ALK positive NSCLC in Oct 17. I am, however, in the fortunate position to have taken out private health insurance a few years ago, in part, to gain better access to cancer drugs.

I did not seriously think I would be using my health insurance before the age of 50

and learning of my diagnosis has been a shock. I have been a healthy, non-smoker taking part in fitness activities most of my life. I have only had a handful of days off sick from work. A similar profile applies to other ALK patients. We are a cohort of lung cancer patients who are young, fit and 'healthy'. With the right targeted treatment, we all aspire to continue our working lives, paying our taxes etc.

Due to my private insurance, I am very lucky to have had access to alectinib as a first line ALK inhibitor. Recent studies all support superiority over crizotinib relating to the Progression Free Survival (PFS) and its ability to cross the blood brain barrier - very important as a third of stage 4 NSCL patients will have brain metastases at diagnosis.

Within five days of taking this medication, my symptoms of shortness of breath climbing up a flight of stairs and cough all improved. My CT scan result at 3 months reported a 50% reduction in tumour size. I am currently training for a 10K run, raising money for charity. Side effects from treatment have been manageable and I am hoping to return to work in the next couple of months. Alectinib has quite literally changed my life. Although I am not curable, I am currently living well with my cancer.

I don't know if my story will add any value to your final decision on alectinib availability on the NHS. I hope you consider what first line drug you would want a friend or relative to take if they were diagnosed. My professional choice after reading all available data, is for alectinib to be available first line. I would really like my fellow 'ALKies' to have access to this drug in the same way I do, without any more delay.

Regards

Name	[redacted]

Comments on the ACD:

Good morning,

As a mother of a [redacted] ([redacted]) aged 30 diagnosed with nsclc stage 1V ALK+ August 2017, I feel that our families voice should be heard before any decisions are made regarding the approval of Alectinib 1st line.
Please make sure my e-mail is shared with all parties involved in the debate and decision making.

To cut a long story short a few weeks after diagnosis, [redacted] biopsy showed [redacted] was ALK+.

A horrific diagnosis was now feeling less horrific and even hopeful. After much research especially on The ALK+ Facebook page which is a closed group of over 1000 members we read of people surviving and thriving on targeted therapy in the USA.
3 years, 5 years and 10+ .

My [redacted] is one of the lucky ones whose diagnosis occurred when the EAMS 1st line Alectinib was available. [redacted] wonderful Oncologist applied for the drug and Roche agreed that [redacted] was eligible(thank you Roche).
After a few weeks of minor side effects [redacted] has continued to work full time as a Personal Trainer and also training to do a half marathon in June. [redacted] ran 11.3 miles last week and averaged an 8.5 minute pace.

My point here is that most people diagnosed ALK+ are below the age of 50.
This drug has far fewer side effects than Crizotinib and allows for a relatively normal and fulfilled life and can contributin to society.

As Im sure youre aware, the ALEX trial showed that progression free survival (PFS) with alectinib as your first line drug is 25.7 mos and 11.1 with crizotinib. In the NP28673 trial, which tested alectinib as the second line drug after criztotinib resistance, the median PFS was 8.9 months. So crizotinib plus alectinib = 20 mos compared to 25.7 with alectinib as first line. WORSE, the NP28673 study showed that only 48% (internationally) responded to alectinib in the second line, while 83% responded to the drug in ALEX as the first-line drug.

Surely these statistics stand alone as a reason to make Alectinib 1st line. [redacted] oncologist obviously agrees with this (other wise he wouldn't have applied for Alectinib) as do all of the leading lung cancer specialists throughout the developed world.

Another huge factor is that unfortunately Crizotinib is known to have very poor protection of the brain and most people on this medication will fail because of brain metastasis. This can often lead to a very complicated progression called LMD.

Alectinib is far superior.at protecting the brain. This reduces the need for other costly therapies alongside Alectinib which invariably happens with Crizotinib.
My [redacted] is so fortunate to have this fantastic drug and we are so grateful!. [redacted] has had 2 scans so far and they show large shrinkage and stability.
I want everybody diagnosed with this senseless disease to have the same opportunity as [redacted]. I therefore implore you to approve the use of Alectiilib 1st line.

I attach my [redacted] blog which shows you the real face of ALK+ [redacted]

Kind regards

Name	[redacted]
Comments on the ACD:	

To whom it may concern,

I'm writing to you to highlight my case for you to approve Alectinib to the NHS.

My name is [redacted] I'm 67 years old, I have lived a quite healthy and active life, when diagnosed with stage 4 lung cancer nearly a year ago, my family, friends and myself was in shock and disbelief as I have lived a health life). Being tested and found the ALK mutation present, I started taking Crizotinib nearly ten months ago, I'm living a full life with very little side effects, I am aware the drug will stop working and I will get progression sooner or later, I would feel more hopeful if I knew Alectinib will be an option for me in the future, just as is for my fellow ALK patients around the world.

Thank you for taking your time to read this email and hope you will pass it on to whoever iwill be making the decision to release Alectinib.
Yours sincerely

Name	[redacted]
Comments on the ACD:	

Dear Sir or Madam,

I wanted to register my disappointment at your provisional refusal to allow alectinib as first line treatment for alk positive NSCLC patients.

I suffer from this disease, and Tyrosine Kinase Inhibitors such as alectinib have made a huge difference to my life. Like many people I am relatively young, in my forties, have dependent children, and have none of the normal risk factors for lung cancer; I have never smoked. Taking these drugs allows me to continue to look after my children, to work, to pay taxes, and to make a contribution to society.

It is too late for me to have alectinib as first line therapy; it was not available when I was first diagnosed. However I do see many other patients through social media, who do very well on it for a very long time, often longer than crizotinib and ceritinib combined. It seems to be the almost universal choice for oncologists when they are able to prescribe it, including oncologists in Britain during the period when it was briefly available on an expanded access scheme.

Therefore I find it very difficult to understand how this decision not to approve alectinib can be made. It will undoubtedly lead to lives being shorter and more unpleasant than they otherwise would for many otherwise blameless people in the prime of their lives. Parents will be torn away from their children sooner. Which would seem to be against the principles of the NHS and any decent society.

Yours faithfully,

Appendix 1: ALEX updated data cut

The primary analysis of ALEX (NCT02075840) showed a superior investigator-assessed PFS with alectinib compared with crizotinib (HR=0.47; 95% CI: 0.34, 0.65, p<0.0001) in untreated patients with ALK-positive NSCLC. Efficacy and safety results from an updated data cut of ALEX (clinical cut-off [redacted]) are presented below.

Primary endpoint

At the latest data analysis, median treatment duration was [redacted] with alectinib and [redacted] with crizotinib. [redacted]

Figure 1: ALEX updated data analysis: Investigator-assessed PFS

[redacted]

Secondary endpoints

Upon completion of primary analysis, the two independent review committee's (IRCs) were disbanded. As such, PFS by IRC and time to CNS progression have not been updated.

Efficacy data for secondary endpoints (ORR, duration of response and overall survival) are consistent with the primary analysis. The proportion of patients with a confirmed response per RECIST v1.1 in the ITT population was [redacted] in the alectinib arm and [redacted]

[redacted] in the crizotinib arm. [redacted]

Table 1: ALEX updated data analysis: summary of ORR

	Alectinib n=152	**Crizotinib n=151**
Responders, n (%) (95% CI)	[redacted]	[redacted]
Complete response, n (%) (95% CI)	[redacted]	[redacted]
Partial response, n (%) (95% CI)	[redacted]	[redacted]
Stable disease, n (%) (95% CI)	[redacted]	[redacted]
Progressive disease, n (%) (95% CI)	[redacted]	[redacted]

The median duration of response (DOR) among responders was [redacted]. Median DOR was [redacted] in the alectinib treatment arm and [redacted] with crizotinib.

Figure 2: ALEX updated data analysis: duration of response

[redacted]

[redacted]

[redacted]

Figure 3: ALEX updated data analysis: overall survival


[redacted]

Subgroup analysis

As seen in the primary analysis, [redacted]

In patients with CNS metastases at baseline, [redacted]

Table 2: ALEX updated data analysis: CNS subgroup analysis

	Alectinib	Crizotinib	HR (95% CI)
No CNS metastases at baseline, mPFS months (95% CI)	[redacted]	[redacted]	[redacted]
CNS metastases at baseline, mPFS months (95% CI)	[redacted]	[redacted]	[redacted]

Safety analysis

[redacted]

[redacted]

Table 3: ALEX updated data analysis: safety summary

	Primary analysis		Updated analysis	
	Alectinib n=152	Crizotinib n=151	Alectinib n=152	Crizotinib n=151
All grade AEs, n (%) No. of events	147 (97) 1196	146 (97) 1365	[redacted]	[redacted]
Serious AEs, n (%)	43 (28)	44 (29)	[redacted]	[redacted]
Grade 3–5 AEs, n (%)	63 (41)	76 (50)	[redacted]	[redacted]
Fatal AEs, n (%)	5 (3)	7 (5)	[redacted]	[redacted]
AEs leading to treatment discontinuation, n (%)	17 (11)	19 (13)	[redacted]	[redacted]
AEs leading to dose reduction, n (%)	24 (16)	31 (21)	[redacted]	[redacted]
AEs leading to dose interruption, n (%)	29 (19)	38 (25)	[redacted]	[redacted]

Updated analysis – efficacy and safety conclusion

[redacted]

Impact on economic model – clinical parameters

OS

Table 4: Summary of goodness of fit for OS: alectinib and crizotinib

	Alectinib			Crizotinib		
Parametric distribution	**AIC**	**BIC**	**Rating**	**AIC**	**BIC**	**Rating**
Exponential	289.07	292.10	1	271.32	274.34	2
Weibull	289.36	295.41	4	272.18	278.21	5
Log-normal	288.56	294.61	2	268.16	274.19	1
Gamma	290.50	299.57	6	269.40	278.45	4
Log-logistic	288.85	294.89	3	270.46	276.49	3

Gompertz	291.07	297.12	5	273.32	279.35	6

Figure 4: Updated data cut OS distributions

Similarly to the February 2017 data cut, the exponential remains the best fitting and most clinically plausible curve for OS.

For the purposes of the scenario analyses as detailed in Appendix 3, in line with the committee preferred assumptions, the KM followed by the exponential tail is utilised, from [redacted] months onwards: where censoring increases.

PFS (INV)

Table 5: Summary of goodness of fit for PFS: alectinib and crizotinib

	Alectinib			Crizotinib		
Parametric distribution	**AIC**	**BIC**	**Rating**	**AIC**	**BIC**	**Rating**
Exponential	418.59	421.61	5	405.99	409.00	5
Weibull	413.20	419.25	4	403.30	409.33	4
Log-normal	405.32	411.37	1	391.99	398.03	1
Gamma	404.48	413.56	2	393.93	402.98	3
Log-logistic	409.49	415.54	3	394.18	400.22	2
Gompertz	420.59	426.63	6	407.73	413.77	6

Figure 5: Updated data cut PFS distributions - alectinib

Figure 6: Updated data cut PFS distributions - crizotinib

Similarly to the Febraury 2017 data cut, clinical plausibility is critical to assess the most appropriate PFS distribution, particularly for alectinib. As previously, the three best fitting curves (log normal, gamma and log logistic) all cross the OS curve. In addition, the weibull converges to the OS curve over time. Therefore, the most clinically plausible distribution remains the exponential for alectinib. Given the similarity of all distributions for crizotinib, and NICE DSU recommendations, separate parametric models of the same type have been fitted, and the KM with an exponential tail is used for both treatment arms.

As the committee has expressed a clear preference for the PFS by IRC endpoint, this updated analysis is not taken in to account in the scenario analyses in Appendix 3.

Further, it should again be highlighted that by utilising the PFS INV endpoint (either data cut), it is not possible to account for the costs and quality of life decrements

associated with CNS progression: in contrast to committee preferences, as detailed in the ACD.

Appendix 2 – Updated base case results

The new base case accounts for the following updates:

- No wastage – crizotinib dosing updated to account for 30 day pack
- Oncologist visit every 4 weeks
- KM+Exponential OS distribution
- RECIST only PFS and CNS PFS
- 50% chemotherapy usage post-alectinib; 70% ceritinib usage post-crizotinib; remaining patients receiving BSC
- 20% SRS, 25% WBRT, 100% steroid usage for management of CNS metastases
- February 2017 ALEX data cut

List price

Alectinib provides a QALY gain of 3.79, and a life-year gain of 5.14. At a total drug cost of £176,217 and a total overall cost of £209,668 at list price. In contrast, crizotinib provides a QALY gain of 2.84, and a life-year gain of 4.32. At a total drug cost of £83,574 and a total overall cost of £143,986 at list price.

As such, the resulting ICER of alectinib versus crizotinib is £69,310 per QALY gained. See Table 6 for a summary of the base case results.

Nevertheless, crizotinib, ceritinib and alectinib are all associated with confidential discounts, therefore this analysis is not the appropriate analysis for decision making purposes.

Table 6: Updated base case results (List price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.84				
Alectinib	£209,668	5.14	3.79	£65,681	0.83	0.95	£69,310

PAS price

In parallel to the ACD consultation, Roche has submitted an updated PAS proposal to the Department of Health to support committee decision making. The discount has been updated to [redacted], equating to a pack price of [redacted].

Results below incorporate this updated discount, however crizotinib and ceritinib are also subject to confidential discounts to which Roche has been unable to include in these analyses.

Table 7: Updated base case results (alectinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.84				
Alectinib	[redacted]	5.14	3.79	[redacted]	0.83	0.95	[redacted]

Appendix 3 – Scenario analyses results

Four scenarios have been explored as part of this response:

Scenario 1:

- 50% chemotherapy usage post-alectinib; 75% ceritinib usage post-crizotinib; remaining patients receiving BSC
- 22.5% SRS, 25% WBRT, 5% surgery, 100% steroid usage for management of CNS metastases

Scenario 2:

- 50% chemotherapy usage post-alectinib; 70% ceritinib usage post-crizotinib; remaining patients receiving BSC
- 20% SRS, 25% WBRT, 0% surgery, 100% steroid usage for management of CNS metastases
- Updated overall survival ([redacted] data cut)

Scenario 3:

- 50% chemotherapy usage post-alectinib; 75% ceritinib usage post-crizotinib; remaining patients receiving BSC
- 22.5% SRS, 25% WBRT, 5% surgery, 100% steroid usage for management of CNS metastases
- Updated overall survival ([redacted] data cut)

Scenario 4:

- 50% chemotherapy usage post-alectinib; 70% ceritinib usage post-crizotinib; remaining patients receiving BSC
- 20% SRS, 25% WBRT, 0% surgery, 100% steroid usage for management of CNS metastases
- Roughley et al utility value for progressed disease (0.65) rather than ALEX than ALEX data to reflect the non-CNS PD health state

Results can be found below. Please note, crizotinib and ceritinib are also subject to confidential discounts to which Roche has been unable to include in these analyses.

Table 8: Scenario analyses results (list price)

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
1	Crizotinib	£146,817	4.32	2.84				
	Alectinib	£210,197	5.14	3.79	£63,380	0.83	0.95	£66,881

2	Crizotinib	£144,255	4.42	2.90				
	Alectinib	£211,490	5.46	4.00	£67,234	1.05	1.10	£61,070
3	Crizotinib	£147,063	4.42	2.90				
	Alectinib	£212,013	5.46	4.00	£64,949	1.05	1.10	£58,994
4	Crizotinib	£143,986	4.32	2.75				
	Alectinib	£209,668	5.14	3.63	£65,681	0.83	0.88	£74,563

Table 9: Scenario analyses results (PAS price)

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
1	Crizotinib	£146,817	4.32	2.84				
	Alectinib	[redacted]	5.14	3.79	[redacted]	0.83	0.95	[redacted]
2	Crizotinib	£144,255	4.42	2.90				
	Alectinib	[redacted]	5.46	4.00	[redacted]	1.05	1.10	[redacted]
3	Crizotinib	£147,063	4.42	2.90				
	Alectinib	[redacted]	5.46	4.00	[redacted]	1.05	1.10	[redacted]
4	Crizotinib	£143,986	4.32	2.75				
	Alectinib	[redacted]	5.14	3.63	[redacted]	0.83	0.88	[redacted]

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

ERG REVIEW OF COMPANY'S RESPONSE TO THE ACD

April 2018

This report was commissioned by the NIHR HTA Programme as project number 17/56/01

BMJ Technology Assessment Group

TABLE OF CONTENTS

1 ERG REVIEW OF THE NEW EVIDENCE

The company submitted a response to address key uncertainties and preferences expressed by the Committee in the Appraisal Consultation Document (ACD). The ERG's review of the response and additional evidence provided by the company is provided under the following subheadings.

1.1 Updated data cut of ALEX

Clinical effectiveness evidence in the company's submission was based on the primary data cut from ALEX in February 2017. After the first appraisal committee meeting (ACM1), the company provided results from a data cut in [redacted] for investigator-assessed progression-free survival (INV PFS, the primary outcome of ALEX), overall survival (OS), objective response rate (ORR), duration of response (DOR), and adverse events. There are no updated results for independent review committee PFS (IRC PFS), which was the appraisal Committee's preferred outcome, because the ALEX review committees have been disbanded. The company included updated OS and INV PFS data and distributions as options in an economic model submitted after ACM1, but did not implement either in their base case; updated OS was used in the company's scenario analyses, but updated INV PFS was not used because it would create internal inconsistency with CNS PFS (IRC).

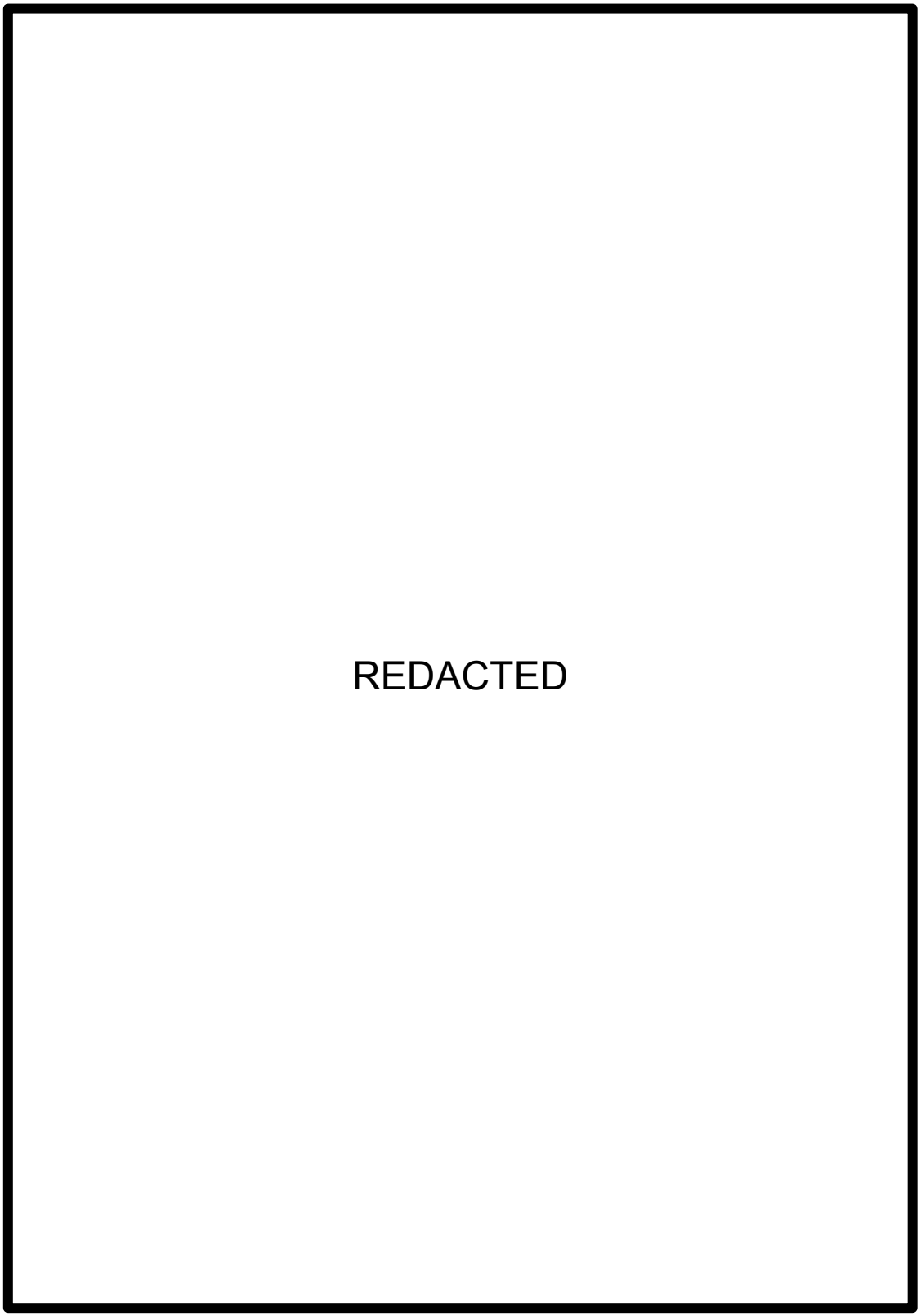
Updated median INV PFS with alectinib was [redacted], showing a substantial [redacted] over crizotinib (shown with February 2017 INV and IRC results in Table 1). The means of assessing the extent and direction of difference between alectinib and crizotinib across data cuts and assessors is limited because there is no updated IRC analysis, median INV PFS was not met for alectinib in February 2017, and the proportional hazards assumption does not hold. The available data indicate a [redacted] alectinib benefit by IRC at the primary data cut (15.3 months) than by INV at the updated analysis ([redacted]), which is substantiated by the shape of curves shown in Figure 1 (note that follow-up has been aligned across curves).

Table 1. RECIST-only PFS and time on treatment at the primary (February 2017) and updated data cuts ([redacted])

	February 2017 data cut (original submission)		**[redacted] data cut**	
	Alectinib (N = 152)	**Crizotinib (N = 151)**	**Alectinib (N = 152)**	**Crizotinib (N = 151)**
Median follow-up	18.6	17.6	[redacted]	[redacted]
Median IRC PFS (months)	25.7 (19.9 to NE)	10.4 (7.7 to 14.6)	IRCs were disbanded before the updated data cut.	
HR (95% CI)	0.50 (0.36 to 0.70)			
Median INV PFS (months)	NE (17.7 to NE)	11.1 (9.1 to 13.1)	[redacted]	
HR (95% CI)	0.47 (0.34 to 0.65)		[redacted]	
Median months on treatment	17.9	10.7	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; IRC, independent review committee; N, number of patients; NE, not estimable.

Figure 1. Kaplan–Meier curves for IRC PFS and INV PFS (February 2017), and INV PFS at [redacted] of ALEX



Abbreviations: CI, confidence interval; INV, investigator-assessed; IRC, independent review committee; NE, not estimable; PFS, progression-free survival.

OS remained immature in both groups at the [redacted] data cut. Text in the K–M figure provided by the company indicated [redacted] in the alectinib group and [redacted] in the

crizotinib group had died by [redacted] compared with 35 (23%) and 40 (27%), respectively, in February 2017. The ERG did not consider the updated results to resolve the uncertainty about comparative OS between the two treatments, but preferred for the most recent OS dataset to be used in the economic model (Section 3.2).

Table 2. OS at the primary (February 2017) and updated data cut ([redacted]) of ALEX

	February 2017 data cut (original submission)		[redacted] data cut	
	Alectinib (N = 152)	Crizotinib (N = 151)	Alectinib (N = 152)	Crizotinib (N = 151)
Patients with events, N (%)	35 (23%)	40 (27%)	[redacted]	[redacted]
Median OS (months)	NE (NE)	NE (NE)	[redacted]	[redacted]
HR (95% CI), p-value	0.76 (0.48 to 1.20), p = 0.24		[redacted]	
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of patients; NE, not estimable.				

Other updated results provided by the company – ORR, DOR and adverse events – are not used in the economic model. Updated results for ORR ([redacted]), DOR ([redacted]), and adverse events were all [redacted]; median DOR was met in both groups at the later data cut, [redacted]).

In the absence of updated IRC PFS, the ERG considers the original IRC PFS analysis (February 2017) and the updated OS analysis ([redacted]) the most appropriate clinical effectiveness evidence for the economic model.

1.2 Appropriate RECIST analysis

The ERG considers the company's decision to use IRC PFS based only on Response Evaluation Criteria in Solid Tumours (IRC RECIST-only) in their base case in line with the Committee's preference as stated in the ACD. Clinical experts advised the committee that central nervous system (CNS) progressions captured by the modified CNS RECIST were likely to be asymptomatic, and therefore not detected or treated in UK clinical practice, so including them in the definition of PFS was inappropriate.

In their response to the ACD, the company highlights that asymptomatic CNS RECIST progressions ultimately become symptomatic, which would not be reflected in the base case extrapolation because progression location was not routinely recorded with RECIST. The ERG notes that IRCs in ALEX did not have the information to assess if CNS progression was symptomatic, but more investigator-assessed CNS progressions in the crizotinib group than the alectinib group were asymptomatic. Asymptomatic CNS progressions also took longer to reach 'systemic' criteria than those in the alectinib group (company response to clarification question A8 and A9).

As such, incomplete capture of progression location by the IRC according to RECIST, and the advance of CNS progression from asymptomatic to symptomatic over time, means the company's base case is likely to be conservative with regard to the CNS activity of alectinib. However, should the alternative combined measure of PFS (IRC RECIST+CNS RECIST) be used in the economic model, treatment costs and utility decrements of CNS progression are likely to be applied prematurely compared with UK clinical practice, which would favour alectinib.

1.3 Overall survival in the economic model

The company's base case analysis includes the February 2017 data cut. Given that a more mature dataset was obtained by the company ([redacted] data cut), the ERG considers that using the updated, more mature data in the model is appropriate. The company modelled the OS curves in a similar fashion to the previous analysis, through the use of the OS KM data up to month 25 (previously month 18), then followed by an exponential tail.

The issues raised by the ERG upon the first Appraisal Committee Meeting with regards to OS data still stand. The ERG considers that ALEX does not provide robust evidence to substantiate a long-term OS benefit of alectinib compared with crizotinib. Furthermore, comparative OS data from ALEX may not be a reasonable reflection of what would be seen in UK clinical practice because treatment beyond disease progression may differ for alectinib and crizotinib in the UK, and subsequent therapies available to patients in ALEX do not reflect the UK pathway for ALK+ advanced NSCLC.

Furthermore, the ERG considers that the company's new analysis and submitted evidence do not mitigate the Committee's concerns related to OS data, given that OS data form the latest data cut off are still immature and median OS was not reached in either treatment arm. There is still no statistically significant difference in OS, despite the statistically significant difference in PFS. There were no new data or analyses provided to mitigate the ERG's and Committee's concerns about subsequent treatments received in ALEX and their likely impact on OS. This is despite the Committee highlighting it as a critical area of concern in the ACD: "*The committee agreed that the extent of the missing data, as well as the uncertainties about the choice and duration of subsequent treatments, could have a large effect on overall survival. The committee agreed that there was substantial uncertainty about the subsequent treatments people had in the trial and their effect on overall survival estimates in ALEX, which would need to be considered in its decision-making*." As such, the ERG remains concerned about the inherent uncertainty in the OS data and the likely bias introduced in the results of the economic model.

1.4 Subsequent therapy distributions

Overall survival data from ALEX cannot be adjusted to account for efficacy derived from subsequent therapies, because data were only captured for 41% of patients who discontinued study treatment. It is

impossible to know how representative this subset is of all patients who discontinued study treatment, and this uncertainty cannot be resolved. As such, any attempt to reflect the costs and QALYs of subsequent therapy distributions for alectinib and crizotinib based on UK clinical practice, is limited by the inability to adjust OS.

The extent of OS benefit derived from subsequent ALK-TKIs in ALEX compared with what might happen in UK clinical practice is likely to be higher in the alectinib arm than the crizotinib arm as no ALK-TKIs received after alectinib in ALEX will be available to patients in the UK, should alectinib be approved, whereas ceritinib is available for use after crizotinib.

The company implemented two analyses to reflect the Committee's view on the expected subsequent therapies available in the NHS after patients receive alectinib or crizotinib. The company's base case is based on the "conservative" scenario reported in Table 3, while the "middle ground" alternative was considered in a scenario analysis.

The ERG considers the implementation of the cost of subsequent treatments to reflect the Committee's preferences. Nonetheless, the ERG disagrees with the company's approach to exclude the impact of subsequent treatments on patients' quality of life. Therefore, the ERG incorporated the impact of subsequent treatments on the QALY analysis. and presents the results in Section 3.

The ERG agrees that subsequent therapies should be incorporated in the base case analysis however, including subsequent therapies in the analysis carries some flaws. For example, the option to include subsequent treatments in the company's model means that the CNS progression-related utility is no longer taken into account in the entire model, and all progressed patients experience a utility value related with their subsequent treatment, regardless of the site of tumour progression. The ERG changed this assumption in the company's model so that patients with CNS progression experience the CNS progression-related utility (0.52 in the company's base case analysis), even when receiving subsequent treatment. This utility value is lower than the utility experienced in the company's analysis of subsequent treatments (0.73 with second line TKI treatment and 0.66 with second line chemotherapy, Table 4). Results are presented in Section 3.

An important caveat to the subsequent treatment analysis is the impossibility to match the analysis of costs and benefits to the effectiveness used in the model, as subsequent treatment-trial data are very incomplete. The ERG agrees with the company that limiting the analysis to second line of treatment helps contain the uncertainty in the final ICER. Nonetheless, in order to avoid the clinically implausible scenario where patients receiving a TKI as second line treatment incur the TKI-related utility (Table 4) for the rest of their lifetime, the ERG assumed that after patients finish their second line treatment in the model (dictated by time on treatment taken from alternative trial data, Table 4), they experience a

utility of 0.47 for the rest of the economic analysis (including patients with CNS progression), regardless of the previous treatment received.

In order to implement the ERG's analysis of subsequent treatments into the model, a simplification had to be made, and weighted utilities were estimated and used in the analysis. For alectinib patients, the second line treatment-related utility value was estimated to be 0.57 (resulting from assuming that 50% receive chemotherapy and the remaining 50% receive BSC, Table 4). Crizotinib patients are assumed to experience a utility of 0.65 as 70% of patients move on to receive a TKI and 30% of patients receive BSC (Table 4). After 9 weeks in the alectinib arm, and 50 weeks in the crizotinib arm, 100% of patients (including the CNS progressed patients), experience a utility of 0.47. The ERG's assumptions regarding the utility analysis are exemplified in Figure 2. Results of the ERG analysis are reported on Section 3.

Table 3. Scenarios ran by the company on subsequent therapies

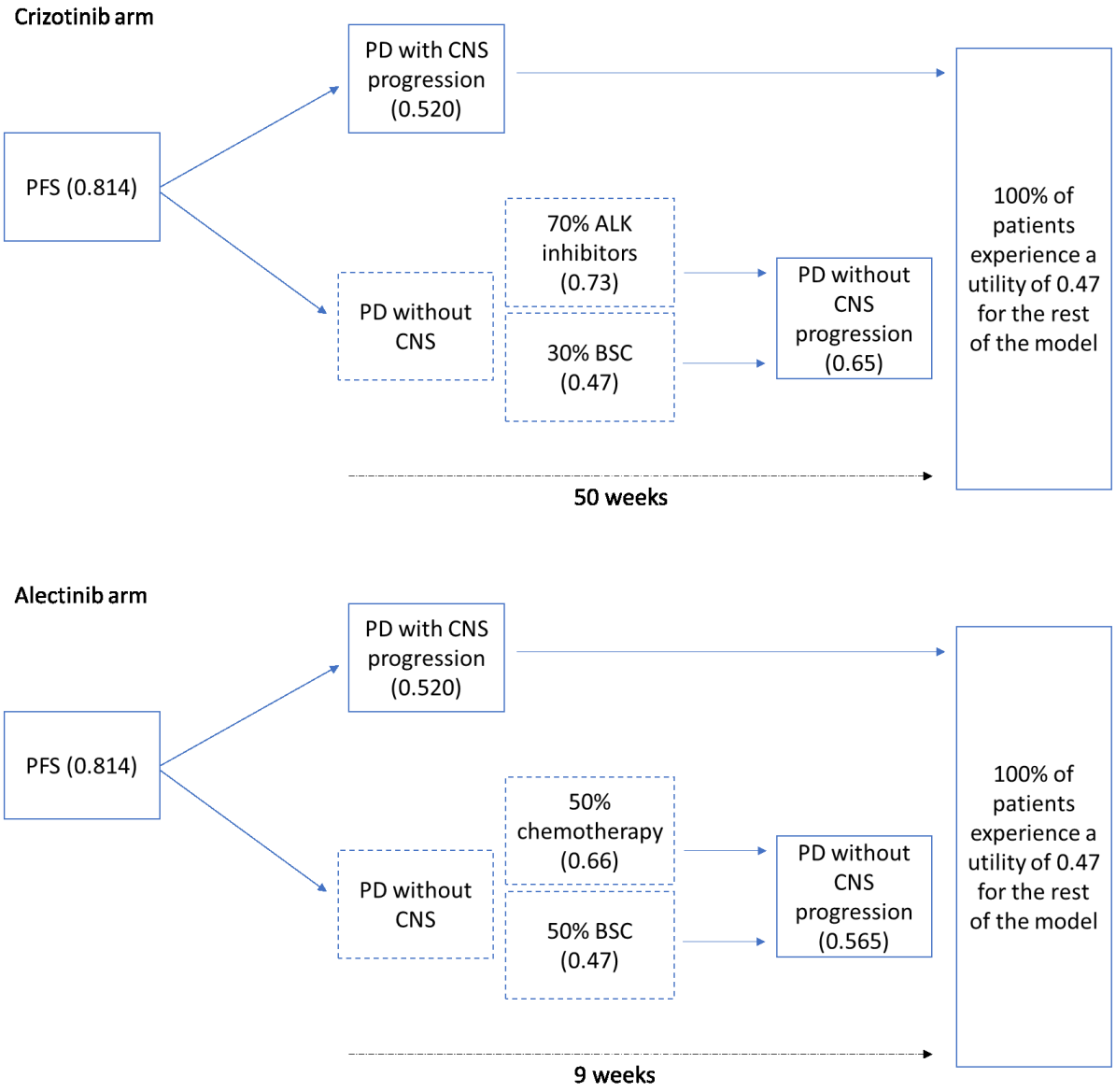
Scenario	**Post-alectinib**		**Post-crizotinib**	
	Chemotherapy	**BSC**	**Ceritinib**	**BSC**
"Middle ground"	50%	50%	75%	25%
"Conservative"	50%	50%	70%	30%
Abbreviations: BSC, best supportive care.				

Table 4. Utility values used in the company's updated analysis and in the ERG analysis

	Company's updated base case (for both treatment arms)	**Company's scenario analysis including subsequent treatments**	**ERG's analysis (alectinib arm)**	**ERG's analysis (crizotinib arm)**
Progression-free survival	0.814	0.814	0.814	0.814
Progressed disease (no CNS progression)	0.725	Depends on subsequent treatment	Depends on subsequent treatment	Depends on subsequent treatment
Progressed disease (with CNS progression)	0.520	Depends on subsequent treatment	0.520	0.520
Second line treatment with TKI (50 weeks)	n/a	0.725	Alectinib patients do not receive subsequent TKI treatment	0.725 * 70% + 0.470 * 30% = 0.649 (for progression outside the CNS. If CNS progression, then 0.52)
Second line treatment with non-TKI (chemotherapy) (9 weeks)	n/a	0.660	0.660 * 50% + 0.470 * 50% = 0.565 (for progression outside the CNS. If CNS progression, then 0.52)	Crizotinib patients do not receive second line chemotherapy
Second line (9 weeks) and third line	n/a	0.470	0.470	0.470

BSC (for the rest of the model)				
Abbreviations: BSC, best supportive care; CNS, central nervous system; ERG, evidence review group; TKI, tyrosine kinase inhibitor.				

Figure 2. Utility assumptions in the ERG scenario analysis



1.5 Management of CNS metastases

The company implemented two analyses to reflect the Committee's view on the expected management of CNS metastases in the NHS. The company's base case result was based on the "conservative" scenario reported in Table 5, while the "middle ground" scenario was provided as a scenario analysis. The ERG is satisfied with the scenarios implemented by the company in the model as these reflect the Committee's preferences.

Table 5. Scenarios ran by the company on CNS management

Scenario	SRS	WBRT	Surgical resection	Steroids
"Middle ground"	22.5%	25%	5%	100%
"Conservative"	20%	25%	0%	100%
Abbreviations: SRS, stereotactic radiotherapy; WBRT, whole brain radiotherapy.				

1.6 Crizotinib cost and oncology visits

The ERG is satisfied with the company's implementation of the crizotinib cost in the model to account for 30 days of treatment with no wastage. The ERG is also satisfied with the estimated frequency of oncology visits in the model (every four weeks).

1.7 Progressed disease utility value

To address the Committee's concerns that the utility value for non-CNS progressed disease (PD) from ALEX may be too high (0.725), the company provided a scenario that incorporated Roughley *et al.* utility values for non-CNS PD (0.65) and CNS PD (0.52). However, it should be reiterated that the ALEX trial population appears to be younger and fitter than the population in Roughley *et al.* according to age, smoking status and ECOG performance score.

Furthermore, given that clinical effectiveness is based on the ALEX trial data, the ERG would prefer to see an analysis which is based on the utility data derived from ALEX. Therefore, the ERG applied a percentage decrement from Roughley *et al.* (0.52/0.65) to the PD utility in ALEX (0.725) to estimate the utility associated with CNS PD (0.58) in the model. The results of the ERG analysis are reported in Section 3.

2 COMPANY'S UPDATED BASE CASE

The company's updated list price results are reported in Table 6. The company updated their patient access scheme (PAS) proposal, resulting in a new PAS of [redacted]. Results with the PAS included are reported in Table 7.

Table 6. Updated base case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.84	–	–	–	–
Alectinib	£209,668	5.14	3.79	£65,681	0.83	0.95	£69,310
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 7. Updated base case results (PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.84	–	–	–	–
Alectinib	[redacted]	5.14	3.79	[redacted]	0.83	0.95	[redacted]
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

The company did not provide probabilistic sensitivity analysis (PSA) results, hence the ERG ran the latter in the company's base case model. The ICER obtained was very similar to the deterministic results at list prices, amounting to £70,555 per QALY gained. The company included several scenario analyses, which can be found in the company's reply to the Appraisal Committee Meeting document.

3 ADDITIONAL WORK UNDERTAKEN BY THE ERG

3.1 Company's base case with ERG corrections

The ERG corrected the company's base case analysis to incorporate the impact of subsequent therapies on the QALY estimation (and not just costs, as per the company's base case analysis). Including the impact of subsequent treatments in the QALY analysis has a considerable effect on the final ICER (£69,310 to £87,486 per QALY gained). The ICER increases because alectinib patients do not receive ALK inhibitors post-alectinib; while this has a beneficial impact on alectinib's costs, it has the opposite effect on alectinib's related QALYs as non-ALK treatments impart a lower quality of life than ALK treatments. The results of the ERG's corrections applied to the company's ICERs are reported in Table 8 and Table 9.

Table 8. Updated base case results with ERG's corrections (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.50	–	–	–	–
Alectinib	£209,668	5.14	3.25	£65,681	0.83	0.75	£87,486
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 9. Updated base case results with ERG's corrections (PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.50	–	–	–	–
Alectinib	[redacted]	5.14	3.25	[redacted]	0.83	0.75	[redacted]
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

3.2 Additional analysis ran by the ERG

The ERG ran the following scenario analyses in the company's updated model (with ERG corrections incorporated):

1. The option to include subsequent treatments in the company's base case analysis means that the CNS progression-related utility is no longer taken into account in the entire model, and all progressed patients experience a utility value related with their subsequent treatment, regardless of the site of tumour progression. The ERG changed this assumption in the company's model so that patients with CNS progression experience the CNS progression-related utility (0.52 in the company's base case analysis), even when receiving subsequent treatment. After finishing their subsequent treatments, all patients with and without CNS progression experience a utility value of 0.47;

2. Applying weighted utility values to estimate QALY gain related with subsequent treatments. For alectinib patients, the second line treatment-related utility value was estimated to be 0.57. Crizotinib patients are assumed to experience a utility of 0.65. After 9 weeks in the alectinib arm, and 50 weeks in the crizotinib arm, 100% of patients (including the CNS progressed patients), experience a utility of 0.47;

3. The ERG applied a decrement from Roughley *et al.* (0.52/0.65) to the PD utility in ALEX (0.725) to estimate the utility associated with CNS PD (0.58) in the model;

4. The ERG replaced the OS dataset to reflect the most recent data cut from [redacted].

Analyses 1 and 2 are extremely related and, given time constrains, and the model manipulation that would be necessary to desegregate these analyses, the ERG ran the two scenarios together. Furthermore, analysis 3 does not impact the company's analysis unless analysis 1 and 2 are implemented (as the company's base case analysis of subsequent therapies does not consider CNS progressed-related utilities). Therefore, scenario 3 was performed in combination with scenario 1 and 2. Results are presented in Table 10 for list prices and Table 11 reports the results including the alectinib PAS. The ERG ran scenarios 1, 2, 3 and 4 altogether and arrived at the results provided in Table 12 (list price) and Table 13 (with alectinib PAS). The ERG's alternative ICER, with scenarios 1 to 4 implemented amounts to £78,555 per QALY gained and a [redacted] ICER for alectinib when the PAS is included.

When analysis 3 and 2 are combined, the utility value used for CNS progressed patients (0.58) is higher than the weighted utility value used for non-CNS progressed patients in the alectinib arm (0.57). This leads to a clinically implausible scenario, where patients who have a CNS progression have a higher quality of life compared to patients with a non-CNS progression. However, the ERG varied the weighted non-CNS progressed utility value in the economic model (the ERG tested replacing the 0.57 estimate by 0.58 and 0.59). The impact on the ERG's alternative ICER, with scenarios 1 to 4 implemented, amounts to a maximum decrease of four pounds per QALY gained, with the ICER being £78,551, when the non-CNS disease progression utility was 0.59 (and two pounds when 0.58 was used). The ICER with the PAS included decreased by two pounds per QALY gained.

Table 10. Results of the ERG's scenario analysis

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£209,668	£143,986	£65,681
	QALYs	3.25	2.50	0.75
	ICER			**£87,486**
1+2+3	**ERG's analysis**			

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
	Total costs (£)	£209,668	£143,986	£65,681
	QALYs	3.25	2.49	0.76
	ICER			**£86,629**
4	**OS dataset from** [redacted]			
	Total costs (£)	£211,490	£144,255	£67,234
	QALYs	3.39	2.54	0.85
	ICER			**£79,242**
Abbreviations: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.				

Table 11. Results of the ERG's scenario analysis (PAS)

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	[redacted]	£143,986	[redacted]
	QALYs	3.25	2.50	0.75
	ICER			[redacted]
1+2+3	**ERG's analysis**			
	Total costs (£)	[redacted]	£143,986	[redacted]
	QALYs	3.25	2.49	0.76
	ICER			[redacted]
4	**OS dataset from** [redacted]			
	Total costs (£)	[redacted]	£144,255	[redacted]
	QALYs	3.39	2.54	0.85
	ICER			[redacted]
Abbreviations: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.				

Table 12. ERG's alternative ICER (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£144,255	2.53	–	–	–
Alectinib	£211,490	3.39	£67,234	0.86	£78,555
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 13. ERG's alternative ICER (PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£144,255	2.53	–	–	–
Alectinib	[redacted]	3.39	[redacted]	0.86	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

Addendum to the ERG report

May 2018

This report was commissioned by the NIHR HTA Programme as project number 17/56/01

BMJ Technology Assessment Group

The company's updated list price results are reported in Table 1. The company updated their patient access scheme (PAS) proposal, resulting in a new PAS of [redacted]. Results with the PAS included are reported in Table 2.

Table 1. Updated base case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.84	–	–	–	–
Alectinib	£209,668	5.14	3.79	£65,681	0.83	0.95	£69,310
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 2. Updated base case results (PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£143,986	4.32	2.84	–	–	–	–
Alectinib	[redacted]	5.14	3.79	[redacted]	0.83	0.95	[redacted]
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Detailed below, are the changes the ERG has implemented to the company's analysis, and the respective impact on the company's base case ICER:

1. The company's base case analysis includes the cost of the subsequent treatments proposed during the first ACM (50% of alectinib patients receive chemotherapy and the remaining 50% receive BSC; 70% of crizotinib patients move on to receive a TKI and 30% of patients receive BSC). The company did not include the impact of subsequent treatments on patients' quality of life, however the company's economic model already included the option to do the latter as a scenario analysis. Therefore, the ERG turned this option on in the company's model (switching cell F49 in tab "Model Inputs" from "One PPS utility – base case" to "2nd and 3rd line PPS utility") and replacing the proportion of patients receiving TKIs and non-TKIs after each treatment to reflect the Committee's preferences (described above), in cells F59:G63 in tab "Model Inputs". When this change was applied, the company's ICER changed from £69,310 ([redacted] with PAS) to £87,486 ([redacted] with PAS) per QALY gained. The ICER increases because alectinib patients do not receive ALK inhibitors post-alectinib; while this has a beneficial impact on alectinib's costs, it has the opposite effect on alectinib's related QALYs as non-ALK treatments impart a lower quality of life than ALK treatments.

2. The ERG did some structural changes to the economic model with regards to the QALY estimation of subsequent treatments, and applied the Roughley *et al.* decrement, discussed by the Committee:

    a. The option to include subsequent treatments in the company's base case analysis means that the CNS progression-related utility is no longer taken into account in the entire model, and all progressed patients experience a utility value related with their subsequent treatment, regardless of the site of tumour progression. The ERG changed this assumption in the company's model so that patients with CNS progression experience the CNS progression-related utility, even when receiving subsequent treatment. After finishing their subsequent treatments, all patients with and without CNS progression experience a utility value of 0.47 (Figure 2 in ERG report);

    b. Applying weighted utility values to estimate QALY gain related with subsequent treatments. For alectinib patients, the second line treatment-related utility value was estimated to be 0.57. The corresponding value for crizotinib patients is a utility of 0.65. After 9 weeks in the alectinib arm, and 50 weeks in the crizotinib arm, 100% of patients including the CNS progressed patients, experience a utility of 0.47 (Table 4 and Figure 2 in the ERG report);

    c. The ERG applied a decrement from Roughley *et al.* (0.52/0.65) to the progressed disease utility in ALEX (0.725) to estimate the utility associated with CNS progressed disease (0.58) in the model;

    Analyses a and b are extremely related and, given time constrains, and the model manipulation that would be necessary to desegregate these analyses, the ERG ran the two scenarios together. Furthermore, analysis c does not impact the company's analysis unless analysis a and b are implemented (as the company's base case analysis of subsequent therapies does not consider CNS progressed-related utilities). Therefore, scenario c was performed in combination with scenario a and b. When this change was applied, the company's ICER, incorporating the QALY analysis of subsequent therapies, changed from £87,486 ([redacted] with PAS) to £86,629 [redacted] with PAS) per QALY gained.

3. The ERG replaced the OS dataset to reflect the most recent data cut from [redacted]. When this change was applied, the company's ICER, incorporating the QALY analysis of subsequent therapies, changed from £87,486 ([redacted] with PAS) to £79,242 ([redacted] with PAS) per QALY gained.

Results are presented in Table 3 for list prices and Table 4 reports the results including the alectinib PAS. The ERG ran scenarios 1, 2 and 3 altogether and arrived at the results provided in Table 5 (list price) and Table 6 (with alectinib PAS). The ERG's alternative ICER, with scenarios 1 to 3 implemented amounts to £78,555 per QALY gained and a [redacted] ICER for alectinib when the PAS is included.

Table 3. Results of the ERG's scenario analysis

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
1	**Company's base case with subsequent treatments included in the QALY analysis**			
	Total costs (£)	£209,668	£143,986	£65,681
	QALYs	3.25	2.50	0.75
	ICER			**£87,486**
2	**ERG's analysis**			
	Total costs (£)	£209,668	£143,986	£65,681
	QALYs	3.25	2.49	0.76
	ICER			**£86,629**
3	**OS dataset from [redacted]**			
	Total costs (£)	£211,490	£144,255	£67,234
	QALYs	3.39	2.54	0.85
	ICER			**£79,242**

Abbreviations: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

Table 4. Results of the ERG's scenario analysis (PAS)

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
1	**Company's base case with subsequent treatments included in the QALY analysis**			
	Total costs (£)	[redacted]	£143,986	[redacted]
	QALYs	3.25	2.50	0.75
	ICER			[redacted]
2	**ERG's analysis**			
	Total costs (£)	[redacted]	£143,986	[redacted]
	QALYs	3.25	2.49	0.76
	ICER			[redacted]
3	**OS dataset from [redacted]**			
	Total costs (£)	[redacted]	£144,255	[redacted]
	QALYs	3.39	2.54	0.85
	ICER			[redacted]

Abbreviations: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

Table 5. ERG's alternative ICER (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£144,255	2.53	–	–	–
Alectinib	£211,490	3.39	£67,234	0.86	£78,555
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 6. ERG's alternative ICER (PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Crizotinib	£144,255	2.53	–	–	–
Alectinib	[redacted]	3.39	[redacted]	0.86	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					