HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

The following documents are made available to 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:
   - Takeda
   - Roy Castle Lung Cancer Foundation
   - BTOG-NCRI-RCP-RCR-ACP

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr [redacted] – Clinical Expert nominated by Takeda
   - Peter Clark, NHS England

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

5. **Additional evidence submitted by Takeda**
   - Company responses to queries on their ACD response
   - Clarification on approach to duration of treatment benefit
   - Factual inaccuracy check of the ERG updated work

6. **Additional documents submitted by the Evidence Review Group - Peninsula Technology Assessment Group (PenTAG)**
   - ERG critique for ACM2
   - ERG erratum to critique for ACM2
   - ERG additional work for ACM3
   - ERG erratum to additional work for ACM3

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

Appraisal title

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	Consultee (company)	Takeda	Please see our ACD response document dated 24th October 2018 and uploaded to NICE Docs on that date – two versions having been provided (one marked CIC and the other marked Redacted). These contain all of our comments on the ACD and our comments on the questions listed above.	Thank you for your comments. The content of the ACD response document has been inserted in comments 2 to 14 below.
2	Consultee (company)	Takeda	**1.1 Executive Summary** Takeda disagree with the Appraisal Committee's provisional negative recommendation for brigatinib for the treatment of anaplastic lymphoma kinase positive (ALK+) non-small-cell lung cancer (NSCLC) as presented in the Appraisal Consultation Document (ACD; 26th September 2018), and we do not consider it to be a sound and suitable basis for guidance to the National Health Service (NHS). We would ask the Committee to reconsider this draft recommendation in light of the considered and constructive points that are presented in this ACD response. In this response Takeda have addressed the key issues raised by the Evidence Review Group (ERG) and the Appraisal Committee, and provided what we think is a fair and balanced response which includes the presentation of an updated base case that we consider to be methodologically sound and clinically plausible. The updated base case incorporates the Committee's concerns associated with: • Sources included in the indirect treatment comparisons; • Duration of treatment benefit beyond treatment discontinuation; • Separate utility values for progression-free, progressed disease on-treatment and progressed disease off-treatment phases and • Drug wastage The updated base case provides what we believe to be the most plausible base case incremental cost-effectiveness ratio (ICER) for patients with ALK+ NSCLC in the post-crizotinib setting. We would emphasise that our updated base	Thank you for your comments. The recommendations in the Final appraisal document (FAD) have changed following consideration of the updated analyses and updated patient access scheme. The FAD now recommends brigatinib within its licensed indication. Responses to individual comments summarised in the executive summary have been provided in the more detailed comments below.

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			case includes a number of conservative assumptions, as discussed in this ACD response. This provides the Committee with a conservative base case ICER that we consider can be used in the decision-making process for brigatinib in the post-crizotinib indication. This updated base case estimates an ICER of £67,449 per quality adjusted life year (QALY), using the NHS list prices for both brigatinib and ceritinib. To continue to show flexibility and commitment in this appraisal process, Takeda have submitted an enhanced simple discount patient access scheme (PAS) proposal to the Patient Access Schemes Liaison Unit (PASLU; Date: 19th October 2018) which reduces the net price per pack (28-day supply) for the 180mg strength to [redacted] (a [redacted]% simple discount on the NHS list price). This compares with the originally submitted PAS net price of [redacted] per pack (28-day supply) for the 180mg strength (a [redacted]% simple discount on the NHS list price). The significantly enhanced PAS is designed specifically to both address the uncertainty regarding the cost-effectiveness of brigatinib and to reduce the ICER to a level that we believe shows cost-effectiveness at the £50,000/QALY end-of-life threshold, when the confidential (and unknown to Takeda) ceritinib PAS is included. Takeda is optimistic that the steps we have taken in this ACD response will allow the Committee to reach a positive recommendation for brigatinib in patients with ALK+ NSCLC in the post-crizotinib setting, thus allowing for routine use on the NHS. This would be a positive development for patients, given the many benefits that brigatinib offers over ceritinib, the only other ALK inhibitor that is currently commissioned by NHS England for the post-crizotinib indication. The benefits of brigatinib over ceritinib, which have been highlighted clearly in the original submission to the National Institute for Health and Care Excellence (NICE), include: • Increased efficacy (significantly extended and unprecedented progression-free survival (PFS) and overall survival (OS) in this indication, as demonstrated in the indirect treatment comparisons); • Increased efficacy in the central nervous system (CNS; a key site of progression on crizotinib); • Improved tolerability, with less need for dose reduction or drug discontinuation (particularly in relation to gastrointestinal side-effects); • More convenient dosing for patients (i.e. one tablet, once-daily with or without food, whereas ceritinib requires multiple capsules to be taken once-daily and with food). While our primary objective in this ACD response is to secure a positive NICE recommendation for brigatinib for routine NHS funding, Takeda wishes to emphasise that we would also be willing to consider funding via the Cancer Drugs Fund (CDF), if required. We note the comment in the NHS England submission to NICE before the first Committee meeting that *"NHS England welcomes Takeda's submission to NICE for this post-crizotinib indication……"*, and we would hope that all stakeholders acknowledge the considerable flexibility and commitment that the company has shown in trying to bring this innovative medicine to patients in need of a better treatment option than currently	

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			available. Takeda would also like to remind the Committee that the number of NSCLC patients with the ALK rearrangement is small and the post-crizotinib population eligible for brigatinib is also a diminishing one because the use of crizotinib in the 1st line is declining rapidly following the availability of alectinib as a 1st line treatment option (positive FAD for alectinib issued June 2018). This has been confirmed by both clinical experts and the NHS England representative at the first Committee meeting (see point 1 of the NHS England submission to NICE for this appraisal). Hence, the potential budget impact of brigatinib for this indication is modest, predictable and in decline, making this a relatively low risk decision for NICE and NHS England. It should, however, be noted that for the pool of existing patients currently receiving treatment with crizotinib, having access to brigatinib would fulfil a significant clinical need following progression of their disease. Based on all the above, we would hope that the Committee will reconsider its draft negative recommendation for brigatinib in the post-crizotinib indication and issue final guidance that will make brigatinib available for routine use on the NHS.	
3	Consultee (company)	Takeda	**2.1 Appraisal Committee's preliminary recommendations** On the 26th September 2018, the NICE Appraisal Committee prepared an ACD summarising the evidence, views and draft recommendations of the Committee regarding the use of brigatinib on the NHS in England for treating ALK+ advanced NSCLC after crizotinib The ACD sets out the draft recommendations made by the Committee which currently state that: *'Brigatinib is not recommended, within its anticipated marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults who have already had crizotinib.'* In this document Takeda have addressed the issues raised by the ERG and the Appraisal Committee and provided what we think is a fair and balanced response which includes the presentation of an updated base case. The updated base case incorporates the Committee's concerns associated with sources included in the indirect treatment comparisons, duration of treatment benefit beyond treatment discontinuation, separate utility values for progression-free, progressed disease on-treatment and progressed disease off-treatment phases and drug wastage. The updated base case provides what we believe to be the most plausible base case ICER for patients with ALK+ NSCLC in the post-crizotinib setting. To continue to show flexibility and commitment in the appraisal process for brigatinib in the post-crizotinib setting, Takeda have submitted an enhanced simple discount patient access scheme (PAS) proposal to PASLU and NHS	Thanks for your comments. The Final appraisal document now recommends brigatinib within its licensed indication following consideration of the updated analyses and updated patient access scheme.

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			England (Date: 19th October 2018) which reduces the net price per pack (28-day supply) for the 180mg strength to £[redacted] (a [redacted]% simple discount on the NHS list price). The enhanced PAS is designed specifically to both address the uncertainty regarding the cost-effectiveness of brigatinib and to reduce the ICER to a level that we believe shows cost-effectiveness at the £50,000/QALY end-of-life threshold, when the confidential (and unknown to Takeda) ceritinib PAS is included. Takeda is optimistic that the steps we have taken in this ACD response will allow the Committee to reach a positive recommendation for brigatinib in patients with ALK+ NSCLC in the post-crizotinib setting, thus allowing for routine use on the NHS. Although it is not our primary objective for brigatinib, Takeda is also willing to give consideration to funding through the Cancer Drugs Fund (CDF), if necessary.	The Final appraisal document now recommends brigatinib within its licensed indication. The committee agreed that many of the uncertainties discussed during the appraisal could not be addressed through data collection from people having brigatinib through the Cancer Drugs Fund because the treatment pathway has changed.
4	Consultee (company)	Takeda	**3.1 Has all the relevant evidence been taken into account?** The main clinical evidence to support the case for the clinical and cost-effectiveness of brigatinib is the ALTA study[1], with supportive efficacy evidence from Study-101[2]. To date, Takeda have provided all relevant data currently available. However, in responding to this ACD, Takeda identified two PFS events and two adverse events which were incorrectly coded as part of the original submission and addendum. The model has been updated with the correct data which has had a very minimal impact on the PFS outcomes and adverse events. This has resulted in a very small increase in the ICER from £54,311 to £54,628. Takeda apologise for the late correction of these data but would like to emphasise the very minimal changes in outcomes and the very small effect on the ICER (+£317). Takeda consider that the Appraisal Committee has taken all relevant data from the original submission, the addendum and the data from Takeda's response to the ERG questions into account. One additional point that Takeda would like to confirm relates to the proposed NHS list prices for brigatinib that we have submitted to the Department of Health and Social Care. These were submitted to the Department of Health and	Thank you for your comments. The amended error and change in list prices have been noted.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>Social Care on October 12th and are presented in Table 1.

Table 1: Proposed list prices for brigatinib

<table>
<tr><th>Drug name</th><th>Brand name</th><th>Preparation</th><th>NHS list price</th></tr>
<tr><td>brigatinib</td><td>Alunbrig</td><td>28 x 30mg tablets

28 x 90mg tablets

28 x 180mg tablets

Starter Pack (7 x 90mg tablets & 21 x 180mg tablets)</td><td>£1,225 per 28 tablet pack

£3,675 per 28 tablet pack

£4,900 per 28 tablet pack

£4,900 per starter pack</td></tr>
</table>
Abbreviations: NHS, National Health Service

These differ from those shown in the original submission to NICE only in relation to the lower prices now proposed for the 30mg and 90mg strengths. The prices proposed for the 180mg strength and the Starter Pack are unchanged from those shown in the original submission. The health economic model has been updated to reflect these NHS list prices, leading to a small decrease in the ICER from £54,628 to £54,390 (-£238).</td><td></td></tr>
<tr><td>5</td><td>Consultee (company)</td><td>Takeda</td><td>3.2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Takeda consider that the summaries of clinical effectiveness presented in the ACD are reasonable interpretations of the evidence (Sections 3.4 to 3.11 of the ACD).

There are a number of issues raised in the ACD relating to the analysis of cost-effectiveness of brigatinib relative to ceritinib in patients with ALK+ advanced NSCLC which we have endeavoured to clarify and address within the economic model and this document, including the following issues:

• Use of ASCEND-5[3] within the indirect treatment comparison for PFS outcomes (Section 3.2.1 of this response document)</td><td>Thank you for your comments. Responses to each of the four points raised can be found next to the more detailed comments on each point below.</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
			• Modelling treatment benefit discontinuation (Section 3.2.2) • Health-related quality of life (HRQL) (Section 3.2.3) • Drug wastage and administration costs (Section 3.2.4) Section 3.2.1 considers the use of ASCEND-5 when calculating the relative PFS estimates; Takeda understand the Committee's preference towards including ASCEND-5 and consider that the sources contributing to relative efficacy estimates should be the same for OS and PFS outcomes, in order to avoid inconsistencies in the modelling outcomes. Section 3.2.2 presents a method to account for treatment benefit discontinuation which is in line with the Committee's feedback. Section 3.2.3 takes note of the Committee's preference for separate progressed disease on-treatment and progressed disease off-treatment utility values; Takeda present the values used in the updated base case. Finally, Section 3.2.4 agrees with the approach taken by the ERG and Committee for capturing drug wastage. However, Takeda consider that applying an additional administration cost within the model will result in double counting – dispensing and administration costs are already captured within the pre-progression resource use. The resulting updated base case estimates an ICER of £67,449/QALY, using the NHS list prices for both brigatinib and ceritinib. The updated economic model has also been submitted to NICE for review under the file name of "Brigatinib NICE model response to ACD (24OCT2018).xlsm". Section 3.2.6 of this document presents the step change from the ICER presented within the addendum (dated: May 2018) of £54,311/QALY to the updated base case reflecting changes from the first Committee meeting and the ACD (dated: September 2018).	The updated economic model has been received.
6	Consultee (company)	Takeda	**3.2.1 Discussion on the indirect comparison of brigatinib and ceritinib (Section 3.6, 3.7 and 3.8 of the ACD)** On page 8 of the ACD it states: "Results from the 4 single-arm studies (see Section 3.3 and Section 3.4) were used, and 2 approaches were taken: a naïve ITC and a matching-adjusted indirect comparison (MAIC)". This is incorrect - we would like to clarify that three single arm trials (ALTA, Study 101 and ASCEND-2) and a double armed randomised controlled trial (ASCEND-5) were incorporated within the indirect treatment comparisons. In our original base case, we used the results of the MAIC ITC that included ALTA and Study-101 (pooled) for brigatinib and ASCEND-2 for ceritinib to estimate the hazard ratio for PFS outcomes for brigatinib relative to ceritinib. These results were selected for three reasons: (1) to make use of the totality of data available for brigatinib, (2) to align with the inputs in the rest of the model and (3) to ensure consistency in the type of PFS assessment (i.e. investigator (INV)-assessed vs. independent review committee (IRC)-assessed). Page 10 of the ACD states: "The ERG preferred using the results of the meta-analysis of the MAIC ITC that included only ALTA for brigatinib compared separately with ASCEND-5 (ceritinib) and ASCEND-2 (ceritinib) (see Section 3.7). The Committee agreed that data	Thank you for your comments. Section 3.6 has now been clarified to highlight that it is referring to 4 single-arms from different studies and that each relevant arm was treated as though they were 'single arm' studies. The committee accepted the approach to remove

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			from ASCEND-5 should be included". Using these sources improves the hazard ratio for PFS in favour of brigatinib (from 0.38 to 0.28). This is driven by two factors: (1) IRC-assessed PFS is being considered and (2) Study-101 is being excluded. Takeda consider that if Study-101 is to be excluded from the indirect treatment comparisons for the PFS outcomes, then this should also be excluded from the OS outcomes. Otherwise, there is an inconsistency within the model where time in pre-progression and time on treatment is increased for brigatinib relative to ceritinib, without any subsequent impact on the relative OS benefit. Therefore, in our updated base case we include the Committee's preference for using ALTA, ASCEND-2 and ASCEND-5 for relative PFS estimates, and we also use these sources for the relative OS estimates. Section 3.2.6 presents the impact of this in our updated base case.	study 101 from the overall survival as well as the progression-free survival outcomes (see section 3.8 of the FAD).
7	Consultee (company)	Takeda	**3.2.2 Discussion on duration of treatment benefit after progression (Section 3.12 of the ACD)** Takeda consider that the heading relevant to Section 3.12 in the ACD should refer to "Duration of treatment benefit after ***discontinuation***" – rather than *"after progression"* as it currently states. Takeda recognise the uncertainty associated with the duration of treatment benefit after a patient has stopped treatment with brigatinib or ceritinib and accept that modelling a lifetime continued treatment benefit may not reflect clinical reality. As discussed in the NICE Committee meeting and the ACD, the method used by the ERG to explore a shortened continued treatment benefit led to outputs that were not clinically plausible. Based on the statement on page 13 of the ACD that *"The Committee agreed that a method similar to the ERG's modelling approach might be suitable for decision-making if the outputs of survival were clinically plausible"*, we have considered a somewhat similar (but different) approach which we believe provides clinical outcomes that (unlike those of the ERG) are clinically plausible and align with the expectations of clinical experts. This approach is described below and is presented within the updated health economic model: "Brigatinib NICE model response to ACD (24OCT2018).xlsm". For this alternative approach that aligns with clinical expectations, Takeda have applied a tapering (waning) of survival rates for brigatinib from week 161 (3.09 years) to week 377 (7.23 years). Up to week 161, survival is estimated as per the parametric curve fit to the brigatinib data. Week 161 was selected because this represents the maximum follow-up from the ALTA clinical trial (148 weeks), which has been used in the analyses informing the model, plus an additional 3 months (approximately 13 weeks). The rationale for the additional 3 months is based on comments made by the clinical experts at the Committee meeting and the statement on page 12 of the ACD that: *"The clinical experts explained that it was reasonable to assume that treatment benefit would continue for a few months after stopping treatment."* This has subsequently been supported by feedback from three other clinical experts that were consulted by Takeda after the Committee meeting. Between week 161 and week 377, the survival rate is weighted across brigatinib and ceritinib rates, with an increasing weight given to the ceritinib rate over time so that by week 377 the rate is equal to the ceritinib survival rate. From week 377, the survival rate for brigatinib is assumed equal to ceritinib.	Thank you for your comments. The section heading has now been amended. The committee considered the company's updated approach to treatment benefit after treatment stopping (see sections 3.12 and 3.13 of the FAD).

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Week 377 was selected because this represents the time at which 1% of patients remained on treatment with brigatinib (364 weeks), plus the additional three months (approximately 13 weeks) as explained above.

Applying the treatment benefit discontinuation, using the method described above, impacts on the proportion of patients surviving at 5-, 10- and 20-years, as predicted by the health economic model. Table 2 presents these proportions for each of the parametric survival curves and compares this with the averaged estimates from five UK clinical experts – details relating to this expert elicitation are presented in the original submission dossier. When applying treatment benefit discontinuation, the Gompertz curve does not align with clinicians' expectations. Although there is uncertainty in clinician estimates, it was agreed by all five UK clinical experts that ~5% of patients would be expected to survive to 10-years. None of the curves align exactly with this expectation; but the exponential provides a conservative estimate of 2.28% survival at 10-years. Therefore, this is applied for OS outcomes along with the treatment benefit discontinuation in the updated base case. In addition to providing a conservative estimate, the exponential curve also has the advantage of providing the best fit to the observed data based on the AIC and BIC values – and produces outcomes that align closely with clinical expert expectations. Section 3.2.6 presents the impact of this in our updated base case.

Table 2: Proportion of patients surviving at 5-, 10- and 20-years as predicted by the model with treatment benefit discontinuation

<table>
<tr><th></th><th>5-years</th><th>10-years</th><th>20-years</th></tr>
<tr><td>Clinical experts average</td><td>28.50%</td><td>5.83%</td><td>0.00%</td></tr>
<tr><td>Exponential</td><td>28.99%</td><td>2.28%</td><td>0.01%</td></tr>
<tr><td>Gamma</td><td>27.27%</td><td>1.67%</td><td>0.00%</td></tr>
<tr><td>Log-normal</td><td>39.27%</td><td>13.77%</td><td>3.13%</td></tr>
<tr><td>Log-logistic</td><td>33.99%</td><td>8.84%</td><td>1.53%</td></tr>
<tr><td>Weibull</td><td>26.87%</td><td>1.46%</td><td>0.00%</td></tr>
<tr><td>Gompertz</td><td>25.21%</td><td>0.54%</td><td>0.00%</td></tr>
<tr><td>Generalised gamma</td><td>27.96%</td><td>2.03%</td><td>0.01%</td></tr>
</table>

Note: all treatment benefit discontinuation scenarios are presented with no change to ceritinib. Therefore, the health economic model does assume a lifetime treatment benefit for ceritinib. However, in the absence of further survival data relating to subsequent therapies following treatment with brigatinib or ceritinib, treatment effect waning has only been applied in the brigatinib arm. This is a conservative assumption because it is likely that in clinical practice the
</td><td>The committee's considerations on the company's choice of parametric survival curves for overall and progression-free survival are described in section 3.9 and 3.10 of the FAD.</td></tr>
</table>

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			benefits of treatment would diminish (wane) in both the brigatinib and ceritinib arms. If a waning effect were applied in the ceritinib arm this would worsen the outcomes for ceritinib, thereby increasing the benefit of brigatinib relative to ceritinib. Additionally, clinical experts suggested at the first Committee meeting that there may be a longer continued treatment benefit with brigatinib relative to ceritinib, due to the increased effectiveness of brigatinib in the CNS and a greater depth of response relative to ceritinib. Due to lack of data, and in line with our conservative approach, this is not captured in the treatment benefit discontinuation scenario we have applied (in fact we have done the opposite in our updated base case by applying the treatment waning effect only in the brigatinib arm). This is a very conservative modelling assumption because increasing the duration of treatment benefit for brigatinib relative to ceritinib would further decrease the base case ICER in favour of brigatinib.	The committee considered that the magnitude and duration of any treatment benefit beyond stopping treatment is uncertain, given the absence of longer term trial data. The committee's consideration of the continued benefit of brigatinib relative to ceritinib is summarised in section 3.12 and 3.13 of the FAD.
8	Consultee (company)	Takeda	**3.2.3 Discussion on health-related quality of life (Section 3.13 and 3.14 of the ACD)** <u>Progressed disease and on-treatment</u> On page 14 of the ACD it states: *"The Committee concluded that the company's utility value for progressed disease on treatment was reasonable, but considered that a decline in utility was needed for people with progressed disease after treatment had stopped."* In the original base case, Takeda applied a utility value of 0.643 for patients in the progressed disease state – regardless of continued treatment with brigatinib or ceritinib. This value was derived by applying the utility decrement from Chouaid *et al.* (2013)[4] to the pre-progression utility value (0.793 - 0.15 = 0.643), which was derived from the ALTA patient level data. In the first Committee meeting, Takeda acknowledged that the clinical experts and the Committee Chair did not expect that utility would remain constant throughout this progression period – most notably, it was expected that there would be a decline in utility for patients stopping treatment with an ALK inhibitor and moving onto treatment with best supportive care (BSC). Therefore, the updated model includes a utility value for progressed disease on-treatment (which reflects continued treatment with brigatinib or ceritinib) and progressed disease off-	Thank you for your comments. The committee accepted the company's amended utility values for progressed disease on and off-treatment (see section 3.15 of the FAD).

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			treatment (which reflects the HRQL after stopping treatment with an ALK inhibitor and receiving BSC). Based on clinical expert feedback, both at the Committee meeting and obtained through interactions we had with eight clinical experts subsequently, Takeda does not believe that progression whilst remaining on treatment with brigatinib or ceritinib would result in a utility decrement of 0.15 from the pre-progression health state. As stated in the submission from NHS England in advance of the first Committee meeting: there are two main scenarios where treatment with brigatinib will continue after RECIST-defined disease progression: (1) When there is a dimensionally small increase in an already small marker lesion which triggers the definition of disease progression but is clinically irrelevant as the patient remains well. Treatment would continue until there is a clinically significant progression (i.e. the development of symptoms) (2) When there is continued systemic response but disease progression in the brain which is then amenable to active treatment with radiotherapy. Treatment would continue until systemic progression or loss of control of the intra-cerebral disease. Therefore, the patients in the progressed disease on-treatment phase are often asymptomatic and still obtaining the clinical benefit of treatment. As stated on page 14 of the ACD: *"The clinical experts explained that, even with central nervous system involvement, people with progressed ALK-positive advanced NSCLC can have a good quality of life."* This was echoed by the feedback received by Takeda from eight clinical experts who stated that they would not anticipate a significant change in the utility value at this point. Takeda consider that the utility value estimated from the ALTA data for the progressed disease health state reflects the small decline in utility associated with RECIST-defined progression and the continued clinical benefit. This utility value was not used in the original base case due to limited follow-up; it was considered that it did not reflect the 'true' progressed disease utility value where patients had moved onto treatment with BSC. However, this utility value does provide HRQL information for those patients who have just progressed. As patients are only in the progressed disease on-treatment phase for an average of 1.53 months within the model, the progressed disease utility value from the ALTA data would be expected to approximate the 'true' utility value for these patients. Therefore, the updated base case applies a utility value of 0.793 (average with age adjustment: 0.773) for pre-progression and on-treatment (0.793 is already accepted by the Committee as appropriate for pre-progressed disease – see page 13 of the ACD) and 0.732 (average with age adjustment: 0.712) for progressed disease and on-treatment (derived from the ALTA data for progressed disease). These values are summarised in Table 3. Section 3.2.6 presents the impact of this in our updated base case. **Note:** as patients are only in the post-progression on-treatment phase for a short time in the economic model (1.53 months) – there is very little impact on the ICER	

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<tr><td></td><td></td><td></td><td>
when assuming a utility of either 0.643 or 0.732 for such patients.

<u>Progressed disease and off-treatment</u>

To reflect the decline in utility associated with patients with progressed disease after treatment with brigatinib or ceritinib has been stopped, the utility decrement of 0.15 from Chouaid et al. (2013) was applied to the progressed disease on-treatment utility value. Therefore, the updated base case uses a utility value of 0.582 (i.e. 0.732 – 0.15 = 0.582; average with age adjustment: 0.562) for progressed disease and off-treatment (Table 3). Section 3.2.6 presents the impact of this in our updated base case.

Takeda acknowledge that this utility value is higher than those seen in the literature (0.46 from Chouaid et al. (2013)[4] and 0.473 from Nafees et al. (2008)[5]). However, as noted on page 14 of the ACD, these utility values reflect the wider NSCLC population. Patients with ALK+ NSCLC tend to be younger and healthier and this is reflected in the higher HRQL estimates and utility values. Clinician feedback indicated that the decline in utility observed at progression would likely be similar between the NSCLC and ALK+ NSCLC populations, but patients with ALK+ NSCLC would have a higher utility to begin with and this would likely be reflected by an improved utility value in the progressed health state.

Table 3: Utility values used in the updated base case

<table>
<tr><th>Phases</th><th>Utility value</th><th>Justification</th></tr>
<tr><td>Pre-progression on-treatment</td><td>0.793*</td><td>Already accepted by the Committee as appropriate for pre-progressed disease – see page 13 of the ACD</td></tr>
<tr><td>Progressed disease on-treatment</td><td>0.732*</td><td>Derived from the progressed utility values from the ALTA clinical trial. These values reflect patients who have just progressed (limited follow-up from the September 2017 data cut) and include patients on- and off-treatment. Considered conservative as the patients who are off-treatment will likely have a worse HRQL and apply a downward pressure on the averaged value.</td></tr>
<tr><td>Progressed disease off-treatment</td><td>0.582*</td><td>Utility decrement of 0.15 obtained from Chouaid et al. (2013)[4] and applied to the progressed disease on-treatment utility value. This represents the decline in utility observed upon progression in a NSCLC</td></tr>
</table>
</td><td></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
			<table><tr><td></td><td></td><td>population. As the ALK+ NSCLC population are generally younger and healthier than the NSCLC population, we expect the decline in utility to be similar but the absolute value to be higher.</td></tr></table> *These values are adjusted downwards within the economic model by decrements associated with age and adverse events Abbreviations: ACD, appraisal consultation document; ALK, anaplastic lymphoma kinase; HRQL, health-related quality of life; NSCLC, non-small-cell lung cancer	
9	Consultee (company)	Takeda	**3.2.4 Discussion on resource use and costs (Section 3.15 and 3.16 of the ACD)** <u>Drug wastage</u> Takeda note that the Committee agreed with the ERG's approach to account for drug wastage within the model; this approach assumed that half of the costs incurred through unfinished packs could be saved by the NHS and half would be wasted. Takeda agrees with this pragmatic approach. Therefore, we have updated the economic model to reflect this. Section 3.2.6 presents the impact of this in our updated base case. <u>Administration and delivery costs</u> Takeda note that the Committee consider that the administration cost of £120 per cycle stated by NHS England and the delivery cost of £42.50 per cycle should have been included in the modelling; weighted by 30% and 70%, respectively based on how these medicines are received by patients (i.e. either in hospital or via HomeCare). However, Takeda consider that applying these costs would result in double-counting within the model as these costs are already accounted for within the resource use accrued per administration. Resource use inputs were obtained from feedback of five UK clinical experts and include all resource use related to: dispensing, administration, dose changes and monitoring. In relation to administration and dispensing costs, an oncologist outpatient appointment and a pharmacy cost are already accounted for at each administration within the base case (for the first administration two outpatient appointments and two pharmacy appointments are costed) – these are presented in the original submission dossier (Section B.3.5.3.1). The resultant cost per cycle is £526 for the first cycle and £217 in subsequent cycles – applied to both the brigatinib and ceritinib arms. To provide a conservative estimate and to capture regional differences, in the economic model the pharmacy time is costed based on one hour of pharmacist time. This is conservative as the case precedent demonstrated across the appraisals by NICE of other ALK-inhibitors highlights that 12-minutes of pharmacist time sufficiently captures the administrative burden of oral TKIs. In TA395 (ceritinib for previously treated ALK+ NSCLC)[6], the Committee accepted	Thank you for your comments. The committee accepted the company's amendments to drug wastage (see section 3.16 of the FAD). The committee accepted the company's approach to capturing administration and delivery costs (see section 3.17 of the FAD).

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>that £13.60 per administration adequately reflected the administrative burden based on 12-minutes of pharmacists' time. The same assumption was applied in TA536 (alectinib for untreated ALK+ advanced NSCLC)[7], with updated costs resulting in a cost of £9.20 per administration. The Committee, in relation to TA536, considered the possibility of a higher cost (£14.40), but there was limited discussion on this at the Committee meeting and no detail was provided in the FAD. In TA500 (ceritinib for untreated ALK+ NSCLC)[8], the company applied an administration cost of £14.26 per administration. This was not discussed in the FAD for TA500. However, in TA500, the ERG explored additional analyses as it considered that the low relative dose intensity seen with ceritinib would induce additional pharmacy costs due to the need for dose modification related to adverse events. Following on from this, in TA500, a statement from NHS England showed agreement with the ERG and provided a cost of £120 per administration. Table 4 compares the pharmacy costs applied across the different NICE appraisals of ALK inhibitors for ALK+ NSCLC with the costs applied in our base case.

Table 4: Comparison of pharmacy fees included in NICE appraisals of ALK inhibitors

<table>
<tr><th>NICE appraisal</th><th>Resource use per administration</th><th>Cost per administration</th></tr>
<tr><td>TA395 (ceritinib for previously treated ALK+ NSCLC)[6]</td><td rowspan="3">12-minutes of pharmacist time</td><td>£13.60</td></tr>
<tr><td>TA536 (alectinib for untreated ALK+ advanced NSCLC)[7]</td><td>£9.20 and £14.40 discussed, no detail in the FAD</td></tr>
<tr><td>TA500 (ceritinib for untreated ALK+ NSCLC)[8]</td><td>£14.26 – ERG and NHSE discussed additional cost of £120. Not discussed in the FAD.</td></tr>
<tr><td>Brigatinib – ID1328</td><td>1-hour of pharmacist time</td><td>£44.00</td></tr>
</table>
Abbreviations: ALK, anaplastic lymphoma kinase; ERG, Evidence Review Group; FAD, final appraisal determination; NICE, National Institute for Health and Care Research; NSCLC, non-small-cell lung cancer

The costs included within our base case economic model reflect higher pharmacy costs than those presented and accepted in all other ALK inhibitor NICE appraisals for ALK+ advanced NSCLC. Additionally, no delivery costs were included in these appraisals.

Therefore, Takeda consider that the application of £217 per administration already in the base case economic model more than reflects relevant administration and delivery fees and is higher than the £120 per cycle stated by NHS England.</td><td></td></tr>
<tr><td>10</td><td>Consultee (company)</td><td>Takeda</td><td>3.2.5 Discussion on end-of-life criteria (Section 3.20, 3.21 and 3.22 of the ACD)</td><td></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
			On page 18-19 of the ACD, the Committee concluded that: *"although the most plausible estimate of life expectancy for people with previously treated ALK-positive advanced NSCLC was close to 24 months, the potential life extension benefit of brigatinib was proportionally substantial. It was therefore satisfied that brigatinib met the criteria for end-of-life treatments."* Takeda agrees with the Committee with regards to the benefit of brigatinib on survival outcomes and that it satisfies the criteria for end-of-life treatments. Takeda would like to highlight to the Committee that the updated base case results in a predicted mean overall survival of 21.83 months for patients treated with ceritinib (compared with 24.03 months in the original base case) and an estimated mean life extension of 21.44 months for brigatinib (compared with 22.49 months in the original base case). Hence, the updated base case further validates that the two end-of-life criteria are indeed satisfied by brigatinib.	Thank you for your comments. Sections 3.21 – 3.23 have been updated to reflect the company's updated base-case results for overall survival.
11	Consultee (company)	Takeda	**3.2.6 Discussion on Cancer Drugs Fund (Section 3.25 of the ACD)** On page 20 of the ACD, the Committee concluded that: *"It therefore did not recommend brigatinib for use within the Cancer Drugs Fund as an option for people with ALK-positive advanced NSCLC who have had treatment with crizotinib."* The reasons given for this recommendation are essentially two-fold: firstly, the company did not express an interest in brigatinib being considered for funding through the Cancer Drugs Fund (CDF); and secondly, *"the committee did not acknowledge any possibility that the clinical uncertainty could be addressed through collection of data from patients having brigatinib treatment through the Cancer Drugs Fund."* We acknowledge that the committee are correct regarding the first point in that our original submission for brigatinib did not include a CDF request; however, we would also point out that the CDF was not raised as a discussion point during Part 1 of the first committee meeting when Takeda representatives were present. Had it been raised during Part 1 of the meeting, then the Takeda representatives would have confirmed that the company is willing to have brigatinib considered for the CDF, if necessary. We would like to confirm again here that while our primary objective is to secure a positive NICE recommendation for brigatinib for routine NHS funding, Takeda would be willing to consider funding through the CDF, if required.	Thank you for your comments. The FAD now recommends brigatinib within its licensed indication following consideration of the updated analyses and updated patient access scheme. Funding through the Cancer Drugs Fund was not considered an appropriate option as the population receiving the treatment is decreasing and it is unlikely any uncertainties will be addressed during a data collection period.
12	Consultee (company)	Takeda	**3.2.7 Updated base case results** <u>Base case results</u> The updated economic model has been submitted to NICE for review under the file name of "Brigatinib NICE model	Thank you for your comments. The recommendations in

<table>
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<tr><td></td><td></td><td></td><td>response to ACD (24OCT2018).xlsm". The model base case has been updated to reflect the following key changes/assumptions:

• Correction for two PFS events and two adverse events, resulting in very minimal impact on these outcomes

• Reduced NHS list price relating to the 90-mg dose of brigatinib (from £4,900 per 28-tablet pack to £3,675 per 28-tablet pack)

• Use of ALTA, ASCEND-2 and ASCEND-5 in relative OS and PFS outcomes

• Application of a reduced treatment benefit (i.e. treatment waning) following treatment discontinuation, applied in the brigatinib arm only. This is applied from the point of maximum follow-up in the ALTA clinical trial of brigatinib

• Utility value of 0.732 (average with age adjustment: 0.712) applied to patients with progressed disease and on-treatment with brigatinib or ceritinib; and a utility value of 0.582 (average with age adjustment: 0.562) for patients with progressed disease and off-treatment with brigatinib or ceritinib.

• Assume that half of the costs incurred through unfinished packs could be saved by the NHS and half would be wasted (as agreed by the Committee)

• Assume administration and delivery costs are already accounted for within the base case model as part of the £217 applied per administration – no change from original submission dossier

The resulting updated base case provides an estimated ICER of £67,449/QALY using the NHS list prices for both brigatinib and ceritinib (Table 5). Table 6 shows the step change from the base case ICER of £54,311/QALY that was presented within the addendum (dated: May 2018) to the updated base case that is now presented in this ACD response (all ICERs being at NHS list prices for brigatinib and ceritinib).

Table 5: Updated base case (at NHS list prices, excluding all PAS)

<table>
<tr><th></th><th>Total Costs</th><th>Total Life Years</th><th>Total QALYs</th><th>Inc Costs</th><th>Inc Life Years</th><th>Inc QALYs</th><th>ICER</th></tr>
<tr><td>Brigatinib</td><td>£123,885</td><td>3.29</td><td>2.23</td><td></td><td></td><td></td><td></td></tr>
</table>
</td><td>the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).</td></tr>
</table>

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Ceritinib	£48,522	1.71	1.11	£75,364	1.57	1.12	£67,449

Abbreviations: ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PAS, patient access scheme; QALYs, quality adjusted life years

Table 6: Step change to updated base case (at NHS list prices, excluding all PAS)

	ICER	Absolute change in each increment	Incremental % change
Original base case	£54,311		
Correction of minor errors in the PFS and adverse event data	£54,628	£317	0.58%
Updated list price relating to the 90-mg dose of brigatinib	£54,390	-£238	-0.44%
Use of ALTA, ASCEND-2 and ASCEND-5 in relative OS and PFS outcomes	£55,766	£1,376	2.53%
Application of a reduced treatment benefit in the brigatinib arm only, from the point of maximum follow-up in the ALTA trial of brigatinib	£63,058	£7,292	13.08%
Utility value of 0.732 (average with age adjustment: 0.712) applied to progressed disease and on-treatment with brigatinib or ceritinib; and a utility value of 0.582 (average with age adjustment: 0.562) for progressed disease and off-treatment with brigatinib or ceritinib.	£64,940	£1,882	2.98%
Assume that half of the costs incurred through unfinished packs could be saved by the NHS and half would be wasted	£67,449	£2,509	3.86%

Abbreviations: ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival

<u>Sensitivity analyses (at NHS list prices, excluding all PAS)</u>

The results of 10,000 probabilistic sensitivity analysis (PSA) iterations are presented in Figure 1 (cost-effectiveness plane) and Figure 2 (cost-effectiveness acceptability curve (CEAC)). Mean probabilistic incremental costs were

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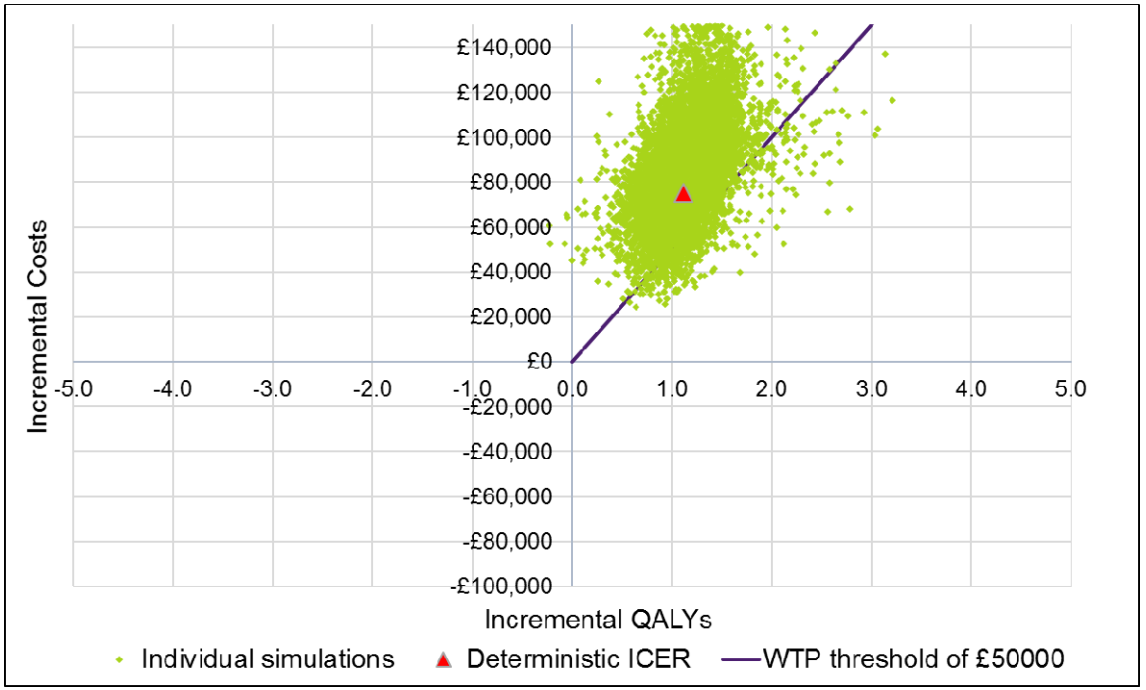
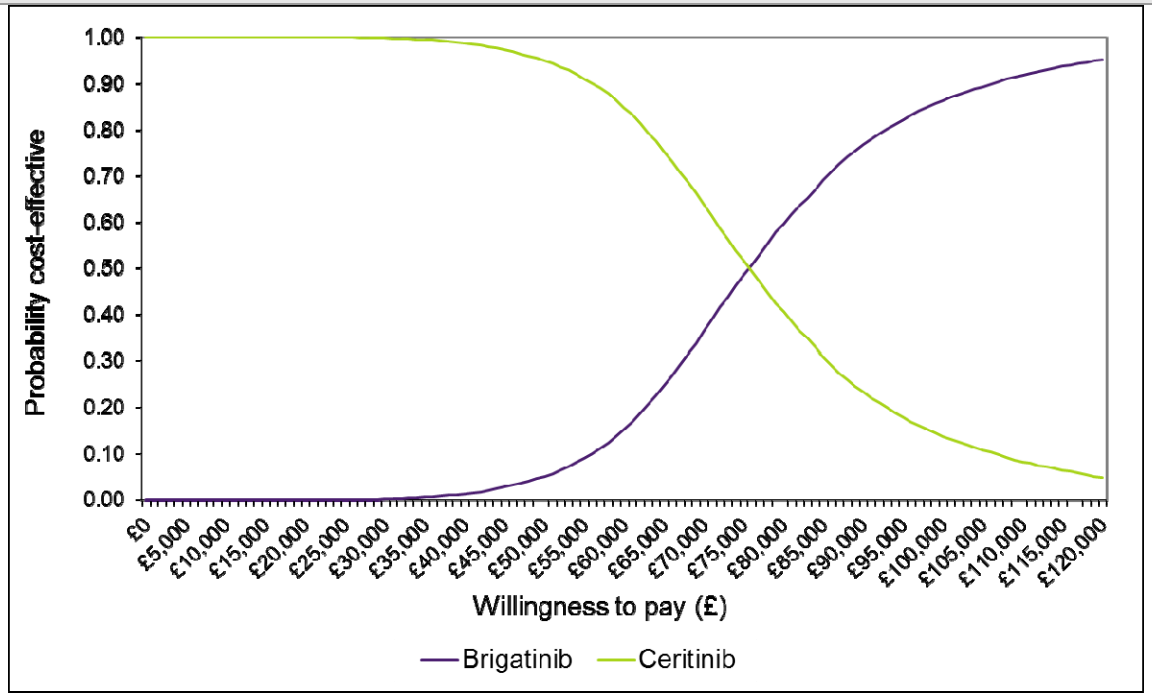
			£89,456 (SD: £26,814). The resulting probabilistic ICER from 10,000 iterations was £76,855/QALY. **Figure 1: Cost-effectiveness plane from 10,000 iterations with uncertainty in OS and PFS curve selection accounted for**  Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; WTP, willingness to pay **Figure 2: CEAC with uncertainty in OS and PFS selection accounted for**	

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
			 Abbreviations: CEAC, cost-effectiveness acceptability curve; OS, overall survival; PFS, progression-free survival Figure 1 presents the updated Tornado diagram with the ten most influential parameters shown in descending order of ICER sensitivity. Table 7 displays this information in a tabular format. **Figure 3: Tornado diagram <u>(at NHS list prices, excluding all PAS)</u>**	

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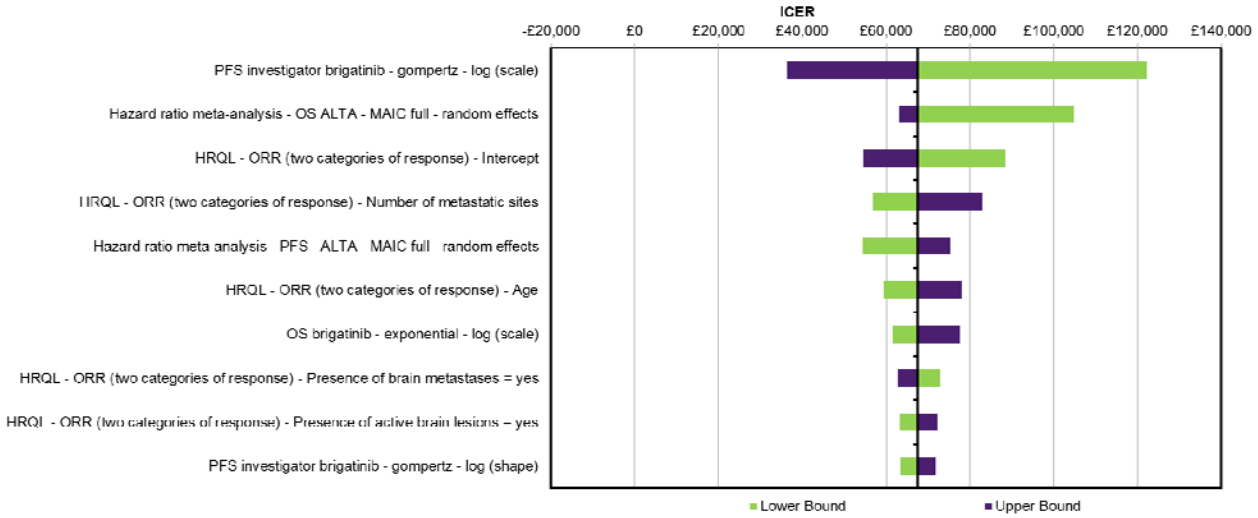

Abbreviations: HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Table 7: Numerical results of one-way sensitivity analysis (at NHS list prices, excluding all PAS)

Parameter	Lower Bound	Upper Bound	Difference
PFS investigator brigatinib - gompertz - log (scale)	£122,116	£36,338	£85,778
Hazard ratio meta-analysis - OS ALTA - MAIC full - random effects	£104,818	£62,995	£41,823
HRQL - ORR (two categories of response) - Intercept	£88,487	£54,493	£33,994
HRQL - ORR (two categories of response) - Number of metastatic sites	£56,810	£82,989	£26,179
Hazard ratio meta-analysis - PFS - ALTA - MAIC full - random effects	£54,421	£75,314	£20,894
HRQL - ORR (two categories of response) - Age	£59,349	£78,110	£18,761
OS brigatinib - exponential - log (scale)	£61,475	£77,616	£16,141

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>HRQL - ORR (two categories of response) - Presence of brain metastases = yes</td><td>£72,926</td><td>£62,737</td><td>£10,190</td></tr>
<tr><td>HRQL - ORR (two categories of response) - Presence of active brain lesions = yes</td><td>£63,234</td><td>£72,266</td><td>£9,033</td></tr>
<tr><td>PFS investigator brigatinib - gompertz - log (shape)</td><td>£63,398</td><td>£71,781</td><td>£8,383</td></tr>
</table>
Abbreviations: HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; OS, overall survival; PFS, progression-free survival
</td><td></td></tr>
<tr><td>13</td><td>Consultee (company)</td><td>Takeda</td><td>
3.3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

In conclusion, Takeda disagree that the Committee's provisional negative recommendation for brigatinib is sound and a suitable basis for guidance to the NHS (see Section 1.1 and Section 3.18 of the ACD). Takeda have acknowledged the issues raised during the first Committee meeting and in the ACD, and we have attempted to address these fully within this ACD response. Arising from this, Takeda have provided an updated base case which we consider to be methodologically sound and clinically plausible. We believe this provides the Committee with a base case ICER that can be used in the decision-making process for brigatinib in this post-crizotinib indication.

Takeda believe that our updated base case includes a number of conservative assumptions and this leads to a base case ICER which is conservative. Examples of this conservative approach include:

• No reduced treatment benefit following treatment discontinuation is applied in the ceritinib arm, but this is applied in the brigatinib arm.

• No treatment benefit associated with brigatinib beyond three months after treatment discontinuation.

• A utility value for patients with progressed disease and on-treatment that includes patients with progressed disease who are off-treatment.

• Higher drug administration/pharmacy costs included within the modelling compared with other NICE appraisals of ALK inhibitors.

To further demonstrate Takeda's commitment to addressing unmet need by making brigatinib available to patients in the post-crizotinib indication, we have submitted to NHS England and PASLU (dated: 19th October 2018) for a significantly enhanced patient access scheme (PAS). This increases the simple discount level from the [redacted]% offered in the original PAS to a new level of [redacted]%; resulting in a per pack (28-day supply) net price of [redacted] for the 180mg strength
</td><td>Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see section 3.5, 3.20 and 3.25).</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
			(compared with a NHS list price of £4,900 per pack; and an original PAS net price of [redacted] per pack). Takeda is optimistic that this price discount, when considered alongside the confidential (and unknown to Takeda) ceritinib PAS, will result in an ICER below the £50,000/QALY end-of-life threshold, and thus achieve a positive recommendation for routine use of brigatinib on the NHS. This would be a positive development for patients, given the many benefits that brigatinib offers over ceritinib, the only other ALK inhibitor that is currently commissioned by NHS England for the post-crizotinib indication. These benefits, which have been highlighted clearly in the original submission to NICE, include: increased efficacy (significantly extended and unprecedented PFS and OS in this indication, as demonstrated in the indirect treatment comparisons); increased efficacy in the CNS (a key site of progression on crizotinib); improved tolerability, with less need for dose reduction or drug discontinuation (particularly in relation to gastrointestinal side-effects); more convenient dosing for patients (one tablet, once-daily with or without food, whereas ceritinib requires multiple capsules to be taken once-daily and with food). Whilst our primary objective is to achieve a positive recommendation for routine use of brigatinib on the NHS, Takeda would also be willing to consider funding via the CDF, if necessary. Takeda would like to remind the Committee that the number of NSCLC patients with the ALK rearrangement is small and the post-crizotinib population eligible for brigatinib in the post-crizotinib indication is small and is also a diminishing one because the use of crizotinib in the 1st line is declining rapidly following the availability of alectinib as a 1st line treatment option (positive FAD for alectinib issued June 2018). This has been confirmed by both clinical experts and the NHS England representative at the first Committee meeting (see point 1 of the NHS England submission to NICE for this appraisal). Hence, the potential budget impact of brigatinib for this indication is modest, predictable and in decline, making this a relatively low risk decision for NICE and NHS England. Based on all the above, we hope that the Committee will reconsider its draft negative recommendation for brigatinib in the post-crizotinib indication and issue final guidance that will make brigatinib available for routine use on the NHS. It should, however, be noted that for the pool of existing patients currently receiving treatment with crizotinib, having access to brigatinib would fulfil a significant clinical need following progression of their disease.	
14	Consultee (company)	Takeda	**3.4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** There are no aspects of this appraisal that need consideration in relation to unlawful discrimination.	Thank you for your comment.
15	Consultees (professional	British Thoracic	We are saddened to learn that Brigatinib has not met the cost effectiveness threshold set out by NICE. We note that NICE do not argue against the superior potential OS and PFS efficacy of Brigatinib compared to Ceritinib and	Thank you for your comments. 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
	groups) Commentator (professional group) - NCRI	Oncology Group (BTOG), National Cancer Research Institute (NCRI), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP)	therefore encourage NICE and the manufacturer to agree a price to allow Brigatinib to be available to NHS patients.	recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
16	Consultees (professional groups) Commentator (professional group) - NCRI	BTOG, NCRI, RCP, RCR, ACP	Whilst the numbers of ALK+ patients now commencing crizotinib will be small (given Alectinib and Ceritinib are now available), there still remain a sizeable proportion of ALK+ patients currently responding to crizotinib that will inevitably relapse in due course for whom the only NICE approved option is Ceritinib. Given the agreed marked PFS and OS superiority of Brigatinib over Ceritinib for these patients, and its superior toxicity profile, we encourage NICE to continue to pursue commissioning of Brigatinib for these patients, for whom Ceritinib would represent a more toxic and less efficacious treatment.	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for

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				this population that should be taken into account (see sections 3.5, 3.20 and 3.25)
17	Consultees (professional groups) Commentator (professional group) - NCRI	BTOG, NCRI, RCP, RCR, ACP	Our experts were disappointed to learn that the manufacturer did not express an interest in Brigatinib being considered for funding through the Cancer Drugs Fund, and would encourage them to consider this if routine NHS commissioning cannot be agreed by NICE	Thank you for your comment. A recommendation for funding through the Cancer Drugs Fund was not considered an appropriate option because the uncertainties raised during the appraisal would not be addressed by further data collection. Following consideration of updated analyses and an updated patient access scheme, as well as exceptional circumstances related to the treatment pathway, the committee concluded that brigatinib is recommended for routine use within the NHS.
18	Consultee (Patient/carer group)	Roy Castle Lung Cancer Foundation	We are disappointed that the Appraisal Committee decision is not to recommend Brigatinib in this indication. We note, in 1.2, the Appraisal Committee concludes, based on clinical evidence from single arm studies, that people having Brigatinib live longer than those having Ceritinib and that they also live longer before their condition worsens. As in 3.15, we note that Brigatinib, has lower toxicity than Ceritinib. Thus, dose reduction with Brgatinib is uncommon, but common with Ceritinib. We note the concerns raised by the Appraisal Committee, with regards to the cost-effective modelling and the resultant negative decision reached. On behalf of the lung cancer patients who would derive clinical benefit from this therapy indication, we would urge constructive dialogue between the Manufacturer, NICE and NHS England. We hope that compromise and agreement can be reached in advance of further discussion by the Appraisal Committee and	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme.

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
			that the ultimate Final Appraisal Decision will be a positive recommendation.	Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
19	Clinical expert	[redacted]	We are concerned that this recommendation will deny ALK positive NSCLC patients access to one of the most effective treatments for brain metastases. ALK positive lung cancer is a rare sub-group of NSCLC with a high proportion of patients experiencing brain metastases (recent first line clinical trials ALEX and ALTA-1L have reported 30-40% of patients with brain metastases at baseline). Furthermore the vast majority of patients will experience brain metastases at some point in their patient pathway. NICE have recently recommended alectinib (TA536) as 1st line therapy (in keeping with international guidelines - ESMO, NCCN) which is highly effective in treating and preventing the development of new brain metastases. As alectinib is now the standard 1st line treatment of choice, this guidance (ID1328) relates to a small ever-diminishing and finite group of patients who have received previous treatment with crizotinib. This recommendation means that patients who have have received crizotinib as first line treatment will only have access to ceritinib second line, both of which have inferior activity in the brain compared to brigatinib and alectinib, and consequently results in inequality in patient care. If patients do not have access to brigatinib following crizotinib they are likely to have more debilitating symptoms, poorer quality of life and shorter survival than those who have been treated with alectinib first line. This judgement appears particularly shortsighted given that there is only small and limited population of patients who would be eligible for this therapy. We are further concerned that this small and finite group of patients will only have access to a second line treatment, which is not only much less effective in terms of overall survival, but is substantially more toxic than brigatinib, leading to a shorter duration of poorer quality life.	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25)
20	Consultee	NHS England	1. There are 3 NICE-recommended monotherapy options for the 1st line treatment of ALK positive non small cell lung cancer (NSCLC): alectinib, ceritinib and crizotinib. The use of crizotinib has fallen away rapidly	Thank you for your comments. 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
			owing to the superiority of alectinib and ceritinib. Alectinib is the main 1st line option currently used in NHS England for newly diagnosed patients on account of its better tolerability (ceritinib has considerable gastrointestinal toxicity). NHS England does not commission the use of crizotinib post ceritinib or alectinib and nor does it commission any treatment sequence other than 1st line crizotinib followed by 2nd line ceritinib. As has been stated already, this commissioned treatment sequence now only applies to patients commenced on 1st line crizotinib in the past or in those rare patients who cannot tolerate alectinib and/or ceritinib. 2. The marketing authorisation for brigatinib for this indication under NICE appraisal is for use following previous treatment with crizotinib. This therefore means that the population of eligible patients for brigatinib for this indication has diminished and will continue to do so. Nevertheless, NHS England welcomes Takeda's submission to NICE for this post-crizotinib indication as brigatinib is likely to be tolerated better than ceritinib and also because Takeda's main focus on reimbursement will not be for this indication but for 1st line use (due to be appraised by NICE in 2019). Roche chose not to submit to NICE when alectinib received its marketing authorisation for 2nd line use after crizotinib. 3. As the committee has already concluded, the current correct comparator for brigatinib in this post-crizotinib indication is ceritinib and as has been stated above. ceritinib has significant tolerance problems. The licensed dose of ceritinib was 750mg daily when appraised by NICE but the dose has since been reduced to 450mg daily when taken with food (this being based on an 81 patient pharmacokinetic equivalence study). Ceritinib is currently supplied in a 150 pill pack and thus at 750mg daily offers the patient a 30 day supply. [redacted] 4. NHS England notes that Takeda has used a total oral drug administration cost per cycle of £217 which is considerably in excess of the current oral chemotherapy administration tariff of £120. As long as this £217 cost is applied to both arms of the brigatinib/ceritinib comparison, NHS England is content in terms of application of reasonable costs of dispensing, review of the patient and drug administration. 5. If NICE recommends brigatinib in this expected indication, NHS England treatment criteria for the use of brigatinib will reflect the MA ie that use of brigatinib is to be confined to patients previously treated with crizotinib for ALK pos NSCLC. In addition, ceritinib post-brigatinib and brigatinib post-ceritinib will not be commissioned unless patients show early intolerance of ceritinib/brigatinib and there is no sign of disease	recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25 The committee have considered what is currently available, the 750 mg/day dose, and at the current cost. Also, the available evidence is based on 750mg/day dosage. The committee have accepted that the administration costs included in the company model are sufficient. (see section 3.17 of the FAD)

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
			progression at the time of any switching from the drug which the patient could not tolerate. 6. NHS England does not view the Cancer Drugs Fund as being a worthwhile use of CDF resources for a NICE recommendation for treatment with brigatinib post-crizotinib. Whilst there are uncertainties as to longer term benefit of brigatinib in this indication, by the time these uncertainties have been resolved the cohort of patients treated with 1st line crizotinib will have almost all, if not all, relapsed and been treated with a 2nd line agent. Thus, NHS England expects the indications of 2nd line TKI use post 1st line crizotinib to be rendered clinically redundant in the relatively near future, especially as 1st line brigatinib is a promising treatment option to be appraised by NICE next year. [redacted]	The Cancer Drugs Fund was not considered an appropriate option because the uncertainties raised during the appraisal would not be addressed by further data collection.
21	Web comment	Patient organisation	I am writing as the medical advocacy lead for ALK Positive UK, which is a new charity set up to support and advocate on behalf of patients with ALK rearrangement lung cancer and their carers. There is real concern in our community that NICE are not going to authorise the use of brigatinib as second line treatment after crizotinib, as outlined in the NICE Appraisal Consultation document from 03 Oct 18. We have many patients in our group who have done very well on brigatinib post crizotinib. As a community, we are all aware how good this new TKI is and what a positive impact this will have on our futures. One of our members, who required an emergency tracheal stent due to disease progression on crizotinib, is now in the position, 4 months later, of the stent being removed. This will allow him to continue playing competitive tennis for his club at a high level and is due to him responding so well to this treatment. Although this relates to one patient, recent studies have shown promising results with a median overall survival rate of 34 months (data from ASCO) and a median PFS of 16.7 months from the ALTA Phase 2 trial. It is disheartening to think that the choice of being treated with this excellent second generation TKI wonâ€™t be available, and this is despite the recent positive trial data, and the positive experiences relating to this drug in our community. Please do not deny us this choice.	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
22	Web comment	Patient 1	I am an ALK positive patient and currently treated with crizotinib. This is my first TKI. I understand that ceretinib which is the next TKI available to me has considerable side effects and is not as effective as Brigatinib as a second TKI. I	Thank you for your comments. 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
			have had a good response to crizotinib for the last 3.5 years and would like to have the opportunity in the future to take another TKI such as Brigatinib. On the Worldwide ALK Positive web page which provides support to ALK Positive patients members have reported very positive responses to Brigatinib which has improved their quality of life and lengthened it. Lung cancer in general has a very poor prognosis when diagnosed in the late stages, which it most often is. It is therefore important that opportunities to improve the care and treatment for lung cancer patients are supported as much as possible and as much as for other cancers to improve care in this field. Thank you for listening	recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
23	Web comment	Patient 2	As an ALK patient, diagnosed in February 2018 I am currently taking Brigatinib via a compassionate access scheme. I progressed on both Crizotinib and Ceritinib (I was not eligible for Alectinib) and so this treatment is a vital lifeline for me. I'm 40 with two children aged 7 and 11. ALK+ NSCLC likes young, fit non-smokers and is threatening to leave my children without their mother. According to current NHS provision, my next course of treatment after Ceritinib would be traditional chemotherapy and then simply palliative care to keep me comfortable. When there are drugs available like Brigatinib which can extend my life expectancy and improve my quality of life I don't understand why this would not be a treatment option of choice. Brigatinib covers a wide range of sub mutations than Ceritinib and Alectinib and I believe it should be available as a second or subsequent line of treatment as Alectinib is only first line treatment at present.	Thank you for your comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE

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
				normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
24	Web comment	Patient 3	I would like to add my comment that without Brigatinib being approved for 2nd line use I have no other TKI options left to me once my current treatment fails. I have lived a healthy lif, never smoked , only drunk occasionally and keep fit. I have worked all my life and paid my taxes accordingly. It isnâ€™t my fault I have stage 4 LC and have never needed the NHS before but now I do! I have a family that needs me to stay alive as long as possible and this treatment would give me that opportunity. I appreciate these decisions arenâ€™t easy and there are many deserving patients requiring high cost medicines but we are a small group of patients in the UK but the impact of having this medicine available to us would be enormous.	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
25	Web comment	Patient 4	A never-smoker in my forties, I've had stage 4 ALK positive NSCLC for more than two years. TKIs have made a huge difference to my life, enabling me to continue to support my family and live a near-normal life, and continue to work nearly full time. From contacts on social media I have seen many sufferers of this disease in other countries benefit from a prolonged response to brigatinib after progressing on crizotinib. Sometimes for several years, and often of much longer duration and better tolerated than is seen with second line ceritinib. So having this drug as an option would make a huge difference to me and my family, and enable me to continue to support them, to work, contribute to	Thank you for your comments. The recommendations in the FAD have changed following consideration of 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
			society, all with a good quality of life. So I would ask you to please approve this drug since it is undoubtedly badly needed by patients.	updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
26	Web comment	Patient 5	I was diagnosed 18 month ago, was on Crizotinib for 14 month and now on ceritinib, I have a good quality of life , I have read about other Alk+ patients doing very well on brigatinib, after Crizotinib and ceritinib, I would give me peace of mind if I knew it would be available to me when I progress on ceritinib. Thank you for taking your time reading this.	Thank you for your comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional

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
				circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
27	Web comment	Patient 6	i was diagnosed ALK+ In june of this year i am currently on Alectinib but i am so worried as to what will be my next line of treatment if Alectinib lets me down to know that this medication would be available to me would make so much difference the alternative is the cancer wins again thank you.	Thank you for your comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
28	Web comment	Patient 7	I did not respond to Crizotinib as my first line TKI. I am currently on Ceritinib as the only second line TKI available. I have lost 7lbs in 6 weeks due to the harsh GI side effects of this TKI. My weight is currently 6st 6lbs. It would be of enormous value to me to have the choice of a TKI such as Brigatinib that is easier on the GI system.	Thank you for your comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. 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
				recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
29	Web comment	Patient 8	The evidence shows that after some while the patient diagnosed with ALK+ nsclc becomes resistant to TKIs. I would like to think all possible options are made available. When alectinib was finally approved by NICE for first line of treatment it opened the doors for many for a return to full health. More options for treatment would mean that stage IV lung cancer changes from being a terminal illness to being a chronic illness that can be managed. It seems that with these drugs, when a patient has a good response to treatment , they enable us to return to their everyday lives. So many ALK+ patients are younger than 70, some considerably younger, that it is possible we will need a series of TKIs throughout our lives with cancer.	Thank you for your comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an

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
				end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
30	Web comment	Carer 1	My husband was dx august 2017 alk+ started on Crisotinib, now on Ceritinib. Brigatinib was going to be his next option when ceritinib stops working. I find it extremely frightening how few options are available in the UK. The ALK worldwide site has so many positive stories where patients are having fantastic results on brigatinib. Please please reconsider and approve in the UK. Give patients some positive hope for the future. Thank you	Thank you for your comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25)..
31	Web	Carer 2	My 30 year old wife mother to a 2 year old and 6 week old is currently on alectinib, and has been on it for 3 weeks with	Thank you for your

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		good results, however it is vital that alternative options are available to her in case she becomes resistant or suffers from side effects	comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
32	Web comment	Carer 3	My 20 year old daughter has ALK positive NSCLC lung cancer. Please approve Brigatinib following crizotinib which she is currently on, and will hopefully be on for some years to come. Such TKIs allow many people worldwide to lead quite normal lives despite their diagnosis. My daughter is her second year at University studying nursing which would have been impossible with conventional chemotherapy. Please allow Brigatinib as this is scheduled to be next in line if crizotinib stops working for her. All sufferers deserve the best chance with these amazing drugs which ultimately give them a better chance of leading a normal life, allowing them to work and so be less of a burden on the NHS/Benefits system.	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers

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				cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
33	Web comment	Carer 4	I am submitting on behalf of my brother, [redacted]. [redacted] was diagnosed aged 54 with stage IV NSCLC in December 2014. He had extensive brain metastases on diagnosis â€“ too many to count â€“ and the largest measured 3.8cm in diameter. He had terrible pain in his brain, he had lost much of his sight, and his memory was shot. He was given 3-6 months to live. The distress for him and his family was unimaginable. However, nearly four years on the picture is very different, and it is thanks to ALK inhibitors. ALK inhibitors have kept [redacted] cancer stable, and at times shrinking. His vision has recovered, his memory is excellent, and he no longer has any noticeable brain issues. So far he has been on Crizotinib and Ceritinib, with tremendous control, even in the brain, and negligible side effects â€“ just transient and minor GI issues. He has never had any radiotherapy. Amazing. Almost four years of good life with stage IV lung cancer. ALK inhibitors have allowed him to positively thrive and be an active member of his family and his community. ******** lives a full life. He does not consider himself to be â€œend of lifeâ€ nor to be on an â€œend of life treatmentâ€ . He feels and looks well. However, if more of the available ALK inhibitors are not approved, what next for [redacted]? Brigatinib has huge potential to control [redacted] disease for another lengthy period. This amazing drug has excellent blood brain barrier penetration and targets many of the mechanisms of resistance that can cause failure of earlier ALK inhibitors. On the worldwide ALK Positive Group we are seeing many people internationally who have had a prolonged response to Brigatinib after other TKIs (not just Crizotinib). We know of at least one person who is still alive 12 years after her diagnosis, due to a succession of ALK inhibitors. Please approve this treatment and allow ALK Positive patients to live longer lives as active members of society, to have longer with their families and friends, and to dare to hope ALK Positive lung cancer will one day be a manageable chronic disease.	Thank you for your comments. The current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
34	Web comment	Carer 5	I am the mother of a 30 year old daughter diagnosed 03/08/17 with stage IV nsclc (ALK)	Thank you for your comments. The

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			My daughter has been fortunate enough to be prescribed Alectinib first line and been leading an almost normal life. This drug has enabled her to work full time, as a personal trainer, run 2 half marathons since diagnosis . She is effectively getting on with life and apart from 4 weekly blood tests and quarterly scans is hardly a drain on the NHS. Without this amazing drug my daughter would probably not be alive today!!!! Sadly this drug will probably stop working and the only other drug available is Ceritinib. To begin with, this drug has very harsh side effects for many and may not cover the resistence built up after Alectinib.. Brigatinib covers different resistances to Ceritinib and seems to have less toxicity. Only approx 2 to 5% of lung cancer patients are ALK and most tend to be under the age of 50. Over the past 40 years treatment for lung cancer worldwide has been seriously underfunded and now that we have these break throughs for the biggest cancer killer how can this fabulous drug be denied for this small subset of people. By authorising Brigatinib you are effectively turning this disease from terminal to chronic. I know so many people in the USA who are members of the ALK Positive foreign who have been living with this awful disease five,, ten and more years please do not deny our citizens to the chance of life. These drugs can give not just months of extra life but years. What price is that?!??? Please , give these usuallyyoung, usually non smoking usually misdiagnosed (due to age, fit ,non smoking)people a chance. Kind regards [redacted]	current marketing authorisation is for the use of brigatinib after crizotinib only. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
35	Web comment	Carer 6	My mum has ALK+ LC a d is in her second line therapy (Ceritinib) after Crizotinib. Iâ€™d like to know why Brigatinib is only being considered for second line after Crizotinib. There are so many other patients that will have had a different sequence if TKIâ€™s that could benefit from Brigatinib. I am on direct contact with patients who are in Brigatinib and doing well with a great quality of life, they have varying TKI sequence history. My mum on no way shape or form considers herself as end of life. She looks after my 3 children while I work part time. She tends her allotments and has an active social life. She and her whole extended family would all benefit mentally from knowing there is another treatment option after Ceritinib. Thank you	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an

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				end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
36	Web comment	NHS Professional 1	Brigatinib will be a useful treatment option in patients progressing on crizotinib Efficacy: IRC PFS 16.7 months is the longest PFS reported in trials post crizotinib (with the limitations of inter-trial comparisons); high efficacy in controlling brain metastases which is often a site of disease progression with devastating consequences and a significant cost in the patients quality of life Ease of administration: Once a day dosing will help patients to adhere to treatment and reduce risk of dosing errors that can have significant cost implications.	Thank you for your comments. The recommendations in the FAD have changed following consideration of the updated analyses and updated patient access scheme. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see sections 3.5, 3.20 and 3.25).
37	Web comment	NHS Professional 2	I disagree with the committee's decision that applying a value of 0.643 for the full duration of progressed disease until death was unreasonable. Given the frequency at which these patients will be scanned, the first hint that these patients have disease progression will be radiological progression on their scan rather than any overt clinical symptom. As such when progressive disease is initially detected, their utility value will in fact not be too far off from 0.793. Whilst some of these patients will progress rapidly and become too unwell to receive further systemic treatment such as chemotherapy or third generation ALK inhibitor like Lorlatanib, a fair proportion will be well enough to be switched to these other treatments and the utility value assigned to these patients should not be less that 0.643. Thus if one were to take a mean value of the utility value for all these patients, from either the time of progression to death,	The company have changed the values in their base-case so that the progressed on-treatment value is 0.732 and the progressed off-treatment value is

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			or from progression to being switched to an alternative systemic treatment, I suspect it may actually not be too far off from 0.643. The decline in utility value from 0.643 should only be applied to a proportion of the patients with progressive disease.	0.582. The committee considered these values to be reasonable (see section 3.15 of the FAD).

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
ID1328 brigatinib BTOG joint response to ACD 16102018RB [AIC].doc	BTOG-NCRI-RCP-RCR-ACP	[Nil]	3	
ID1328 brigatinib BTOG joint response to ACD 16102018RB [redacted].doc	BTOG-NCRI-RCP-RCR-ACP	[Nil]	3	

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib [ID1328]: Response to the first ACD

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute of Health and Care Excellence

Submitted 24th October 2018

Contents

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List of Abbreviations

ACD	Appraisal consultation document
AIC	Akaike Information Criterion
ALK+	Anaplastic lymphoma kinase
BIC	Bayes Information Criterion
BSC	Best supportive care
CDF	Cancer Drug's Fund
CNS	Central nervous system
DSU	Decision support unit
ERG	Evidence review group
FAD	Final appraisal document
HRQL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
INV	Investigator
IRC	Independent review committee
ITC	Indirect treatment comparison
MAIC	Matched adjusted indirect comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PFS	Progression-free survival
QALY	Quality adjusted life year
TSD	Technical support document

1. Executive Summary

Takeda disagree with the Appraisal Committee's provisional negative recommendation for brigatinib for the treatment of anaplastic lymphoma kinase positive (ALK+) non-small-cell lung cancer (NSCLC) as presented in the Appraisal Consultation Document (ACD; 26th September 2018), and we do not consider it to be a sound and suitable basis for guidance to the National Health Service (NHS). We would ask the Committee to reconsider this draft recommendation in light of the considered and constructive points that are presented in this ACD response.

In this response Takeda have addressed the key issues raised by the Evidence Review Group (ERG) and the Appraisal Committee, and provided what we think is a fair and balanced response which includes the presentation of an updated base case that we consider to be methodologically sound and clinically plausible. The updated base case incorporates the Committee's concerns associated with:

- Sources included in the indirect treatment comparisons;
- Duration of treatment benefit beyond treatment discontinuation;
- Separate utility values for progression-free, progressed disease on-treatment and progressed disease off-treatment phases and
- Drug wastage

The updated base case provides what we believe to be the most plausible base case incremental cost-effectiveness ratio (ICER) for patients with ALK+ NSCLC in the post-crizotinib setting. We would emphasise that our updated base case includes a number of conservative assumptions, as discussed in this ACD response. This provides the Committee with a conservative base case ICER that we consider can be used in the decision-making process for brigatinib in the post-crizotinib indication. This updated base case estimates an ICER of £67,449 per quality adjusted life year (QALY), using the NHS list prices for both brigatinib and ceritinib.

To continue to show flexibility and commitment in this appraisal process, Takeda have submitted an enhanced simple discount patient access scheme (PAS) proposal to the Patient Access Schemes Liaison Unit (PASLU; Date: 19th October 2018) which reduces the net price per pack (28-day supply) for the 180mg strength to £[redacted] (a [redacted]% simple discount on the NHS list price). This compares with the originally submitted PAS net price of [redacted] per pack (28-day supply) for the 180mg strength (a [redacted]% simple discount on the NHS list price). The significantly enhanced PAS is designed specifically to both address the uncertainty regarding the cost-effectiveness of brigatinib and to reduce the ICER to a level that we believe shows cost-effectiveness at the £50,000/QALY end-of-life threshold, when the confidential (and unknown to Takeda) ceritinib PAS is included.

Takeda is optimistic that the steps we have taken in this ACD response will allow the Committee to reach a positive recommendation for brigatinib in patients with ALK+ NSCLC in the post-crizotinib setting, thus allowing for routine use on the NHS. This would be a positive development for patients, given the many benefits that brigatinib offers over ceritinib,

the only other ALK inhibitor that is currently commissioned by NHS England for the post-crizotinib indication.

The benefits of brigatinib over ceritinib, which have been highlighted clearly in the original submission to the National Institute for Health and Care Excellence (NICE), include:

- Increased efficacy (significantly extended and unprecedented progression-free survival (PFS) and overall survival (OS) in this indication, as demonstrated in the indirect treatment comparisons);
- Increased efficacy in the central nervous system (CNS; a key site of progression on crizotinib);
- Improved tolerability, with less need for dose reduction or drug discontinuation (particularly in relation to gastrointestinal side-effects);
- More convenient dosing for patients (i.e. one tablet, once-daily with or without food, whereas ceritinib requires multiple capsules to be taken once-daily and with food).

While our primary objective in this ACD response is to secure a positive NICE recommendation for brigatinib for routine NHS funding, Takeda wishes to emphasise that we would also be willing to consider funding via the Cancer Drugs Fund (CDF), if required. We note the comment in the NHS England submission to NICE before the first Committee meeting that *"NHS England welcomes Takeda's submission to NICE for this post-crizotinib indication……"*, and we would hope that all stakeholders acknowledge the considerable flexibility and commitment that the company has shown in trying to bring this innovative medicine to patients in need of a better treatment option than currently available.

Takeda would also like to remind the Committee that the number of NSCLC patients with the ALK rearrangement is small and the post-crizotinib population eligible for brigatinib is also a diminishing one because the use of crizotinib in the 1st line is declining rapidly following the availability of alectinib as a 1st line treatment option (positive FAD for alectinib issued June 2018). This has been confirmed by both clinical experts and the NHS England representative at the first Committee meeting (see point 1 of the NHS England submission to NICE for this appraisal). Hence, the potential budget impact of brigatinib for this indication is modest, predictable and in decline, making this a relatively low risk decision for NICE and NHS England. It should, however, be noted that for the pool of existing patients currently receiving treatment with crizotinib, having access to brigatinib would fulfil a significant clinical need following progression of their disease.

Based on all the above, we would hope that the Committee will reconsider its draft negative recommendation for brigatinib in the post-crizotinib indication and issue final guidance that will make brigatinib available for routine use on the NHS.

2. Introduction

2.1 Appraisal Committee's preliminary recommendations

On the 26th September 2018, the NICE Appraisal Committee prepared an ACD summarising the evidence, views and draft recommendations of the Committee regarding the use of brigatinib on the NHS in England for treating ALK+ advanced NSCLC after crizotinib The ACD sets out the draft recommendations made by the Committee which currently state that:

'Brigatinib is not recommended, within its anticipated marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults who have already had crizotinib.'

In this document Takeda have addressed the issues raised by the ERG and the Appraisal Committee and provided what we think is a fair and balanced response which includes the presentation of an updated base case.

The updated base case incorporates the Committee's concerns associated with sources included in the indirect treatment comparisons, duration of treatment benefit beyond treatment discontinuation, separate utility values for progression-free, progressed disease on-treatment and progressed disease off-treatment phases and drug wastage. The updated base case provides what we believe to be the most plausible base case ICER for patients with ALK+ NSCLC in the post-crizotinib setting.

To continue to show flexibility and commitment in the appraisal process for brigatinib in the post-crizotinib setting, Takeda have submitted an enhanced simple discount patient access scheme (PAS) proposal to PASLU and NHS England (Date: 19th October 2018) which reduces the net price per pack (28-day supply) for the 180mg strength to £[redacted] (a [redacted]% simple discount on the NHS list price). The enhanced PAS is designed specifically to both address the uncertainty regarding the cost-effectiveness of brigatinib and to reduce the ICER to a level that we believe shows cost-effectiveness at the £50,000/QALY end-of-life threshold, when the confidential (and unknown to Takeda) ceritinib PAS is included.

Takeda is optimistic that the steps we have taken in this ACD response will allow the Committee to reach a positive recommendation for brigatinib in patients with ALK+ NSCLC in the post-crizotinib setting, thus allowing for routine use on the NHS. Although it is not our primary objective for brigatinib, Takeda is also willing to give consideration to funding through the Cancer Drugs Fund (CDF), if necessary.

3. Response to the Appraisal Committee's standard key questions

Please find below the responses of Takeda to the questions from the Appraisal Committee listed on page 1 of the ACD.

3.1 Has all the relevant evidence been taken into account?

The main clinical evidence to support the case for the clinical and cost-effectiveness of brigatinib is the ALTA study[1], with supportive efficacy evidence from Study-101[2]. To date, Takeda have provided all relevant data currently available. However, in responding to this ACD, Takeda identified two PFS events and two adverse events which were incorrectly coded as part of the original submission and addendum. The model has been updated with the correct data which has had a very minimal impact on the PFS outcomes and adverse events. This has resulted in a very small increase in the ICER from £54,311 to £54,628. Takeda apologise for the late correction of these data but would like to emphasise the very minimal changes in outcomes and the very small effect on the ICER (+£317).

Takeda consider that the Appraisal Committee has taken all relevant data from the original submission, the addendum and the data from Takeda's response to the ERG questions into account.

One additional point that Takeda would like to confirm relates to the proposed NHS list prices for brigatinib that we have submitted to the Department of Health and Social Care. These were submitted to the Department of Health and Social Care on October 12th and are presented in Table 1.

Table 1: Proposed list prices for brigatinib

Drug name	Brand name	Preparation	NHS list price
brigatinib	Alunbrig	28 x 30mg tablets	£1,225 per 28 tablet pack
		28 x 90mg tablets	£3,675 per 28 tablet pack
		28 x 180mg tablets	£4,900 per 28 tablet pack
		Starter Pack (7 x 90mg tablets & 21 x 180mg tablets)	£4,900 per starter pack

Abbreviations: NHS, National Health Service

These differ from those shown in the original submission to NICE only in relation to the lower prices now proposed for the 30mg and 90mg strengths. The prices proposed for the 180mg strength and the Starter Pack are unchanged from those shown in the original submission. The health economic model has been updated to reflect these NHS list prices, leading to a small decrease in the ICER from £54,628 to £54,390 (-£238).

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

Takeda consider that the summaries of clinical effectiveness presented in the ACD are reasonable interpretations of the evidence (Sections 3.4 to 3.11 of the ACD).

There are a number of issues raised in the ACD relating to the analysis of cost-effectiveness of brigatinib relative to ceritinib in patients with ALK+ advanced NSCLC which we have endeavoured to clarify and address within the economic model and this document, including the following issues:

- Use of ASCEND-5[3] within the indirect treatment comparison for PFS outcomes (Section 3.2.1 of this response document)
- Modelling treatment benefit discontinuation (Section 3.2.2)
- Health-related quality of life (HRQL) (Section 3.2.3)
- Drug wastage and administration costs (Section 3.2.4)

Section 3.2.1 considers the use of ASCEND-5 when calculating the relative PFS estimates; Takeda understand the Committee's preference towards including ASCEND-5 and consider that the sources contributing to relative efficacy estimates should be the same for OS and PFS outcomes, in order to avoid inconsistencies in the modelling outcomes. Section 3.2.2 presents a method to account for treatment benefit discontinuation which is in line with the Committee's feedback. Section 3.2.3 takes note of the Committee's preference for separate progressed disease on-treatment and progressed disease off-treatment utility values; Takeda present the values used in the updated base case. Finally, Section 3.2.4 agrees with the approach taken by the ERG and Committee for capturing drug wastage. However, Takeda consider that applying an additional administration cost within the model will result in double counting – dispensing and administration costs are already captured within the pre-progression resource use.

The resulting updated base case estimates an ICER of £67,449/QALY, using the NHS list prices for both brigatinib and ceritinib. The updated economic model has also been submitted to NICE for review under the file name of "Brigatinib NICE model response to ACD (24OCT2018).xlsm". Section 3.2.6 of this document presents the step change from the ICER presented within the addendum (dated: May 2018) of £54,311/QALY to the updated base case reflecting changes from the first Committee meeting and the ACD (dated: September 2018).

3.2.1 Discussion on the indirect comparison of brigatinib and ceritinib (Section 3.6, 3.7 and 3.8 of the ACD)

On page 8 of the ACD it states: "Results from the 4 single-arm studies (see Section 3.3 and Section 3.4) were used, and 2 approaches were taken: a naïve ITC and a matching-adjusted indirect comparison (MAIC)". This is incorrect - we would like to clarify that three single arm trials (ALTA, Study 101 and ASCEND-2) and a double armed randomised controlled trial (ASCEND-5) were incorporated within the indirect treatment comparisons.

In our original base case, we used the results of the MAIC ITC that included ALTA and Study-101 (pooled) for brigatinib and ASCEND-2 for ceritinib to estimate the hazard ratio for PFS outcomes for brigatinib relative to ceritinib. These results were selected for three reasons: (1) to make use of the totality of data available for brigatinib, (2) to align with the inputs in the rest of the model and (3) to ensure consistency in the type of PFS assessment (i.e. investigator (INV)-assessed vs. independent review committee (IRC)-assessed). Page 10 of the ACD states: "The ERG preferred using the results of the meta-analysis of the MAIC ITC that included only ALTA for brigatinib compared separately with ASCEND-5 (ceritinib) and ASCEND-2 (ceritinib) (see Section 3.7). The Committee agreed that data from ASCEND-5 should be included".

Using these sources improves the hazard ratio for PFS in favour of brigatinib (from 0.38 to 0.28). This is driven by two factors: (1) IRC-assessed PFS is being considered and (2) Study-101 is being excluded. Takeda consider that if Study-101 is to be excluded from the indirect treatment comparisons for the PFS outcomes, then this should also be excluded from the OS outcomes. Otherwise, there is an inconsistency within the model where time in pre-progression and time on treatment is increased for brigatinib relative to ceritinib, without any subsequent impact on the relative OS benefit. Therefore, in our updated base case we include the Committee's preference for using ALTA, ASCEND-2 and ASCEND-5 for relative PFS estimates, and we also use these sources for the relative OS estimates. Section 3.2.6 presents the impact of this in our updated base case.

3.2.2 Discussion on duration of treatment benefit after progression (Section 3.12 of the ACD)

Takeda consider that the heading relevant to Section 3.12 in the ACD should refer to "Duration of treatment benefit after ***discontinuation***" – rather than *"after progression"* as it currently states.

Takeda recognise the uncertainty associated with the duration of treatment benefit after a patient has stopped treatment with brigatinib or ceritinib and accept that modelling a lifetime continued treatment benefit may not reflect clinical reality. As discussed in the NICE Committee meeting and the ACD, the method used by the ERG to explore a shortened continued treatment benefit led to outputs that were not clinically plausible. Based on the statement on page 13 of the ACD that *"The Committee agreed that a method similar to the ERG's modelling approach might be suitable for decision-making if the outputs of survival were clinically plausible"*, we have considered a somewhat similar (but different) approach which we believe provides clinical outcomes that (unlike those of the ERG) are clinically plausible and align with the expectations of clinical experts. This approach is described below and is presented within the updated health economic model: "Brigatinib NICE model response to ACD (24OCT2018).xlsm".

For this alternative approach that aligns with clinical expectations, Takeda have applied a tapering (waning) of survival rates for brigatinib from week 161 (3.09 years) to week 377 (7.23 years). Up to week 161, survival is estimated as per the parametric curve fit to the brigatinib data. Week 161 was selected because this represents the maximum follow-up from the ALTA clinical trial (148 weeks), which has been used in the analyses informing the model, plus an additional 3 months (approximately 13 weeks). The rationale for the

additional 3 months is based on comments made by the clinical experts at the Committee meeting and the statement on page 12 of the ACD that: *"The clinical experts explained that it was reasonable to assume that treatment benefit would continue for a few months after stopping treatment."* This has subsequently been supported by feedback from three other clinical experts that were consulted by Takeda after the Committee meeting. Between week 161 and week 377, the survival rate is weighted across brigatinib and ceritinib rates, with an increasing weight given to the ceritinib rate over time so that by week 377 the rate is equal to the ceritinib survival rate. From week 377, the survival rate for brigatinib is assumed equal to ceritinib. Week 377 was selected because this represents the time at which 1% of patients remained on treatment with brigatinib (364 weeks), plus the additional three months (approximately 13 weeks) as explained above.

Applying the treatment benefit discontinuation, using the method described above, impacts on the proportion of patients surviving at 5-, 10- and 20-years, as predicted by the health economic model. Table 2 presents these proportions for each of the parametric survival curves and compares this with the averaged estimates from five UK clinical experts – details relating to this expert elicitation are presented in the original submission dossier. When applying treatment benefit discontinuation, the Gompertz curve does not align with clinicians' expectations. Although there is uncertainty in clinician estimates, it was agreed by all five UK clinical experts that ~5% of patients would be expected to survive to 10-years. None of the curves align exactly with this expectation; but the exponential provides a conservative estimate of 2.28% survival at 10-years. Therefore, this is applied for OS outcomes along with the treatment benefit discontinuation in the updated base case. In addition to providing a conservative estimate, the exponential curve also has the advantage of providing the best fit to the observed data based on the AIC and BIC values – and produces outcomes that align closely with clinical expert expectations. Section 3.2.6 presents the impact of this in our updated base case.

Table 2: Proportion of patients surviving at 5-, 10- and 20-years as predicted by the model with treatment benefit discontinuation

	5-years	10-years	20-years
Clinical experts average	28.50%	5.83%	0.00%
Exponential	28.99%	2.28%	0.01%
Gamma	27.27%	1.67%	0.00%
Log-normal	39.27%	13.77%	3.13%
Log-logistic	33.99%	8.84%	1.53%
Weibull	26.87%	1.46%	0.00%
Gompertz	25.21%	0.54%	0.00%
Generalised gamma	27.96%	2.03%	0.01%

Note: all treatment benefit discontinuation scenarios are presented with no change to ceritinib. Therefore, the health economic model does assume a lifetime treatment benefit for ceritinib. However, in the absence of further survival data relating to subsequent therapies following treatment with brigatinib or ceritinib, treatment effect waning has only been applied in the brigatinib arm. This is a conservative assumption because it is likely that in clinical practice the benefits of treatment would diminish (wane) in both the brigatinib and ceritinib

arms. If a waning effect were applied in the ceritinib arm this would worsen the outcomes for ceritinib, thereby increasing the benefit of brigatinib relative to ceritinib.

Additionally, clinical experts suggested at the first Committee meeting that there may be a longer continued treatment benefit with brigatinib relative to ceritinib, due to the increased effectiveness of brigatinib in the CNS and a greater depth of response relative to ceritinib. Due to lack of data, and in line with our conservative approach, this is not captured in the treatment benefit discontinuation scenario we have applied (in fact we have done the opposite in our updated base case by applying the treatment waning effect only in the brigatinib arm). This is a very conservative modelling assumption because increasing the duration of treatment benefit for brigatinib relative to ceritinib would further decrease the base case ICER in favour of brigatinib.

3.2.3 Discussion on health-related quality of life (Section 3.13 and 3.14 of the ACD)

Progressed disease and on-treatment

On page 14 of the ACD it states: *"The Committee concluded that the company's utility value for progressed disease on treatment was reasonable, but considered that a decline in utility was needed for people with progressed disease after treatment had stopped."*

In the original base case, Takeda applied a utility value of 0.643 for patients in the progressed disease state – regardless of continued treatment with brigatinib or ceritinib. This value was derived by applying the utility decrement from Chouaid *et al.* (2013)[4] to the pre-progression utility value (0.793 - 0.15 = 0.643), which was derived from the ALTA patient level data. In the first Committee meeting, Takeda acknowledged that the clinical experts and the Committee Chair did not expect that utility would remain constant throughout this progression period – most notably, it was expected that there would be a decline in utility for patients stopping treatment with an ALK inhibitor and moving onto treatment with best supportive care (BSC). Therefore, the updated model includes a utility value for progressed disease on-treatment (which reflects continued treatment with brigatinib or ceritinib) and progressed disease off-treatment (which reflects the HRQL after stopping treatment with an ALK inhibitor and receiving BSC).

Based on clinical expert feedback, both at the Committee meeting and obtained through interactions we had with eight clinical experts subsequently, Takeda does not believe that progression whilst remaining on treatment with brigatinib or ceritinib would result in a utility decrement of 0.15 from the pre-progression health state. As stated in the submission from NHS England in advance of the first Committee meeting: there are two main scenarios where treatment with brigatinib will continue after RECIST-defined disease progression:

(1) When there is a dimensionally small increase in an already small marker lesion which triggers the definition of disease progression but is clinically irrelevant as the patient remains well. Treatment would continue until there is a clinically significant progression (i.e. the development of symptoms)

(2) When there is continued systemic response but disease progression in the brain which is then amenable to active treatment with radiotherapy. Treatment would continue until systemic progression or loss of control of the intra-cerebral disease.

Therefore, the patients in the progressed disease on-treatment phase are often asymptomatic and still obtaining the clinical benefit of treatment. As stated on page 14 of the ACD: *"The clinical experts explained that, even with central nervous system involvement, people with progressed ALK-positive advanced NSCLC can have a good quality of life."* This was echoed by the feedback received by Takeda from eight clinical experts who stated that they would not anticipate a significant change in the utility value at this point.

Takeda consider that the utility value estimated from the ALTA data for the progressed disease health state reflects the small decline in utility associated with RECIST-defined progression and the continued clinical benefit. This utility value was not used in the original base case due to limited follow-up; it was considered that it did not reflect the 'true' progressed disease utility value where patients had moved onto treatment with BSC. However, this utility value does provide HRQL information for those patients who have just progressed. As patients are only in the progressed disease on-treatment phase for an average of 1.53 months within the model, the progressed disease utility value from the ALTA data would be expected to approximate the 'true' utility value for these patients.

Therefore, the updated base case applies a utility value of 0.793 (average with age adjustment: 0.773) for pre-progression and on-treatment (0.793 is already accepted by the Committee as appropriate for pre-progressed disease – see page 13 of the ACD) and 0.732 (average with age adjustment: 0.712) for progressed disease and on-treatment (derived from the ALTA data for progressed disease). These values are summarised in Table 3.

Section 3.2.6 presents the impact of this in our updated base case. **Note:** as patients are only in the post-progression on-treatment phase for a short time in the economic model (1.53 months) – there is very little impact on the ICER when assuming a utility of either 0.643 or 0.732 for such patients.

<u>Progressed disease and off-treatment</u>

To reflect the decline in utility associated with patients with progressed disease after treatment with brigatinib or ceritinib has been stopped, the utility decrement of 0.15 from Chouaid *et al.* (2013) was applied to the progressed disease on-treatment utility value. Therefore, the updated base case uses a utility value of 0.582 (i.e. 0.732 – 0.15 = 0.582; average with age adjustment: 0.562) for progressed disease and off-treatment (Table 3). Section 3.2.6 presents the impact of this in our updated base case.

Takeda acknowledge that this utility value is higher than those seen in the literature (0.46 from Chouaid *et al.* (2013)[4] and 0.473 from Nafees *et al.* (2008)[5]). However, as noted on page 14 of the ACD, these utility values reflect the wider NSCLC population. Patients with ALK+ NSCLC tend to be younger and healthier and this is reflected in the higher HRQL estimates and utility values. Clinician feedback indicated that the decline in utility observed at progression would likely be similar between the NSCLC and ALK+ NSCLC populations, but patients with ALK+ NSCLC would have a higher utility to begin with and this would likely be reflected by an improved utility value in the progressed health state.

Table 3: Utility values used in the updated base case

Phases	Utility value	Justification
Pre-progression on-treatment	0.793*	Already accepted by the Committee as appropriate for pre-progressed disease – see page 13 of the ACD
Progressed disease on-treatment	0.732*	Derived from the progressed utility values from the ALTA clinical trial. These values reflect patients who have just progressed (limited follow-up from the September 2017 data cut) and include patients on- and off-treatment. Considered conservative as the patients who are off-treatment will likely have a worse HRQL and apply a downward pressure on the averaged value.
Progressed disease off-treatment	0.582*	Utility decrement of 0.15 obtained from Chouaid *et al.* (2013)[4] and applied to the progressed disease on-treatment utility value. This represents the decline in utility observed upon progression in a NSCLC population. As the ALK+ NSCLC population are generally younger and healthier than the NSCLC population, we expect the decline in utility to be similar but the absolute value to be higher.

*These values are adjusted downwards within the economic model by decrements associated with age and adverse events

Abbreviations: ACD, appraisal consultation document; ALK, anaplastic lymphoma kinase; HRQL, health-related quality of life; NSCLC, non-small-cell lung cancer

3.2.4 Discussion on resource use and costs (Section 3.15 and 3.16 of the ACD)

Drug wastage

Takeda note that the Committee agreed with the ERG's approach to account for drug wastage within the model; this approach assumed that half of the costs incurred through unfinished packs could be saved by the NHS and half would be wasted. Takeda agrees with this pragmatic approach. Therefore, we have updated the economic model to reflect this. Section 3.2.6 presents the impact of this in our updated base case.

Administration and delivery costs

Takeda note that the Committee consider that the administration cost of £120 per cycle stated by NHS England and the delivery cost of £42.50 per cycle should have been included in the modelling; weighted by 30% and 70%, respectively based on how these medicines are received by patients (i.e. either in hospital or via HomeCare).

However, Takeda consider that applying these costs would result in double-counting within the model as these costs are already accounted for within the resource use accrued per administration. Resource use inputs were obtained from feedback of five UK clinical experts and include all resource use related to: dispensing, administration, dose changes and

monitoring. In relation to administration and dispensing costs, an oncologist outpatient appointment and a pharmacy cost are already accounted for at each administration within the base case (for the first administration two outpatient appointments and two pharmacy appointments are costed) – these are presented in the original submission dossier (Section B.3.5.3.1). The resultant cost per cycle is £526 for the first cycle and £217 in subsequent cycles – applied to both the brigatinib and ceritinib arms.

To provide a conservative estimate and to capture regional differences, in the economic model the pharmacy time is costed based on one hour of pharmacist time. This is conservative as the case precedent demonstrated across the appraisals by NICE of other ALK-inhibitors highlights that 12-minutes of pharmacist time sufficiently captures the administrative burden of oral TKIs. In TA395 (ceritinib for previously treated ALK+ NSCLC)[6], the Committee accepted that £13.60 per administration adequately reflected the administrative burden based on 12-minutes of pharmacists' time. The same assumption was applied in TA536 (alectinib for untreated ALK+ advanced NSCLC)[7], with updated costs resulting in a cost of £9.20 per administration. The Committee, in relation to TA536, considered the possibility of a higher cost (£14.40), but there was limited discussion on this at the Committee meeting and no detail was provided in the FAD. In TA500 (ceritinib for untreated ALK+ NSCLC)[8], the company applied an administration cost of £14.26 per administration. This was not discussed in the FAD for TA500. However, in TA500, the ERG explored additional analyses as it considered that the low relative dose intensity seen with ceritinib would induce additional pharmacy costs due to the need for dose modification related to adverse events. Following on from this, in TA500, a statement from NHS England showed agreement with the ERG and provided a cost of £120 per administration. Table 4 compares the pharmacy costs applied across the different NICE appraisals of ALK inhibitors for ALK+ NSCLC with the costs applied in our base case.

Table 4: Comparison of pharmacy fees included in NICE appraisals of ALK inhibitors

NICE appraisal	Resource use per administration	Cost per administration
TA395 (ceritinib for previously treated ALK+ NSCLC)[6]	12-minutes of pharmacist time	£13.60
TA536 (alectinib for untreated ALK+ advanced NSCLC)[7]		£9.20 and £14.40 discussed, no detail in the FAD
TA500 (ceritinib for untreated ALK+ NSCLC)[8]		£14.26 – ERG and NHSE discussed additional cost of £120. Not discussed in the FAD.
Brigatinib – ID1328	1-hour of pharmacist time	£44.00

Abbreviations: ALK, anaplastic lymphoma kinase; ERG, Evidence Review Group; FAD, final appraisal determination; NICE, National Institute for Health and Care Research; NSCLC, non-small-cell lung cancer

The costs included within our base case economic model reflect higher pharmacy costs than those presented and accepted in all other ALK inhibitor NICE appraisals for ALK+ advanced NSCLC. Additionally, no delivery costs were included in these appraisals.

Therefore, Takeda consider that the application of £217 per administration already in the base case economic model more than reflects relevant administration and delivery fees and is higher than the £120 per cycle stated by NHS England.

3.2.5 Discussion on end-of-life criteria (Section 3.20, 3.21 and 3.22 of the ACD)

On page 18-19 of the ACD, the Committee concluded that: *"although the most plausible estimate of life expectancy for people with previously treated ALK-positive advanced NSCLC was close to 24 months, the potential life extension benefit of brigatinib was proportionally substantial. It was therefore satisfied that brigatinib met the criteria for end-of-life treatments."*

Takeda agrees with the Committee with regards to the benefit of brigatinib on survival outcomes and that it satisfies the criteria for end-of-life treatments. Takeda would like to highlight to the Committee that the updated base case results in a predicted mean overall survival of 21.83 months for patients treated with ceritinib (compared with 24.03 months in the original base case) and an estimated mean life extension of 21.44 months for brigatinib (compared with 22.49 months in the original base case). Hence, the updated base case further validates that the two end-of-life criteria are indeed satisfied by brigatinib.

3.2.6 Discussion on Cancer Drugs Fund (Section 3.25 of the ACD)

On page 20 of the ACD, the Committee concluded that: *"It therefore did not recommend brigatinib for use within the Cancer Drugs Fund as an option for people with ALK-positive advanced NSCLC who have had treatment with crizotinib."* The reasons given for this recommendation are essentially two-fold: firstly, the company did not express an interest in brigatinib being considered for funding through the Cancer Drugs Fund (CDF); and secondly, *"the committee did not acknowledge any possibility that the clinical uncertainty could be addressed through collection of data from patients having brigatinib treatment through the Cancer Drugs Fund."*

We acknowledge that the committee are correct regarding the first point in that our original submission for brigatinib did not include a CDF request; however, we would also point out that the CDF was not raised as a discussion point during Part 1 of the first committee meeting when Takeda representatives were present. Had it been raised during Part 1 of the meeting, then the Takeda representatives would have confirmed that the company is willing to have brigatinib considered for the CDF, if necessary.

We would like to confirm again here that while our primary objective is to secure a positive NICE recommendation for brigatinib for routine NHS funding, Takeda would be willing to consider funding through the CDF, if required.

3.2.7 Updated base case results

Base case results

The updated economic model has been submitted to NICE for review under the file name of "Brigatinib NICE model response to ACD (24OCT2018).xlsm". The model base case has been updated to reflect the following key changes/assumptions:

- Correction for two PFS events and two adverse events, resulting in very minimal impact on these outcomes
- Reduced NHS list price relating to the 90-mg dose of brigatinib (from £4,900 per 28-tablet pack to £3,675 per 28-tablet pack)
- Use of ALTA, ASCEND-2 and ASCEND-5 in relative OS and PFS outcomes
- Application of a reduced treatment benefit (i.e. treatment waning) following treatment discontinuation, applied in the brigatinib arm only. This is applied from the point of maximum follow-up in the ALTA clinical trial of brigatinib
- Utility value of 0.732 (average with age adjustment: 0.712) applied to patients with progressed disease and on-treatment with brigatinib or ceritinib; and a utility value of 0.582 (average with age adjustment: 0.562) for patients with progressed disease and off-treatment with brigatinib or ceritinib.
- Assume that half of the costs incurred through unfinished packs could be saved by the NHS and half would be wasted (as agreed by the Committee)
- Assume administration and delivery costs are already accounted for within the base case model as part of the £217 applied per administration – no change from original submission dossier

The resulting updated base case provides an estimated ICER of £67,449/QALY using the NHS list prices for both brigatinib and ceritinib (Table 5). Table 6 shows the step change from the base case ICER of £54,311/QALY that was presented within the addendum (dated: May 2018) to the updated base case that is now presented in this ACD response (all ICERs being at NHS list prices for brigatinib and ceritinib).

Table 5: Updated base case (at NHS list prices, excluding all PAS)

	Total Costs	Total Life Years	Total QALYs	Inc Costs	Inc Life Years	Inc QALYs	ICER
Brigatinib	£123,885	3.29	2.23				
Ceritinib	£48,522	1.71	1.11	£75,364	1.57	1.12	£67,449

Abbreviations: ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PAS, patient access scheme; QALYs, quality adjusted life years

Table 6: Step change to updated base case (at NHS list prices, excluding all PAS)

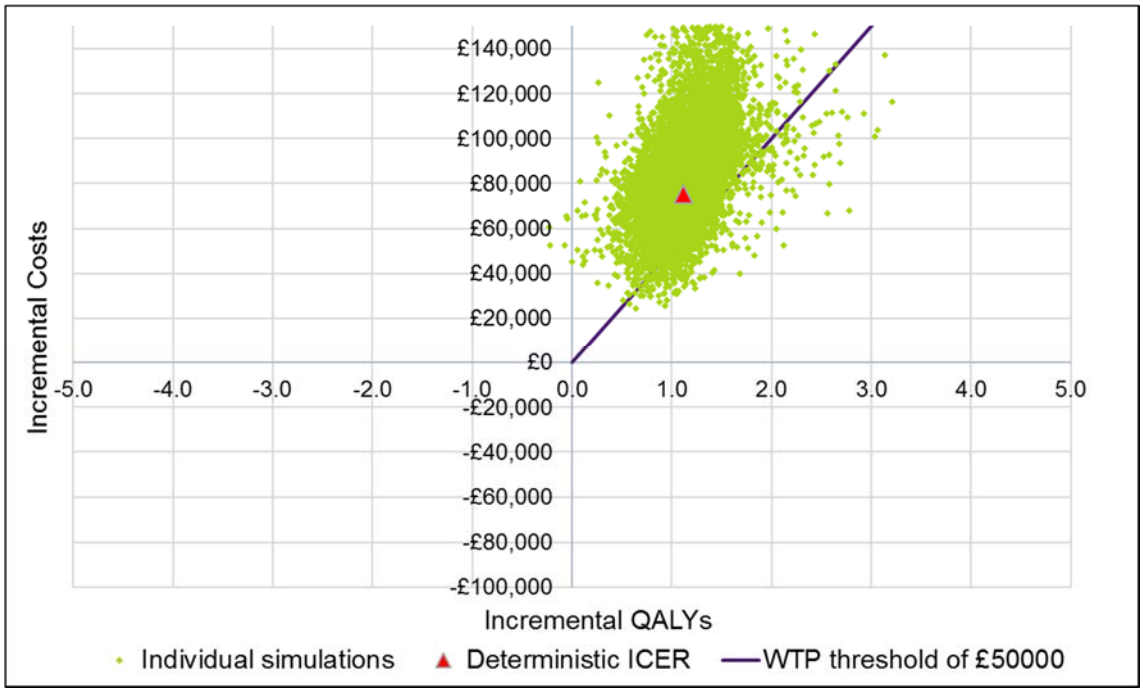
	ICER	Absolute change in each increment	Incremental % change
Original base case	£54,311		
Correction of minor errors in the PFS and adverse event data	£54,628	£317	0.58%
Updated list price relating to the 90-mg dose of brigatinib	£54,390	-£238	-0.44%
Use of ALTA, ASCEND-2 and ASCEND-5 in relative OS and PFS outcomes	£55,766	£1,376	2.53%
Application of a reduced treatment benefit in the brigatinib arm only, from the point of maximum follow-up in the ALTA trial of brigatinib	£63,058	£7,292	13.08%
Utility value of 0.732 (average with age adjustment: 0.712) applied to progressed disease and on-treatment with brigatinib or ceritinib; and a utility value of 0.582 (average with age adjustment: 0.562) for progressed disease and off-treatment with brigatinib or ceritinib.	£64,940	£1,882	2.98%
Assume that half of the costs incurred through unfinished packs could be saved by the NHS and half would be wasted	£67,449	£2,509	3.86%

Abbreviations: ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival

Sensitivity analyses (at NHS list prices, excluding all PAS)

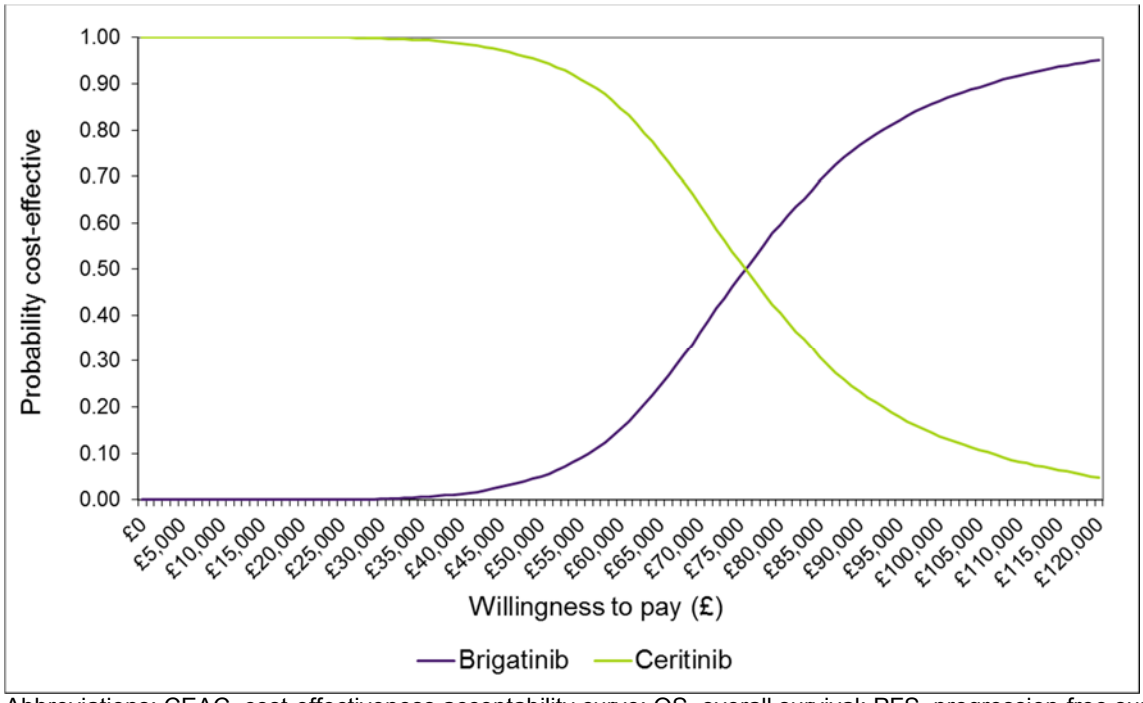
The results of 10,000 probabilistic sensitivity analysis (PSA) iterations are presented in Figure 1 (cost-effectiveness plane) and Figure 2 (cost-effectiveness acceptability curve (CEAC)). Mean probabilistic incremental costs were £89,456 (SD: £26,814). The resulting probabilistic ICER from 10,000 iterations was £76,855/QALY.

Figure 1: Cost-effectiveness plane from 10,000 iterations with uncertainty in OS and PFS curve selection accounted for



Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; WTP, willingness to pay

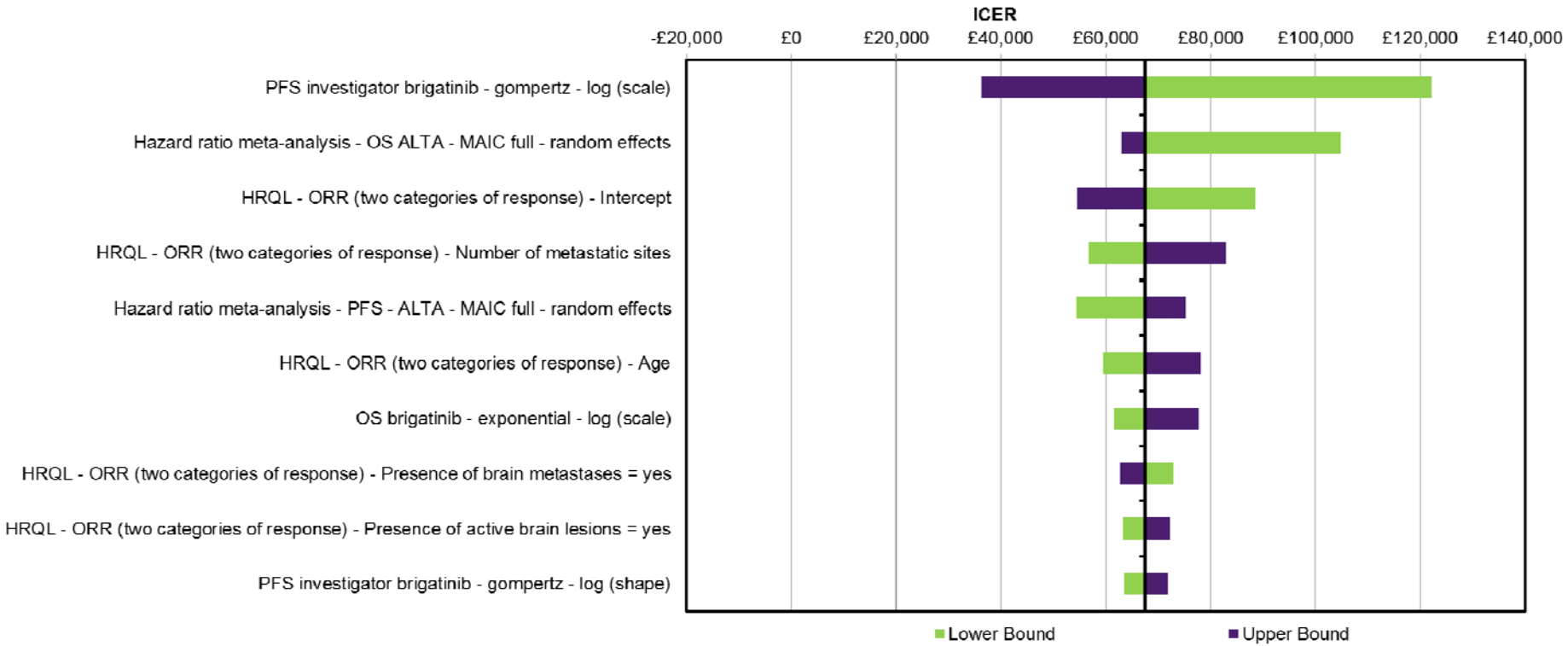
Figure 2: CEAC with uncertainty in OS and PFS selection accounted for



Abbreviations: CEAC, cost-effectiveness acceptability curve; OS, overall survival; PFS, progression-free survival

Figure 1 presents the updated Tornado diagram with the ten most influential parameters shown in descending order of ICER sensitivity. Table 7 displays this information in a tabular format.

Figure 3: Tornado diagram <u>(at NHS list prices, excluding all PAS)</u>



Abbreviations: HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Table 7: Numerical results of one-way sensitivity analysis (at NHS list prices, excluding all PAS)

Parameter	Lower Bound	Upper Bound	Difference
PFS investigator brigatinib - gompertz - log (scale)	£122,116	£36,338	£85,778
Hazard ratio meta-analysis - OS ALTA - MAIC full - random effects	£104,818	£62,995	£41,823
HRQL - ORR (two categories of response) - Intercept	£88,487	£54,493	£33,994
HRQL - ORR (two categories of response) - Number of metastatic sites	£56,810	£82,989	£26,179
Hazard ratio meta-analysis - PFS - ALTA - MAIC full - random effects	£54,421	£75,314	£20,894
HRQL - ORR (two categories of response) - Age	£59,349	£78,110	£18,761
OS brigatinib - exponential - log (scale)	£61,475	£77,616	£16,141
HRQL - ORR (two categories of response) - Presence of brain metastases = yes	£72,926	£62,737	£10,190
HRQL - ORR (two categories of response) - Presence of active brain lesions = yes	£63,234	£72,266	£9,033
PFS investigator brigatinib - gompertz - log (shape)	£63,398	£71,781	£8,383

Abbreviations: HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

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

In conclusion, Takeda disagree that the Committee's provisional negative recommendation for brigatinib is sound and a suitable basis for guidance to the NHS (see Section 1.1 and Section 3.18 of the ACD). Takeda have acknowledged the issues raised during the first Committee meeting and in the ACD, and we have attempted to address these fully within this ACD response. Arising from this, Takeda have provided an updated base case which we consider to be methodologically sound and clinically plausible. We believe this provides the Committee with a base case ICER that can be used in the decision-making process for brigatinib in this post-crizotinib indication.

Takeda believe that our updated base case includes a number of conservative assumptions and this leads to a base case ICER which is conservative. Examples of this conservative approach include:

- No reduced treatment benefit following treatment discontinuation is applied in the ceritinib arm, but this is applied in the brigatinib arm.
- No treatment benefit associated with brigatinib beyond three months after treatment discontinuation.
- A utility value for patients with progressed disease and on-treatment that includes patients with progressed disease who are off-treatment.

- Higher drug administration/pharmacy costs included within the modelling compared with other NICE appraisals of ALK inhibitors.

To further demonstrate Takeda's commitment to addressing unmet need by making brigatinib available to patients in the post-crizotinib indication, we have submitted to NHS England and PASLU (dated: 19th October 2018) for a significantly enhanced patient access scheme (PAS). This increases the simple discount level from the [redacted]% offered in the original PAS to a new level of [redacted]%; resulting in a per pack (28-day supply) net price of £[redacted] for the 180mg strength (compared with a NHS list price of £4,900 per pack; and an original PAS net price of £[redacted] per pack).

Takeda is optimistic that this price discount, when considered alongside the confidential (and unknown to Takeda) ceritinib PAS, will result in an ICER below the £50,000/QALY end-of-life threshold, and thus achieve a positive recommendation for routine use of brigatinib on the NHS. This would be a positive development for patients, given the many benefits that brigatinib offers over ceritinib, the only other ALK inhibitor that is currently commissioned by NHS England for the post-crizotinib indication. These benefits, which have been highlighted clearly in the original submission to NICE, include: increased efficacy (significantly extended and unprecedented PFS and OS in this indication, as demonstrated in the indirect treatment comparisons); increased efficacy in the CNS (a key site of progression on crizotinib); improved tolerability, with less need for dose reduction or drug discontinuation (particularly in relation to gastrointestinal side-effects); more convenient dosing for patients (one tablet, once-daily with or without food, whereas ceritinib requires multiple capsules to be taken once-daily and with food).

Whilst our primary objective is to achieve a positive recommendation for routine use of brigatinib on the NHS, Takeda would also be willing to consider funding via the CDF, if necessary.

Takeda would like to remind the Committee that the number of NSCLC patients with the ALK rearrangement is small and the post-crizotinib population eligible for brigatinib in the post-crizotinib indication is small and is also a diminishing one because the use of crizotinib in the 1st line is declining rapidly following the availability of alectinib as a 1st line treatment option (positive FAD for alectinib issued June 2018). This has been confirmed by both clinical experts and the NHS England representative at the first Committee meeting (see point 1 of the NHS England submission to NICE for this appraisal). Hence, the potential budget impact of brigatinib for this indication is modest, predictable and in decline, making this a relatively low risk decision for NICE and NHS England.

Based on all the above, we hope that the Committee will reconsider its draft negative recommendation for brigatinib in the post-crizotinib indication and issue final guidance that will make brigatinib available for routine use on the NHS. It should, however, be noted that for the pool of existing patients currently receiving treatment with crizotinib, having access to brigatinib would fulfil a significant clinical need following progression of their disease.

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

There are no aspects of this appraisal that need consideration in relation to unlawful discrimination.

4. References

1. Kim D-W, Tiseo M, Ahn M-J, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase–positive non–small-cell lung cancer: A randomized, multicenter phase II trial. Journal of Clinical Oncology. 2017;35:1-9.

2. Bazhenova L, Gettinger S, Langer C, et al. Brigatinib (BRG) in patients (pts) with anaplastic lymphoma kinase (ALK)–positive non–small cell lung cancer (NSCLC) in a phase 1/2 trial. In: Oncology Ao, editor. European Society for Medical Oncology; Denmark 2016.

3. Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK -rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. The Lancet Oncology. 2017;18(7):874-86.

4. Chouaid C AJ, Goker E, Herder GJ, Lester JF, Vansteenkiste J, et al. . Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2013;8(8):997-1003.

5. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health & Quality of Life Outcomes. 2008;6:84.

6. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance 395 (TA395): Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer. 2016.

7. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance TA536: Alectinib for untreated ALK-positive advanced non-small-cell lung cancer 2018.

8. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance 500 (TA500): Ceritinib for untreated ALK-positive nonsmall-cell lung cancer. 2018.

Response to the National Institute for Health and Care Excellence's Appraisal Committee Decision on Brigatinib for treating ALK- positive non-small cell lung cancer after Crizotinib [ID1328]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are disappointed that the Appraisal Committee decision is not to recommend Brigatinib in this indication.

- We note, in 1.2, the Appraisal Committee concludes, based on clinical evidence from single arm studies, that people having Brigatinib live longer than those having Ceritinib and that they also live longer before their condition worsens.

- As in 3.15, we note that Brigatinib, has lower toxicity than Ceritinib. Thus, dose reduction with Brigatinib is uncommon, but common with Ceritinib.

- We note the concerns raised by the Appraisal Committee, with regards to the cost-effective modelling and the resultant negative decision reached. On behalf of the lung cancer patients who would derive clinical benefit from this therapy indication, we would urge constructive dialogue between the Manufacturer, NICE and NHS England. We hope that compromise and agreement can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation.

[redacted]
Medical Director
Roy Castle Lung Cancer Foundation
October 2018

NICE National Institute for Health and Care Excellence

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 24 October 2018**. Please submit these through 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):	**BTOG-NCRI-RCP-RCR-ACP**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Nil**]
Name of commentator person completing form:	Professor [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.

Please submit your response through NICE Docs.

NICE National Institute for Health and Care Excellence

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

Consultation on the appraisal consultation document – deadline for comments **5pm on Wednesday 24 October 2018**. Please submit these through NICE Docs.

General	The BTOG-NCRI-RCP-RCR-ACP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
1	We are saddened to learn that Brigatinib has not met the cost effectiveness threshold set out by NICE. We note that NICE do not argue against the superior potential OS and PFS efficacy of Brigatinib compared to Ceritinib and therefore encourage NICE and the manufacturer to agree a price to allow Brigatinib to be available to NHS patients.
2	Whilst the numbers of ALK+ patients now commencing crizotinib will be small (given Alectinib and Ceritinib are now available), there still remain a sizeable proportion of ALK+ patients currently responding to crizotinib that will inevitably relapse in due course for whom the only NICE approved option is Ceritinib. Given the agreed marked PFS and OS superiority of Brigatinib over Ceritinib for these patients, and its superior toxicity profile, we encourage NICE to continue to pursue commissioning of Brigatinib for these patients, for whom Ceritinib would represent a more toxic and less efficacious treatment.
3	Our experts were disappointed to learn that the manufacturer did not express an interest in Brigatinib being considered for funding through the Cancer Drugs Fund, and would encourage them to consider this if routine NHS commissioning cannot be agreed by NICE

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 submit your response through NICE Docs.

NICE National Institute for Health and Care Excellence

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Response prepared by Dr Yvonne Summers who has participated in advisory boards for several of the manufacturers of ALK inhibitors: Roche, Pfizer, Takeda
Name of commentator person completing form:	[redacted]

Please submit your response through NICE Docs.

NICE National Institute for Health and Care Excellence

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

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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.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation will deny ALK positive NSCLC patients access to one of the most effective treatments for brain metastases. ALK positive lung cancer is a rare sub-group of NSCLC with a high proportion of patients experiencing brain metastases (recent first line clinical trials ALEX and ALTA-1L have reported 30-40% of patients with brain metastases at baseline). Furthermore the vast majority of patients will experience brain metastases at some point in their patient pathway. NICE have recently recommended alectinib (TA536) as 1st line therapy (in keeping with international guidelines - ESMO, NCCN) which is highly effective in treating and preventing the development of new brain metastases. As alectinib is now the standard 1st line treatment of choice, this guidance (ID1328) relates to a small ever-diminishing and finite group of patients who have received previous treatment with crizotinib. This recommendation means that patients who have have received crizotinib as first line treatment will only have access to ceritinib second line, both of which have inferior activity in the brain compared to brigatinib and alectinib, and consequently results in inequality in patient care. If patients do not have access to brigatinib following crizotinib they are likely to have more debilitating symptoms, poorer quality of life and shorter survival than those who have been treated with alectinib first line. This judgement appears particularly shortsighted given that there is only small and limited population of patients who would be eligible for this therapy.
2	We are further concerned that this small and finite group of patients will only have access to a second line treatment, which is not only much less effective in terms of overall survival, but is substantially more toxic than brigatinib, leading to a shorter duration of poorer quality life.
3	
4	
5	
6	

Insert extra rows as needed

Please submit your response through NICE Docs.

NICE National Institute for Health and Care Excellence

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

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- 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.
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- 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.
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Please submit your response through NICE Docs.

NHS England submission for the 2nd meeting of the NICE appraisal of brigatinib after previous treatment with crizotinib in the treatment of locally advanced/metastatic ALK mutation positive non small cell lung cancer

1. There are 3 NICE-recommended monotherapy options for the 1st line treatment of ALK positive non small cell lung cancer (NSCLC): alectinib, ceritinib and crizotinib. The use of crizotinib has fallen away rapidly owing to the superiority of alectinib and ceritinib. Alectinib is the main 1st line option currently used in NHS England for newly diagnosed patients on account of its better tolerability (ceritinib has considerable gastrointestinal toxicity). NHS England does not commission the use of crizotinib post ceritinib or alectinib and nor does it commission any treatment sequence other than 1st line crizotinib followed by 2nd line ceritinib. As has been stated already, this commissioned treatment sequence now only applies to patients commenced on 1st line crizotinib in the past or in those rare patients who cannot tolerate alectinib and/or ceritinib.
2. The marketing authorisation for brigatinib for this indication under NICE appraisal is for use following previous treatment with crizotinib. This therefore means that the population of eligible patients for brigatinib for this indication has diminished and will continue to do so. Nevertheless, NHS England welcomes Takeda's submission to NICE for this post-crizotinib indication as brigatinib is likely to be tolerated better than ceritinib and also because Takeda's main focus on reimbursement will not be for this indication but for 1st line use (due to be appraised by NICE in 2019). Roche chose not to submit to NICE when alectinib received its marketing authorisation for 2nd line use after crizotinib.

[redacted]As the committee has already concluded, the current correct comparator for brigatinib in this post-crizotinib indication is ceritinib and as has been stated above. ceritinib has significant tolerance problems. The licensed dose of ceritinib was 750mg daily when appraised by NICE but the dose has since been reduced to 450mg daily when taken with food (this being based on an 81 patient pharmacokinetic equivalence study). Ceritinib is currently supplied in a 150 pill pack and thus at 750mg daily offers the patient a 30 day supply.

[redacted]

4. NHS England notes that Takeda has used a total oral drug administration cost per cycle of £217 which is considerably in excess of the current oral chemotherapy administration tariff of £120. As long as this £217 cost is applied to both arms of the brigatinib/ceritinib comparison, NHS England is content in terms of application of reasonable costs of dispensing, review of the patient and drug administration.
5. If NICE recommends brigatinib in this expected indication, NHS England treatment criteria for the use of brigatinib will reflect the MA ie that use of brigatinib is to be confined to patients previously treated with crizotinib for ALK pos NSCLC. In addition, ceritinib post-brigatinib and brigatinib post-ceritinib will not be commissioned unless patients show early intolerance of ceritinib/brigatinib and there is no sign of disease progression at the time of any switching from the drug which the patient could not tolerate.
6. NHS England does not view the Cancer Drugs Fund as being a worthwhile use of CDF resources for a NICE recommendation for treatment with brigatinib post-crizotinib. Whilst there are uncertainties as to longer term benefit of brigatinib in this indication, by the time these uncertainties have been resolved the cohort of patients treated with 1st line crizotinib will have almost all, if not all, relapsed and been treated with a 2nd line agent. Thus, NHS England expects the indications of 2nd line TKI use post 1st line crizotinib to be rendered clinically redundant in the relatively near future, especially as 1st line brigatinib is a promising treatment option to be appraised by NICE next year.

Prof Peter Clark

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

November 2018

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

Name	[redacted]
Role	Patient
Other role	Medical Advocay lead
Organisation	ALK Positive UK
Location	England
Conflict	None
Notes	

Comments on the ACD:

I am writing as the medical advocacy lead for ALK Positive UK, which is a new charity set up to support and advocate on behalf of patients with ALK rearrangement lung cancer and their carers.

There is real concern in our community that NICE are not going to authorise the use of brigatinib as second line treatment after crizotinib, as outlined in the NICE Appraisal Consultation document from 03 Oct 18.

We have many patients in our group who have done very well on brigatinib post crizotinib. As a community, we are all aware how good this new TKI is and what a positive impact this will have on our futures. One of our members, who required an emergency tracheal stent due to disease progression on crizotinib, is now in the position, 4 months later, of the stent being removed. This will allow him to continue playing competitive tennis for his club at a high level and is due to him responding so well to this treatment.

Although this relates to one patient, recent studies have shown promising results with a median overall survival rate of 34 months (data from ASCO) and a median PFS of 16.7 months from the ALTA Phase 2 trial.

It is disheartening to think that the choice of being treated with this excellent second generation TKI won't be available, and this is despite the recent positive trial data, and the positive experiences relating to this drug in our community.

Please do not deny us this choice.

Name	[redacted]
Role	Patient
Other role	ALK Patient
Organisation	Patient
Location	England
Conflict	None
Notes	
Comments on the ACD:	
I am an ALK positive patient and currently treated with crizotinib. This is my first TKI. I understand that ceretinib which is the next TKI available to me has considerable side effects and is not as effective as Brigatinib as a second TKI. I have had a good response to crizotinib for the last 3.5 years and would like to have the opportunity in the future to take another TKI such as Brigatinib. On the Worldwide ALK Positive web page which provides support to ALK Positive patients members have reported very positive responses to Brigatinib which has improved their quality of life and lengthened it. Lung cancer in general has a very poor prognosis when diagnosed in the late stages, which it most often is. It is therefore important that opportunities to improve the care and treatment for lung cancer patients are supported as much as possible and as much as for other cancers to improve care in this field. Thank you for listening	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on the ACD:	
My husband was dx august 2017 alk+ started on Crisotinib, now on Ceritinib. Brigatinib was going to be his next option when ceritinib stops working. I find it extremely frightening how few options are available in the UK. The ALK worldwide site has so many positive stories where patients are having fantastic results on brigatinib. Please please reconsider and approve in the UK. Give patients some positive hope for the future. Thank you	

Name	[redacted]
Role	Carer
Other role	Logistics manager
Organisation	
Location	England
Conflict	None
Notes	
Comments on the ACD:	
My 30 year old wife mother to a [redacted] year old and [redacted] week old is currently on alectinib, and has been on it for 3 weeks with good results, however it is vital that alternative options are available to her in case she becomes resistant or suffers from side effects	

Name	[redacted]
Role	NHS Professional
Other role	Consultant in Medical Oncology
Organisation	
Location	England
Conflict	I have a consultancy agreement with the manufacturer
Notes	
Comments on the ACD:	
Brigatinib will be a useful treatment option in patients progressing on crizotinib Efficacy: IRC PFS 16.7 months is the longest PFS reported in trials post crizotinib (with the limitations of inter-trial comparisons); high efficacy in controlling brain metastases which is often a site of disease progression with devastating consequences and a significant cost in the patients quality of life Ease of administration: Once a day dosing will help patients to adhere to treatment and reduce risk of dosing errors that can have significant cost implications.	

Name	[redacted]
Role	Patient
Other role	ALK patient
Organisation	
Location	England
Conflict	None
Notes	
Comments on the ACD:	
As an ALK patient, diagnosed in February 2018 I am currently taking Brigatinib via a compassionate access scheme. I progressed on both Crizotinib and Ceritinib (I was not eligible for Alectinib) and so this treatment is a vital lifeline for me. I'm [redacted] with [redacted] children aged [redacted] and [redacted]. ALK+ NSCLC likes young, fit non-smokers and is threatening to leave my children without their mother. According to current NHS provision, my next course of treatment after Ceritinib would be traditional chemotherapy and then simply palliative care to keep me comfortable. When there are drugs available like Brigatinib which can extend my life expectancy and improve my quality of life I don't understand why this would not be a treatment option of choice. Brigatinib covers a wide range of sub mutations than Ceritinib and Alectinib and I believe it should be available as a second or subsequent line of treatment as Alectinib is only first line treatment at present.	

Name	[redacted]
Role	Patient
Other role	ALK + LC patient
Organisation	
Location	England
Conflict	None
Notes	
Comments on the ACD:	
I would like to add my comment that without Brigatinib being approved for 2nd line use I have no other TKI options left to me once my current treatment fails. I have lived a healthy life, never smoked, only drunk occasionally and keep fit. I have worked all my life and paid my taxes accordingly. It isn't my fault I have stage 4 LC and have never needed the NHS before but now I do! I have a family that needs me to stay alive as long as possible and this treatment would give me that opportunity. I appreciate these decisions aren't easy and there are many deserving patients requiring high cost medicines but we are a small group of patients in the UK but the impact of having this medicine available to us would be enormous.	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	None
Notes	

Comments on the ACD:

A never-smoker in my forties, I've had stage 4 ALK positive NSCLC for more than two years. TKIs have made a huge difference to my life, enabling me to continue to support my family and live a near-normal life, and continue to work nearly full time. From contacts on social media I have seen many sufferers of this disease in other countries benefit from a prolonged response to brigatinib after progressing on crizotinib. Sometimes for several years, and often of much longer duration and better tolerated than is seen with second line ceritinib. So having this drug as an option would make a huge difference to me and my family, and enable me to continue to support them, to work, contribute to society, all with a good quality of life. So I would ask you to please approve this drug since it is undoubtedly badly needed by patients.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	
Notes	

Comments on the ACD:

My [redacted] year old [redacted] has ALK positive NSCLC lung cancer. Please approve Brigatinib following crizotinib which [redacted] is currently on, and will hopefully be on for some years to come.

Such TKIs allow many people worldwide to lead quite normal lives despite their diagnosis.

My [redacted] is her second year at University studying [redacted] which would have been impossible with conventional chemotherapy.

Please allow Brigatinib as this is scheduled to be next in line if crizotinib stops working for [redacted].

All sufferers deserve the best chance with these amazing drugs which ultimately give them a better chance of leading a normal life, allowing them to work and so be less of a burden on the NHS/Benefits system.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	Scotland
Conflict	
Notes	

Comments on the ACD:

I am submitting on behalf of my [redacted], [redacted]. [redacted] was diagnosed aged [redacted] with stage IV NSCLC in December 2014. He had extensive brain metastases on diagnosis "too many to count" and the largest measured [redacted]cm in diameter. He had terrible pain in his brain, he had lost much of his sight, and his memory was shot. He was given [redacted] months to live. The distress for him and his family was unimaginable.

However, nearly four years on the picture is very different, and it is thanks to ALK inhibitors. ALK inhibitors have kept [redacted] cancer stable, and at times shrinking. His vision has recovered, his memory is excellent, and he no longer has any noticeable brain issues. So far he has been on Crizotinib and Ceritinib, with tremendous control, even in the brain, and negligible side effects "just transient and minor GI issues". He has never had any radiotherapy. Amazing. Almost four years of good life with stage IV lung cancer.

ALK inhibitors have allowed him to positively thrive and be an active member of his family and his community. [redacted] lives a full life. He does not consider himself to be "end of life" nor to be on an end of life treatment. He feels and looks well. However, if more of the available ALK inhibitors are not approved, what next for [redacted]? Brigatinib has huge potential to control [redacted] disease for another lengthy period. This amazing drug has excellent blood brain barrier penetration and targets many of the mechanisms of resistance that can cause failure of earlier ALK inhibitors. On the worldwide ALK Positive Group we are seeing many people internationally who have had a prolonged response to Brigatinib after other TKIs (not just Crizotinib). We know of at least one person who is still alive 12 years after her diagnosis, due to a succession of ALK inhibitors.

Please approve this treatment and allow ALK Positive patients to live longer lives as active members of society, to have longer with their families and friends, and to dare to hope ALK Positive lung cancer will one day be a manageable chronic disease.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on the ACD:	
I was diagnosed [redacted] month ago, was on Crizotinib for 14 month and now on ceritinib, I have a good quality of life , I have read about other Alk+ patients doing very well on brigatinib, after Crizotinib and ceritinib, I would give me peace of mind if I knew it would be available to me when I progress on ceritinib. Thank you for taking your time reading this.	

Name	[redacted]
Role	Patient
Other role	semi-retired social worker
Organisation	
Location	England
Conflict	
Notes	
Comments on the ACD:	
i was diagnosed ALK+ In [redacted] of this year i am currently on Alectinib but i am so worried as to what will be my next line of treatment if Alectinib lets me down to know that this medication would be available to me would make so much difference the alternative is the cancer wins again thank you.	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clnical Oncologist
Organisation	
Location	
Conflict	I have received payment from Takeda to serve on their advisory boards on numerous occasions. I have also received support from Takeda to attend academic conferences.
Notes	

Comments on the ACD:

I disagree with the committee's decision that applying a value of 0.643 for the full duration of progressed disease until death was unreasonable. Given the frequency at which these patients will be scanned, the first hint that these patients have disease progression will be radiological progression on their scan rather than any overt clinical symptom. As such when progressive disease is initially detected, their utility value will in fact not be too far off from 0.793. Whilst some of these patients will progress rapidly and become too unwell to receive further systemic treatment such as chemotherapy or third generation ALK inhibitor like Lorlatanib, a fair proportion will be well enough to be switched to these other treatments and the utility value assigned to these patients should not be less that 0.643. Thus if one were to take a mean value of the utility value for all these patients, from either the time of progression to death, or from progression to being switched to an alternative systemic treatment, I suspect it may actually not be too far off from 0.643. The decline in utility value from 0.643 should only be applied to a proportion of the patients with progressive disease.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on the ACD:	

I am the [redacted] of a [redacted] year old [redacted] diagnosed [redacted] with stage IV nsclc (ALK)

My [redacted] has been fortunate enough to be prescribed Alectinib first line and been leading an almost normal life.

This drug has enabled her to work full time, as a personal trainer, run 2 half marathons since diagnosis . She is effectively getting on with life and apart from 4 weekly blood tests and quarterly scans is hardly a drain on the NHS. Without this amazing drug my [redacted] would probably not be alive today!!!!

Sadly this drug will probably stop working and the only other drug available is Ceritinib. To begin with, this drug has very harsh side effects for many and may not cover the resistence built up after Alectinib..

Brigatinib covers different resistances to Ceritinib and seems to have less toxicity.

Only approx 2 to 5% of lung cancer patients are ALK and most tend to be under the age of 50. Over the past 40 years treatment for lung cancer worldwide has been seriously underfunded and now that we have these break throughs for the biggest cancer killer how can this fabulous drug be denied for this small subset of people.

By authorising Brigatinib you are effectively turning this disease from terminal to chronic.

I know so many people in the USA who are members of the ALK Positive foreign who have been living with this awful disease five,, ten and more years please do not deny our citizens to the chance of life.

These drugs can give not just months of extra life but years. What price is that?!???

Please , give these usually young, usually non smoking usually misdiagnosed (due to age, fit ,non smoking)people a chance.

Kind regards

[redacted]

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	
Location	Wales
Conflict	
Notes	
Comments on the ACD:	

I did not respond to Crizotinib as my first line TKI.

I am currently on Ceritinib as the only second line TKI available. I have lost [redacted] in [redacted] weeks due to the harsh GI side effects of this TKI. My weight is currently [redacted].

It would be of enormous value to me to have the choice of a TKI such as Brigatinib that is easier on the GI system.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on the ACD:	

The evidence shows that after some while the patient diagnosed with ALK+ nsclc becomes resistant to TKIs. I would like to think all possible options are made available. When alectinib was finally approved by NICE for first line of treatment it opened the doors for many for a return to full health. More options for treatment would mean that stage IV lung cancer changes from being a terminal illness to being a chronic illness that can be managed. It seems that with these drugs, when a patient has a good response to treatment , they enable us to return to their everyday lives. So many ALK+ patients are younger than 70, some considerably younger, that it is possible we will need a series of TKIs throughout our lives with cancer.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on the ACD:	

My [redacted] has ALK+ LC and is in her second line therapy (Ceritinib) after Crizotinib. I'd like to know why Brigatinib is only being considered for second line after Crizotinib. There are so many other patients that will have had a different sequence if TKIs that could benefit from Brigatinib. I am on direct contact with patients who are in Brigatinib and doing well with a great quality of life, they have varying TKI sequence history. My [redacted] on no way shape or form considers herself as end of life. She looks after my [redacted] children while I work part time. She tends her allotments and has an active social life. She and her whole extended family would all benefit mentally from knowing there is another treatment option after Ceritinib. Thank you

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1

Treatment benefit after stopping treatment

We note that you removed best supportive care in the calculation of the treatment benefit after treatment stopped in your updated base case. Could you explain the rationale?

Takeda response

Following the feedback from the first Committee Meeting, the ACD and the preference of the Committee to include treatment benefit discontinuation in the base case, Takeda sought a more robust and representative method to account for this loss of benefit. The outcomes predicted using the BSC data from Duruisseaux *et al.* (2017) resulted in clinically implausible outcomes in both the original submission's scenarios and in the later scenarios conducted by the ERG.

Table 1 and Figure 1 demonstrate the scenarios explored in the original submission dossier. Table 1 indicates that the long-term survival outcomes were only reflective of clinical expectations when the 10-year cut-off was assumed. Figure 1 shows that the parametric curves were subject to a sharp decline at pre-specified time points (cut-offs at 2-, 3-, 4-, 5- and 10-years were considered). The survival projection of these curves is not considered representative of clinical practice in terms of the sharp decline in survival at these points.

The method used by the ERG also resulted in clinically implausible outcomes in terms of the long-term outcomes (Table 1) and median survival predictions (median survival: 18.40 months vs. 34.1 from the ALTA trial) – as discussed in the first Appraisal Committee meeting.

Table 1: Long-term survival predictions from clinicians and the economic model when using the Duruisseaux *et al.* (2017) data (company's original scenario and ERG scenario)

	Proportion surviving at			
	3-years	5-years	10-years	20-years
Average from clinicians	50.00%	28.50%	5.83%	0.00%
2-year cut-off	12.85%	0.37%	0.00%	0.00%
3-year cut-off	51.05%	1.81%	0.00%	0.00%
4-year cut-off	51.05%	7.86%	0.00%	0.00%
5-year cut-off	51.05%	30.24%	0.00%	0.00%
10-year cut-off	51.05%	30.24%	5.90%	0.00%
ERG scenario	0.42%	0.01%	0.00%	0.00%

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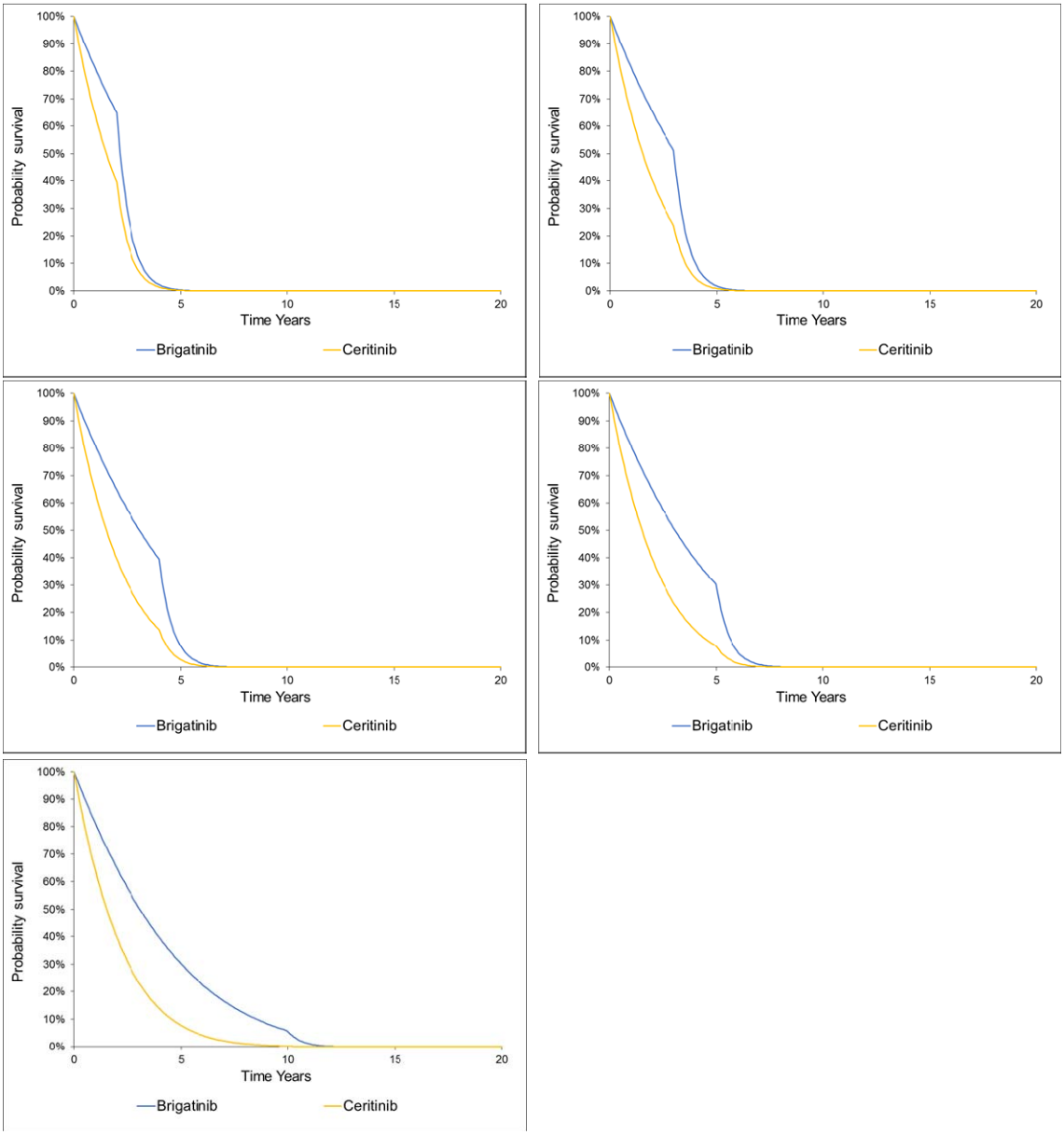
Company responses to queries on their ACD response

Figure 1: Overall survival parametric curves predicting clinically implausible outcomes when using the BSC data from Duruisseaux *et al.* (2017) in the company's original scenarios



As well as methodological issues, there are also generalisability issues associated with the Duruisseaux paper which may explain why inclusion of these data result in clinically implausible outcomes: (1) the data are retrospective, (2) French setting, (3) patients receiving BSC were relatively old, with poor performance status and heavily pre-treated. In the study, patient characteristics are only presented at the start of treatment with crizotinib. However, even at this stage in the pathway patients were older (34.3% ≥65 years vs. 27.3% in ALTA and vs. 20% in Study 101), with worse performance status (35.3% PS 2-4 vs. 8.2% in ALTA and vs. 0% in Study 101) and more heavily pre-treated (49.5% ≥2 lines before crizotinib vs. 40.9% ≥2 lines before brigatinib in ALTA) than patients at a later stage in the pathway as reflected by the ALTA and Study 101 data (baseline characteristics in the ALTA and Study 101 trials were post-crizotinib). Therefore, the data are not representative of patients in the ALTA and Study 101 trials.

The revised method used to account for treatment benefit discontinuation submitted by Takeda in our response to the ACD reflects the feedback we heard from clinical experts at the first Appraisal Committee meeting and also from subsequent discussions we have had with clinicians. Based on these,

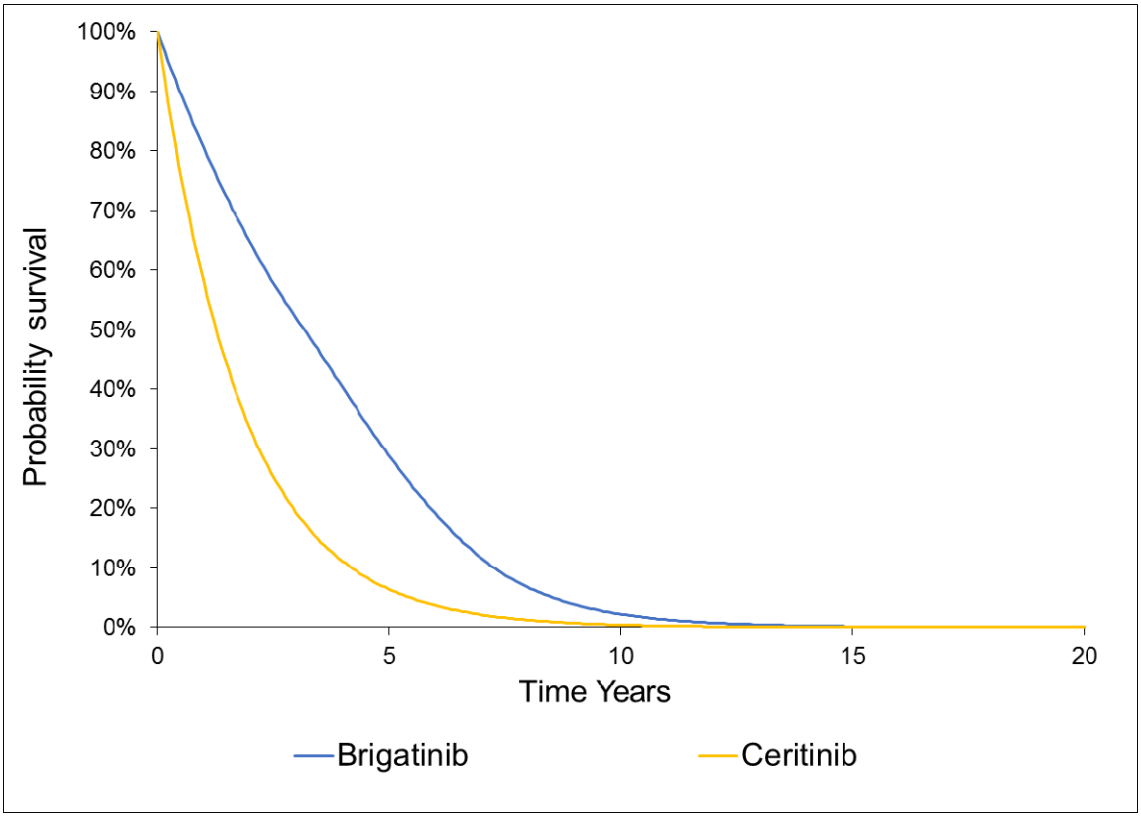
the treatment benefit associated with brigatinib is sustained for three months after treatment discontinuation. We have heard that this is the minimum duration for which clinicians would expect the brigatinib treatment effect to last after discontinuation; in fact, clinicians expect that the CNS efficacy of brigatinib would likely translate into longer benefits after treatment discontinuation – albeit there are no data to support this. The updated results predict long-term survival outcomes which are aligned with expectations from clinicians (Table 2) and produce survival curves with a smoother projection (Figure 2). This method assumes that the treatment benefit associated with brigatinib is lost after 3 months – from which point the survival rate is equal to the survival rate in the ceritinib arm.

This methodology has been validated with clinical experts. Therefore, in the absence of more robust data on subsequent therapies after brigatinib and ceritinib, we believe that this scenario best reflects outcomes in clinical practice.

Table 2: Long-term survival predictions from clinicians and the economic model when using the revised method to account for treatment benefit discontinuation

	3-years	5-years	10-years	20-years
Average from clinicians	50.00%	28.50%	5.83%	0.00%
Brigatinib	52.01%	28.99%	2.28%	0.01%

Figure 2: Overall survival parametric curves when using the revised method to account for treatment benefit discontinuation



2	**Use of Study 101 in OS analysis**

Please submit your response through NICE Docs.

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Company responses to queries on their ACD response

	We note that in addition to removing the Study 101 data from the PFS analyses (as the committee preferred) you chose to remove study 101 from the OS analysis used in the calculation of the hazard ratio to be consistent that both are using ALTA data only. However, we note that you used pooled data on brigatinib for baseline OS. Why was Study 101 not removed from the OS baseline calculation? **Takeda response** The impact of using ALTA data only for baseline OS and PFS (i.e. removing Study 101) was explored in scenario analyses presented within the updated economic model submitted as part of the ACD response. The range of ICERs produced in these scenarios is £51,855 - £73,412 (excluding the results of the log-normal and log-logistic curves for PFS outcomes, which predict clinically implausible results). Takeda recognise that, ideally, the totality of data would contribute to both baseline OS and PFS and the relative OS and PFS benefit estimations. However, due to the unavailability of comparator data this is not possible. We removed Study 101 from the estimation of the OS benefit in the ACD response to align with the data sources preferred by the Committee for the estimation of the PFS benefit. It is important to use the same data sources for the estimates of treatment benefit for both outcomes to avoid inconsistencies. In the ACD response, the baseline OS and PFS curves consider the totality of data from ALTA and Study 101. We maintain that the preference is to make use of all available data for brigatinib where possible. Although this means the data sources used in the indirect treatment comparisons differ from the baseline curves, this does not result in inconsistent outcomes because the magnitude of relative benefit observed in the PFS outcomes is reflected in the relative benefit observed in the OS outcomes. These hazard ratios are applied to the pooled data from brigatinib without causing inconsistent outcomes (i.e. an increase in PFS and hence time on treatment [ToT], with no increase in OS). However, we acknowledge this as a limitation which is explored in the scenario analyses.
3	**Use of decrement from Chouaid in progressed health state** **We see the 0.15 decrement in the Chouaid paper applies from the progression-free to progressed health state. However, your updated base case applies this decrement to the progressed 'on-treatment' state to obtain a progressed 'off-treatment'. Please would you explain the rationale for applying this here?** **Takeda response** With regards to utility values, two points were made clear at the first Committee meeting and supported by subsequent discussions with clinicians: 1. the utility value associated with progressed disease on-treatment would be almost the same as pre-progression because these patients are still receiving clinical benefit from treatment and are often clinically asymptomatic with a good quality of life, and 2. the point at which you would expect to see a significant decline in utility is at symptomatic progression, which is also the time point at which a clinician decides to discontinue treatment (because the patient is no longer receiving benefit from it). There are no data in the NSCLC population exploring the utility decline caused by treatment discontinuation. Therefore, as a proxy, the utility decrement from the Chouaid *et al*. (2013) paper (-0.15 representing the decrease in utility arising from disease progression) was applied to the utility value for the progressed disease on-treatment phase – resulting in a utility value for progressed disease of 0.582. Applying the utility decrement to the progression-free state (rather than the progressed disease on-treatment phase) results in a utility value for progressed disease of 0.643; a higher utility value for the progressed disease state improves the ICER in favour of brigatinib. Therefore, we believe we have selected conservative inputs in our updated base case. The updated base case applies: • A utility value of 0.793 (average with age adjustment: 0.773) for pre-progression and on-

	treatment (0.793 is already accepted by the Committee as appropriate for pre-progressed disease – see page 13 of the ACD) • A utility value of 0.732 (average with age adjustment: 0.712) for progressed disease and on-treatment (derived from the ALTA data for progressed disease) • A utility value of 0.582 (i.e. 0.732 – 0.15 = 0.582; average with age adjustment: 0.562) for progressed disease and off-treatment These utility values have been validated with clinical experts.
4	**We note that the summary of product characteristics for ceritinib was amended to change the recommended dose from 750 mg/d to 450 mg/d (that is from 5 tablets per day to 3 tablets per day) in April 2018. We believe that this should have been reflected in the model. The ERG will explore the impact of this in their critique.** **Takeda response** We are concerned to see NICE and/or the ERG introduce this issue for the first time at such a late stage in this appraisal. Our concerns are based on the following: • The final scope for this appraisal was agreed and published on 2nd February 2018, more than two months before the SmPC for ceritinib was updated to include the 450mg/day with food dosing regimen. Hence, we believe the 450mg/day with food dose of ceritinib is not included in the agreed final scope for this appraisal. We consider it outside of scope to introduce this new dosing regimen into this appraisal at this stage. • Our dossier was submitted to NICE on 6th April 2018, almost three weeks before the ceritinib SmPC was updated to reflect this new dosing regimen. Our understanding is that the SmPC for ceritinib was not updated until near the end of April 2018. • We note that ceritinib (at any dosing regimen) was not included as a comparator in the recent NICE appraisal of alectinib (TA536) for untreated ALK-positive NSCLC, on the basis that it *"was not routinely commissioned as a first-line treatment when the NICE scope and company submission for alectinib were written"* (see Section 3.2 of the published NICE guidance for alectinib, TA536). We would suggest that the same principle applies here in relation to the ceritinib 450mg/day dosing regimen (i.e. it should not be included in this current appraisal). • The ceritinib 450mg/day dosing regimen has never been appraised by NICE in any of the prior ceritinib STAs referenced in the scope for this appraisal of brigatinib (i.e. TA395 and TA500). These appraisals were all based on the ceritinib 750mg/day without food dosing regimen. • There are significant limitations with the data that supports the ceritinib 450mg/day with food dosing regimen. These are discussed in detail below (see Appendix: ASCEND-8 study summary) but, in summary, the dose change was based on the Phase I ASCEND-8 study which included a mixed population of patients with advanced ALK-positive NSCLC, who were either treatment naïve or had been pre-treated with chemotherapy and/or crizotinib.[1] • ASCEND-8 was primarily a pharmacokinetic (PK) study which assessed the PK equivalence of three different dosing regimens of ceritinib.[1] The efficacy assessment component of ASCEND-8 (Part 2 of the study, and a secondary objective) was limited and was undertaken only in patients that were treatment naïve[2] – a population that is not relevant to the scope for this current appraisal which is in the post-crizotinib setting. Hence, there is no clinical data that would allow a fair comparison to be made between the efficacy of brigatinib and ceritinib 450mg/day with food in the population of patients that is included in this appraisal (i.e. the post-crizotinib population). • In addition, the clinical endpoints assessed in ASCEND-8 did not include any assessment of the intracranial efficacy of the different dosing regimens of ceritinib and this is seen as a major limitation of this study by the clinical experts we have spoken with. This is because there is

evidence to show that the intracranial efficacy of ALK inhibitors is dose-dependent, and that dose intensification may be necessary to overcome incomplete ALK inhibition in the CNS and prolong the durability of responses in patients with CNS metastases.[3] Because this issue of the 450mg ceritinib dose has been introduced by NICE/ERG so late in the appraisal process, there has been no opportunity for clinical experts to comment on its relevance (or not) to this appraisal. In our opinion, this is a significant concern and we would therefore request NICE, even at this late stage, to seek clinical expert opinions on this matter.

- The clinical outcomes for ceritinib that are included in our health economic model are derived from the ASCEND-2 and ASCEND-5 clinical trials, both of which used the 750mg/day dose of ceritinib, and the observed dose intensity was accounted for in the economic model. We believe it would be inappropriate to assume that the same outcomes would be achieved with the ceritinib 450mg/day with food dosing regimen.

On a practical level, we also do not see the relevance of the ceritinib 450mg vs. 750mg debate to this current appraisal for the following reasons:

- Our understanding is that there will be no cost saving to be made by using the lower dose of ceritinib because the pricing on a per 30-day supply will be the same irrespective of whether the original pack of 150 capsules (30 days' supply at 750mg/day) or the new pack of 90 capsules (30 days' supply at 450mg/day) is used.
- We note that in Germany the original 150-capsule pack is no longer available and has been replaced in the market by the 90-capsule pack.

Based on all of the above, we do not agree that the health economic model developed and submitted by Takeda as part of this appraisal of brigatinib should have included the ceritinib 450mg dose. In addition, given the issues we have highlighted in this response, we do not regard any scenario based on the ceritinib 450mg/day dose as being one that should be used by NICE for decision making purposes in relation to this appraisal of brigatinib.

Appendix

ASCEND-8 study summary

ASCEND-8 is a multicentre, randomised, open-label, Phase I study. Part 1 of this study investigated the steady-state pharmacokinetics (PK) and safety of ceritinib 450mg or 600mg, taken with a low-fat meal, vs. 750mg in the fasting state in patients with advanced ALK-positive NSCLC who were either treatment-naïve or pre-treated with chemotherapy and/or crizotinib. Part 2 of the study assessed the efficacy of ceritinib in treatment-naïve patients, as a secondary objective.

The primary PK results showed that the 450mg with food dose had a similar steady-state exposure as the 750mg dose given in the fasting state. At steady state, relative to 750mg fasted, the 450 mg with food dose demonstrated comparable PK as assessed by maximum (peak) concentration of drug in plasma and area under the plasma concentration–time curve from time zero to 24 hours.

NOTE: In the 450mg dose group, only 22 of the 44 patients included (50%) had received crizotinib previously. In total, including the other two dosing cohorts (i.e. 600mg with food, and 750mg in the fasting state), only 66 out of the 137 patients included (48.2%) had received prior crizotinib. It is also noteworthy that the median duration of follow up was only 4.1 months for Part 1 of the ASCEND-8 study.

The secondary efficacy analysis from Part 2 of ASCEND-8 was presented at ESMO 2018 meeting held in October 2018. As stated earlier, this efficacy analysis was undertaken only in treatment naïve patients and is thus not relevant to the current appraisal. Updated safety results from ASCEND-8 were also presented and these were for the overall population in the study (treatment naïve and pre-treated patients).

References

1. Cho BC, Kim DW, Bearz A, *et al*. ASCEND-8: A Randomized Phase 1 Study of Ceritinib, 450 mg or 600 mg, Taken with a Low-Fat Meal versus 750 mg in Fasted State in Patients with Anaplastic Lymphoma Kinase (ALK)-Rearranged Metastatic Non-Small Cell Lung Cancer (NSCLC). J Thorac

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	Oncol, 2017, 12(9): 1357-1367. 2. Cho BC, Obermannova R, Orlov SV et al. LBA59 - Primary efficacy and updated safety of ceritinib (450 mg or 600 mg) with food vs 750 mg fasted in ALK+ metastatic NSCLC ASCEND-8). Poster discussion session at ESMO 2018, Munich, October 19th 2018. 3. Gainor JF, Chi AS, Logan J et al. Alectinib Dose Escalation Reinduces Central Nervous System Responses in Patients with Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer Relapsing on Standard Dose Alectinib. *J Thorac Oncol*. 2016 February ; 11(2): 256–260.

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib [ID1328]

Clarification points for the Committee on the modelling of treatment benefit

Submitted by Takeda UK Ltd

21st November 2018

Modelling of treatment benefit beyond treatment discontinuation

This document describes the method used to extrapolate overall survival (OS) data in the economic model, with a particular focus on the modelling of reduced treatment benefit following treatment discontinuation (hereafter referred to as "treatment waning"). For ease of understanding, this document has been separated into two parts:

- Part 1 describes how OS has been estimated during the within-trial period using an ***average*** treatment effect or hazard ratio derived from this – as well as highlighting the inconsistencies that arise from any modelling that, in effect, manipulates this within-trial period data.

- Part 2 describes our method of extrapolating OS which takes into account treatment waning and presents key outcomes from the model such that its clinical plausibility can be assessed. We also describe the updated modelling approach that we believe is being explored by the ERG and NICE and we provide our perspective on this.

Following communication with the NICE technical team and reflecting back on the discussions in the two Committee meetings held to date, Takeda consider it important to emphasise that in a partitioned survival model the outcomes represent the average patient. Therefore, all inputs relate to the average of a cohort – including the lower and upper extremities. Individual patient level outcomes are not modelled.

Part 1 – the average treatment effect

The hazard ratio used to estimate OS in the model base case is 0.40. This is estimated using data up to 148 weeks for brigatinib (maximum follow-up in the ALTA trial) and up to 120 weeks for ceritinib (~82 weeks from ASCEND-2 and ~120 weeks from ASCEND-5).

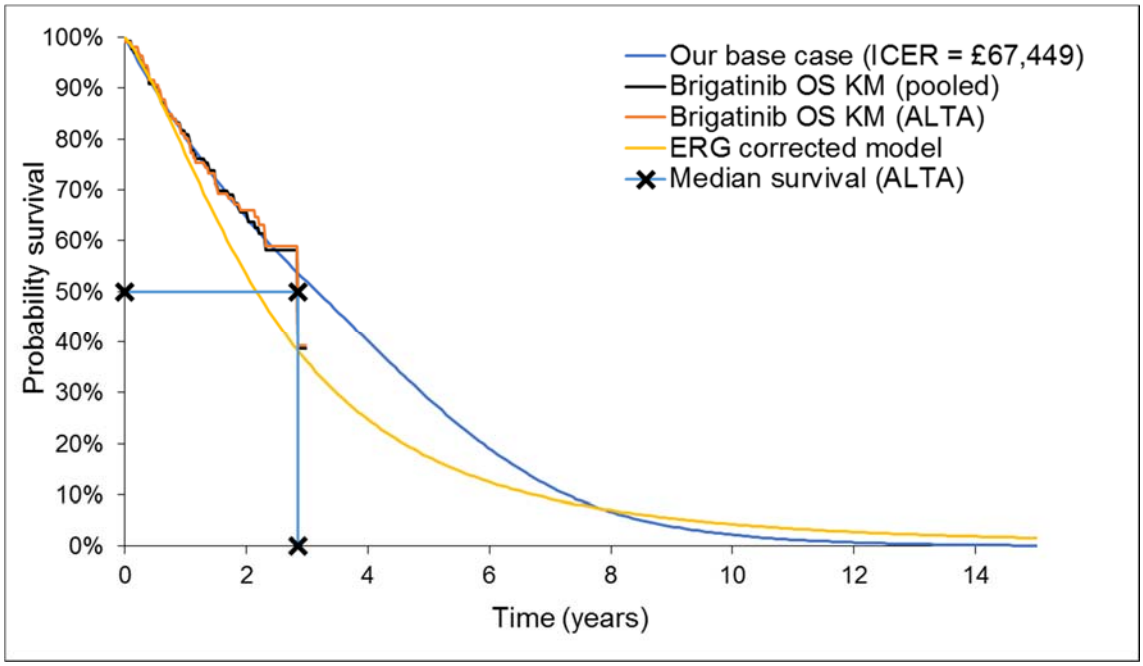
This hazard ratio is the ***average*** treatment effect from the observed clinical trial data based on the current follow-up. Therefore, this hazard ratio already captures the impact of treatment discontinuation on the OS that is observed up until this time-point. Hence, this treatment effect is not actually the "full treatment effect" of brigatinib; it takes into account the survival relevant to those patients that have already discontinued treatment during the trial period. If patients were censored upon treatment discontinuation then the treatment effect of brigatinib on survival would likely be much higher than that seen in the ***average*** treatment effect over the trial period. This is not unique to the ALTA trial; 63.6% and 67% of patients had discontinued treatment with ceritinib over the trial period in the ASCEND-2 and ASCEND-5 trials, respectively. By comparison, 72.69% of patients discontinued brigatinib over the ALTA trial period.

In relation to a specific example brought up at the second Committee meeting: a patient who discontinues treatment after 6 weeks **does** receive the same treatment benefit and same duration of treatment benefit as a patient who discontinues after 150 weeks, within the model. This is because the model inputs and outputs reflect the average patient – including those on treatment for a short time and also the long-runners. In other words, the outcomes of the early and late discontinuers are included in the aggregate estimates (including the OS Kaplan-Meier curves and the hazard ratio).

In conclusion, the hazard ratio of 0.40 represents the ***average*** treatment effect of brigatinib and therefore should not in our opinion be referred to as the "full treatment effect". The uncertainty associated with the hazard ratio is explored in extensive sensitivity analyses presented in our original submission (dated: 6th April 2018) and with the September 2017 data cut in the addendum (dated: 14th May 2018).

Manipulating survival outcomes within the model during the within-trial period will result in inconsistent outcomes vs. the ALTA trial (as was seen in the ERG's revised model sent to the company on 7th November 2018). Figure 1 presents the Kaplan-Meier OS curves from ALTA and from the pooled brigatinib data (ALTA and Study 101) compared with our base case OS curve and the ERG's base case OS curve. The graph shows that the ERG's modelling approach significantly underestimates the survival outcomes that were actually observed in the ALTA trial.

Figure 1: Comparison of observed brigatinib data with fitted curves from our base case and the ERG's base case



Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival

Part 2 – accounting for treatment waning beyond the trial period

The uncertainty stems from what happens beyond the observed trial period (i.e. beyond week 148 for brigatinib). There are no relevant data which could be used to inform outcomes post-brigatinib, nor post two TKIs, in the ALK+ NSCLC setting. Therefore, the model applies a tapering treatment effect on OS (i.e. treatment waning). The rationale for continuing some treatment effect beyond the trial period is that some patients are still on treatment within the model. Therefore, the model is accruing treatment costs and should be accruing treatment benefit. This method has been used in a number of previous NICE technology appraisals to address the uncertainty around long-term treatment effects.

As presented in our response to the ACD, Takeda have applied a tapering (waning) of survival to the brigatinib arm from week 161 (3.09 years) to week 377 (7.23 years). Up until week 161, survival is estimated as per the parametric curve fitted to the brigatinib data. Week 161 was selected because this represents the maximum follow-up from the ALTA clinical trial (148 weeks), which has been used in the analyses informing the model, plus an additional 3 months (approximately 13 weeks). The rationale for the additional 3 months is based on comments made by the clinical experts at the first Committee meeting (on 12th July 2018) and the statement on page 12 of the ACD that: "*The clinical experts explained that it was reasonable to assume that treatment benefit would continue for a few months after stopping treatment*." This has subsequently been supported by feedback from three other clinical experts who were consulted by Takeda after the first Committee meeting. Between week 161 and week 377, survival is weighted across the brigatinib and ceritinib rates, with an increasing weight being given to the ceritinib rate over time so that by week 377 the brigatinib survival rate is equal to the ceritinib survival rate. From week 377 onwards, the survival rate for brigatinib is assumed equal to ceritinib. Week 377 was selected because this represents the time at which 1% of patients remained on treatment with brigatinib (364 weeks), plus the additional three months (approximately 13 weeks) as explained above.

Applying this treatment waning effect impacts on the proportion of patients surviving at 5, 10 and 20 years, as predicted by the health economic model. Table 1 presents these proportions for each of the parametric survival curves and compares this with the averaged estimates from five UK clinical experts – details relating to this expert elicitation are presented in the original submission dossier. When applying this treatment waning effect, the Gompertz curve does not align with clinicians' expectations. Although there is uncertainty in clinician estimates, it was agreed by all five UK clinical experts that ~5% of patients would be expected to survive to 10 years. None of the curves align exactly with this expectation; but the exponential provides a conservative estimate of 2.28% survival at 10 years. Therefore, this curve is applied to OS outcomes, along with the treatment waning effect, in the company's updated base case. In addition to providing a conservative estimate, the exponential curve also has the advantage of providing the best fit to the observed data based on the AIC and BIC values – and produces outcomes that align closely with clinical expert expectations.

Table 1: Proportion of patients surviving at 5, 10 and 20 years as predicted by the model with treatment waning applied

	5 years	10 years	20 years
Clinical experts average	28.50%	5.83%	0.00%
Exponential	28.99%	2.28%	0.01%
Gamma	27.27%	1.67%	0.00%
Log-normal	39.27%	13.77%	3.13%
Log-logistic	33.99%	8.84%	1.53%
Weibull	26.87%	1.46%	0.00%
Gompertz	25.21%	0.54%	0.00%
Generalised gamma	27.96%	2.03%	0.01%

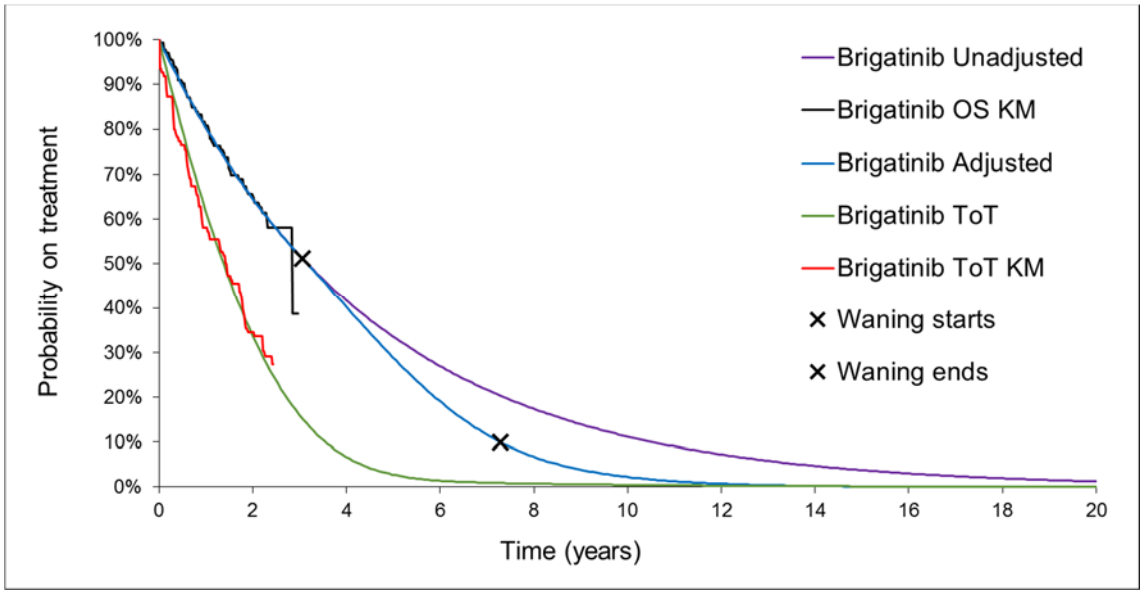
It is important to recognise that this method reflects the average waning effect. It is recognised that not all patients will necessarily continue to receive a treatment benefit for 3 months beyond

discontinuation. However, on average, a benefit extension of 3 months beyond treatment discontinuation is modelled.

Figure 1 presents the Kaplan-Meier curves for OS and ToT for brigatinib from the ALTA clinical trial and compares these with the model extrapolations for OS (unadjusted and adjusted for treatment waning) and ToT. The black crosses in Figure 2 represent the point at which the waning of the treatment effect starts and stops. As described earlier, the rationale for continuing some treatment effect beyond the trial period is that some patients are still on treatment within the model. Therefore, the model is accruing treatment costs and should be accruing a corresponding treatment benefit.

The proportion of treatment effect applied is not proportional to the proportion of patients on treatment. As explained above, the hazard ratio or treatment effect represents the ***average*** treatment effect from the clinical trial and takes into account that only 27.31% of patients are still on treatment with brigatinib at the end of the trial period. Therefore, the ***average*** treatment effect represents an effect diluted by 72.69% of discontinued patients.

Figure 2: Comparison of observed and extrapolated OS and ToT outcomes



Abbreviations: KM, Kaplan-Meier; OS, overall survival; ToT, time on treatment

Table 2 presents the proportion of patients on treatment and the proportion of the ***average*** treatment effect applied to the brigatinib arm.

Table 2: Proportion on treatment relative to proportion of *average* treatment effect applied (our method)

Year	Proportion on treatment	% of hazard ratio applied	Rationale
0	100.00%	100.00%	Hazard ratio estimated based on trial data which considers treatment discontinuation over trial period
1	61.92%	100.00%	
2	33.90%	100.00%	
3	16.14%	100.00%	
4	6.77%	78.24%	Reduction in ***average*** hazard ratio/treatment effect is not proportional to reduction in ToT as the ***average*** hazard ratio/treatment effect has already been diluted by 72.69% of patients discontinuing treatment with brigatinib across the ALTA trial period
5	2.79%	54.17%	
6	1.43%	30.09%	
7*	0.98%*	6.02%*	
8	0.77%	0.00%	Less than 1% of patients on treatment. Therefore, survival is assumed equal to ceritinib
9	0.62%	0.00%	
10	0.50%	0.00%	

*Less than 1% of patients on treatment at 7-years but a small treatment effect is still applied for those patients who have only just come off treatment and experience a benefit up to 3-months beyond discontinuation.

Our treatment waning method considers two book-ends for the treatment benefit, which are supported by the data and clinical plausibility: (1) 148 weeks based on the maximum follow-up from the ALTA trial of brigatinib and (2) the point at which the majority of patients are off treatment (>99%). The rate at which the treatment effect wanes between these two time points is unknown. Therefore, we consider a simplistic linear function although we accept that there are no data to support this. However, we do know that there must still be some clinical benefit being accrued up to 7 years within the model because some patients are still on treatment until this time. Given the lack of data, we believe we have made the most conservative assumptions with the most conservative methods whilst still maintaining clinical plausibility.

Our base case waning assumptions reduce the treatment effect from 161 weeks (148 weeks + 3 months) to 377 weeks (364 weeks + 3 months). As explained earlier, this is based on initial clinical expert feedback received during the first Committee meeting from the two clinical experts present (Dr Yvonne Summers and Dr Sanjay Popat). However, more recent written feedback from Dr. Yvonne Summers submitted immediately prior to the second Committee meeting, indicates that the treatment benefit may extend even further than this: Dr Summers stated that *"the survival data suggests more than a year, but less than 4.5 years"*. Based on this more recent clinical expert feedback, Takeda has explored scenarios which consider a 6, 9 and 12-month additional benefit beyond treatment discontinuation (these results were submitted to NICE via email on 16th November 2018), as presented in Table 3. We consider the scenario which assumes 12 months of additional treatment benefit as being the one that most closely reflects the latest clinical expert input. In line with the model structure, these scenarios are applied as an average.

Table 3: Scenarios exploring additional benefit beyond treatment discontinuation

	Start of waning (weeks)	End of waning (weeks)	ICER
0 months additional benefit	148	364	£68,730
3 months additional benefit	161	377	£67,449
6 months additional benefit	174	390	£66,296
9 months additional benefit	187	403	£65,256
12 months additional benefit	200	416	£64,314

Abbreviations: ICER, incremental cost-effectiveness ratio

ERG additional exploratory analysis

During a call with the NICE technical team on Friday 16th November, Takeda was made aware that another scenario which is being explored by the ERG is treatment waning from 161 weeks to one year later (213 weeks). Our understanding is that this approach means that the treatment effect is assumed to be zero after 213 weeks. Based on our version of the model, this modelling approach results in an ICER of £75,594/QALY. Table 4 presents the proportion of patients on treatment, relative to the proportion of the ***average*** treatment effect applied under this scenario. Figure 3 presents the OS curve associated with this method and compares this with the Kaplan-Meier data, our base case OS curve and the original method used by the ERG to account for treatment waning (as presented in Figure 1).

We welcome the fact that the ERG and the NICE technical team are exploring a scenario that seems to accept the more recent clinical feedback indicating that the treatment benefit may extend for up to one year after treatment discontinuation. However, we are concerned by the way this is being done. In the model at week 213, 5.88% of patients are still on treatment. Therefore, under this ERG exploratory scenario, these patients are receiving the cost of treatment whilst receiving no benefit from that treatment. Takeda consider this to be unfair and also clinically implausible because clinicians will only continue treatment if a patient is still receiving benefit from it.

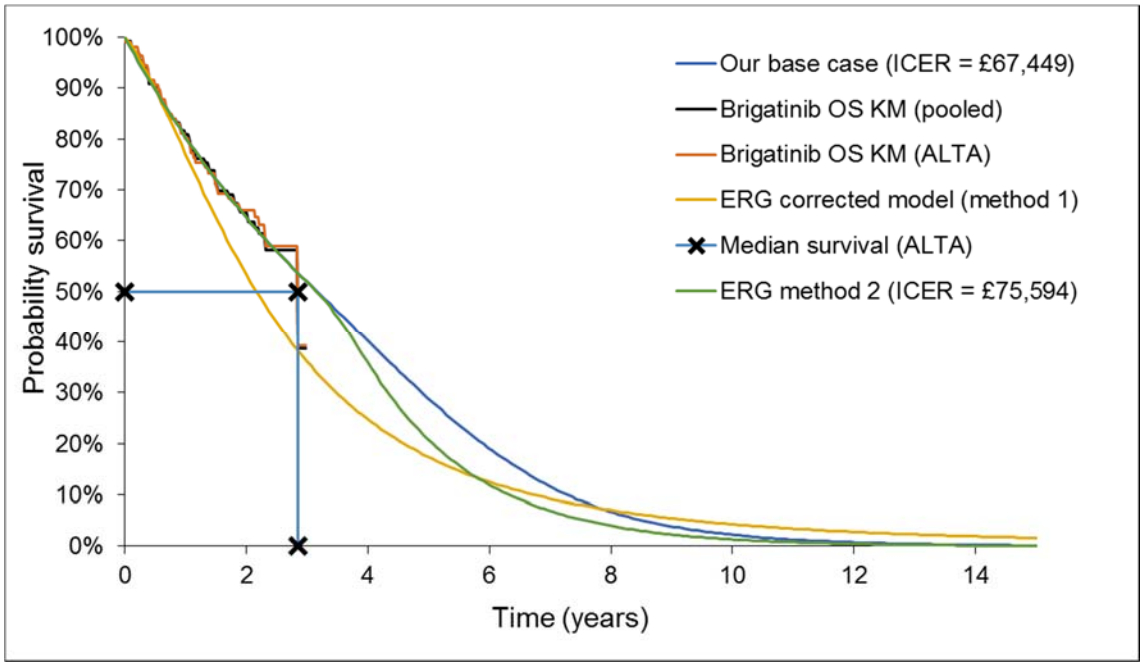
In addition, we believe that in the ERG exploratory scenario the treatment effect is waned too fast, based on what is observed in the clinical trial data. The ***average*** hazard ratio or treatment effect is based on 27.31% of patients remaining on treatment at the end of the observed clinical trial period. Therefore, you would expect ~25% of this treatment effect to be remaining at the point where 6-7% of patients are still on treatment. As explained above, the hazard ratio or treatment effect represents the average treatment effect from the clinical trial and takes into account that only 27.31% of patients are on treatment with brigatinib at the end of the trial period.

Table 4: Proportion of patients on treatment relative to proportion of average treatment effect applied (ERG's new method)

Year	Proportion of patients on treatment	% of hazard ratio applied
0	100.00%	100.00%
1	61.92%	100.00%
2	33.90%	100.00%
3	16.14%	100.00%
4	6.77%	9.62%
5	2.79%	0.00%
6	1.43%	0.00%
7	0.98%	0.00%
8	0.77%	0.00%
9	0.62%	0.00%
10	0.50%	0.00%

Abbreviations: ERG, Evidence Review Group

Figure 3: Comparison of observed brigatinib data with fitted curves from our base case, the ERG's base case (method 1) and the ERG's new scenario (method 2)



Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival

Conclusion

We hope that the information presented in this document adds to the Committee's understanding of the brigatinib treatment benefit within the model, and addresses the Committee's concerns regarding the methods used to model the treatment waning effect.

Takeda are happy to take part as necessary in further discussions with the NICE technical team and/or the NICE Committee to aid their understanding of the methods used to incorporate treatment waning within the model. If there are any aspects of this that are unclear or require further explanation, then Takeda would like to be made aware of these and be given the opportunity to provide further clarification to NICE and/or the Committee prior to the third Committee meeting scheduled for 6th December 2018.

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib [ID1328]: Response to "ERG Analyses for ACM3"

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute of Health and Care Excellence

Submitted 3rd December 2018

1. Introduction

On Friday 23rd November, Takeda received a report from the Evidence Review Group (ERG) entitled *"ERG Analyses for ACM3"*. This was followed by the supporting economic model on Monday 26th November. Subsequently, on 30th November, Takeda received an addendum to this ERG report (entitled *"ERG Analyses for ACM3 – Addendum"*) and an updated and combined version of the ERG report which contained an additional Section 5 (called *"5. Additional scenario added on 30th November 2018"*). The additional Section 5, included in the combined ERG report, was identical to the addendum.

This document contains Takeda's factual accuracy check of the combined ERG report as received on 30th November 2018 (i.e. including the additional Section 5). We hope this will help the Committee further understand the application of treatment benefit discontinuation (TBD) in the model and ultimately aid the decision-making process.

2. Factual and methodological inaccuracies

2.1 Time on treatment (ToT)

The ERG state the following on page 6 of the report entitled *"ERG Analyses for ACM3"*:

> *"In this revised ERG base case the direct observation of ToT (using KM plots based on observation in ALTA) is used to drive TKI costs"*

Modelling of ToT was discussed at the first Committee meeting (on 12th July 2018) and it was concluded by the Committee (see page 12 of the ACD, September 2018) that:

> *"treatment duration after progression would be similar for brigatinib and ceritinib and that, without any better data, the company's estimate of 1.53 months was appropriate for decision-making".*

This was supported by clinical experts at the meeting who stated that there was no clinical rationale as to why the duration of treatment beyond progression would differ for patients treated with brigatinib vs. patients treated with ceritinib.

In this ERG report, the model uses the ToT data from ALTA for brigatinib, with a gamma parametric curve used to extrapolate long-term outcomes. However, as was stated in the first Committee meeting, there are no ToT data available for ceritinib. Therefore, the hazard ratio estimated for PFS outcomes is applied by the ERG to the brigatinib ToT data to estimate the ceritinib ToT. As stated in the first Committee meeting this results in clinically implausible outcomes, whereby patients are treated for up to four months post-progression in the brigatinib arm but for about one month less than progression in the ceritinib arm. These estimates are based on the company's base case model. However, the implications of this approach (and the resulting clinical implausibility) also remain in the ERG's revised base case; because patients are still being treated beyond progression in the brigatinib arm but for less time than progression in the ceritinib arm.

Takeda consider that this does not reflect clinical practice and should not be included in the ERG's revised analyses, particularly as the Committee have previously concluded that the

company's estimate of 1.53 months treatment beyond progression for both brigatinib and ceritinib is appropriate for decision-making. Updating the ERG's revised analyses with this approach to estimating ToT (i.e. the 1.53 months beyond progression as stated in the ACD) results in the ICER falling from £91,123/QALY to £85,309/QALY.

Takeda note the additional Section 5 included within the combined ERG report explores the impact of varying the hazard ratio that is applied to the Kaplan-Meier fitted brigatinib ToT curve (gamma distribution) to produce the ceritinib ToT curve. Takeda agrees with the ERG that the gamma-based hazard ratio of 0.481 may represent a reasonable alternative to the base case hazard ratio of 0.282, and we note that the ICER in this scenario is reduced by £20,623/QALY compared to the ERG base case (i.e. £70,500/QALY vs. £91,123/QALY).

Related to ToT, Takeda would like to specify that Figure 1 as reported in the ERG report is not from the company base case; this is an ERG scenario. Furthermore, on page 6 it is stated that the estimate of 1.53 months of treatment beyond progression is derived from the February 2017 data cut of ALTA. This is incorrect as it has been determined based on the September 2017 data cut of ALTA (median PFS = 67.90 weeks (15.62 months) and median ToT = 74.57 weeks (17.15 months) – difference = 1.53 months).

2.2 Treatment benefit discontinuation (TBD; also referred to as treatment waning)

To summarise the history of the application of TBD in this appraisal:

- The first ERG report[1] (dated 14th June 2018) stated the following in Section 5.2.6.4 (page 115):

  > *"The ERG consider it plausible that the benefit of brigatinib gained over ceritinib during trial observation is carried through the model's lifetime horizon."*

  And the same Section of the ERG report[1] stated

  > *"The ERG adopt the assumption that treatment benefits for both drugs extend beyond the end of treatment, although there is limited evidence for a strong position either way, other than expert clinical opinion, which the ERG found to be mixed."*

- The addendum to this report[2] (dated 10th July 2018) stated the following (on Page 2 of the addendum):

  > *"expert clinical opinion is that treatment effect is lost earlier; the loss of clinically meaningful effect triggers discontinuation (for those who tolerate treatment)."*

  This was accompanied by scenarios which resulted in outcomes that the committee considered as lacking clinical plausibility. Therefore, the Committee could not accept these scenarios for decision-making (as discussed on page 13 of the ACD[3]).

- The outcome from the first Committee meeting (held on July 12th, 2018), as reported on page 13 of the ACD was:

> *"The committee concluded that the modelling of a lifetime continued treatment benefit was not clinically plausible in people with symptomatic ALK-positive advanced NSCLC who had stopped treatment."*

- Takeda considered this feedback in their response to the ACD by including TBD in their base case. The methods used by the company have been fully reported in previous documents sent to NICE (i.e. the response to the ACD[4] and the subsequent document further describing TBD sent on 21st November 2018). To summarise, Takeda waned the treatment effect seen in the clinical trial data from the end of follow-up in the ALTA trial (plus an additional 3 months) to the point where <1% of patients remain on treatment with brigatinib in the model (plus an additional 3 months). Between these two time-points, the treatment effect was waned at a linear rate. This simplification was used as there are no data to suggest how the treatment effect associated with brigatinib would wane after the trial period and to what extent the estimated treatment effect had already been diluted from discontinuations in the trial.
- The first revision from the ERG aimed to correct for the clinical implausibility identified in their first method used to account for TBD.[5] This method was discussed at the second Committee meeting (held on November 8th 2018), where two key issues were identified: the within trial outcomes did not align with the outcomes observed in the ALTA clinical trial, leading to predicted model outcomes that did not align with the observed clinical data.
- Following the second Committee meeting, it was communicated to Takeda by NICE that further work was needed to explore TBD by NICE and the ERG. To support this, Takeda sent to NICE a detailed document describing the concept of TBD, the interaction of TBD in the economic model and more detail on our method of applying TBD in the model.
- The second revision from the ERG aimed to correct for the clinical implausibility identified in the first and second methods that had been used by the ERG to account for TBD.[6] The inaccuracies associated with this second revision are discussed in this document which has been sent to NICE prior to the third Committee meeting (scheduled for 6th December 2018).

In its latest report[6], the ERG recognises that maintaining the mortality rate during the observed period

> *"implies that observed mortality inherently incorporates any reduced benefit on survival owing to brigatinib discontinuation"* (see page 5 of the report entitled *"ERG Analyses for ACM3"* [6]).

However, this is not consistent with the revised ERG base case. Table 1 shows the proportion of patients on treatment and the proportion of the treatment benefit applied in the brigatinib treatment arm in the updated ERG analysis. **Note:** these proportions are derived from the ERG's revised base case which uses different methods and parametric curves to

estimate overall survival (OS) and time on treatment (ToT). Therefore, these may differ from previous estimates reported by Takeda.

Table 1: Proportion of patients on treatment with brigatinib compared with the proportion of estimated treatment benefit applied

Time (weeks)	Trial period	Proportion on treatment	Proportion of estimated treatment benefit applied
144	Trial period	26.46%	100.00%
148		25.62%	100.00%
152	Trial period + 3 months	24.81%	100.00%
156		24.03%	100.00%
160		23.27%	100.00%
164	Extrapolated period	22.54%	22.54%
168		21.84%	21.84%
172		21.15%	21.15%

In the ERG's revised analysis, up to the end of the trial period +3 months (to account for some continued benefit beyond treatment discontinuation) the estimated treatment benefit derived from the indirect treatment comparisons is applied. As the ERG state on page 5 of this report[6], this treatment benefit accounts for some discontinuations within the observed follow-up period of the trial. Therefore, the proportion of treatment benefit applied does not equal the proportion on-treatment within the model – for example, at week 148 (maximal follow-up) ~26% of patients are on treatment but are receiving 100% of the estimated average treatment benefit which has already been diluted based on a high proportion of patients having already discontinued during the trial period.

However, after the trial period +3 months, the ERG's revised base case applies a proportion of treatment benefit corresponding to the proportion of patients on treatment. This is underestimating the benefit for patients remaining on treatment as the estimated treatment effect has already been diluted from the discontinuations that have taken place within the observed trial period. This is highlighted by 0.73% of patients discontinuing between week 160 and week 164, yet 77.46% of the treatment benefit is lost across this 4-week period. This is visible in the sudden steep drop in the ERG's revised OS curve presented in Figure 2 of this ERG report[6], which clinicians have emphasised is not clinically plausible. This sudden drop in the survival rate is apparent across all ERG scenarios.

Therefore, Takeda consider the ERG's revised base case is not a factually correct reflection of outcomes in UK clinical practice; and nor do we consider it a clinically plausible scenario.

The revised ERG base case also applies a hazard ratio of 1.33 (1/0.75) to estimate outcomes of best supportive care (BSC) relative to ceritinib. This is applied to capture the survival outcomes associated with subsequent therapy within the model – which, based on the current clinical pathway, would be BSC after discontinuation of either brigatinib or ceritinib. However, it is unclear to Takeda how this hazard ratio has been estimated and how it is supported by the data. The ERG report implies that the hazard ratio is derived from the NICE submission of ceritinib in the post-crizotinib setting (TA395).[7] However, this appraisal did not calculate a hazard ratio. A further concern is that Novartis (the company responsible for the ceritinib submission) clearly state that their statistical analyses showed that the

hazards between ceritinib and BSC were not constant with respect to time, nor parallel, showing that the hazards were not proportional over time. Therefore, hazard ratios could not be used to estimate the treatment effect of ceritinib relative to BSC (see Page 95 of the Company's submission [TA395][7]). Therefore, Takeda consider the use of an arbitrary hazard ratio in the ERG's revised base case as methodologically incorrect as well as having concerns with regards to the source of the hazard ratio that was used.

Additionally, Takeda consider it important to recognise that the data used in the ceritinib submission (TA395) were intended to inform the BSC outcomes in the post-crizotinib setting (i.e. after treatment with only one ALK inhibitor). There are no data available for outcomes with BSC after two ALK inhibitors – which is the relevant positioning to inform our economic model for this appraisal. Despite this, there is literature available showing that sequential treatment with ALK inhibitors substantially prolongs survival in patients with ALK+ NSCLC.[8] However, these data are only available for patients who have received multiple ALK inhibitors post-crizotinib and are not shown for patients having only one ALK inhibitor post-crizotinib. Therefore, we are unable to use these data in the modelling. Nevertheless, the data infer that using ALK inhibitors in sequence prolong survival. Consequently, we do not consider the survival outcomes for patients receiving BSC after crizotinib to be equivalent to survival outcomes for patients receiving BSC after two prior ALK inhibitors (i.e. after crizotinib and either brigatinib or ceritinib).

This ERG report[6] also identifies ASCEND-5[9] as a relevant source from which to draw BSC data. However, this is incorrect as ASCEND-5 compares ceritinib with single-agent chemotherapy, not BSC.

As there are no data on BSC in this setting, Takeda have modelled TBD to be consistent with previous NICE submissions; the survival rate for patients in the brigatinib arm is waned to the survival rate observed in the comparator arm (i.e. ceritinib). This is consistent with the NICE submissions for ceritinib (TA395)[7] and alectinib (TA536).[10] The case precedence and consistency related to modelling TBD in ALK+ NSCLC are discussed in Section 2.3.

2.3 Case precedence and consistency

Discussions about how to model TBD are often contentious as there are usually limited data available for outcomes after treatment discontinuation. This is particularly true in ALK+ NSCLC where any real-world data are often confounded by the use of multiple sequential ALK inhibitors accessed through clinical trials or compassionate access programs, and are quickly outdated by a rapidly evolving landscape. In the face of increased uncertainty, Takeda consider that the importance of case precedence and consistency is emphasised across NICE appraisals of ALK inhibitors for ALK+ NSCLC.

Modelling of TBD was explored in the ceritinib post-crizotinib submission (TA395)[7] and the alectinib untreated population submission (TA536).[10] Notably, it was not explored in the ceritinib untreated population submission (TA500)[11] nor the crizotinib untreated population submission (TA406).[12]

The ceritinib post-crizotinib submission (TA395)[7] discussed how extrapolating using the Kaplan-Meier data did not imply that the benefits from ceritinib continue indefinitely after stopping treatment (see page 15 of the final appraisal determination [FAD]). In this appraisal,

the ERG explored reducing the duration of treatment benefit with ceritinib from a lifetime to between 2- and 9-years. Beyond these time points, the ERG set the probabilities of dying on ceritinib to be the same as for the comparator arm (i.e. BSC). The company then submitted an updated model looking at TBD where the benefits and costs associated with ceritinib were arbitrarily stopped at 18-months and 2-years. This had a minimal impact on the ICER. **Note:** TBD was not considered in the comparator arm.

The alectinib untreated population submission (TA536)[10] provided very little information on how their TBD scenarios were applied. However, with the information available, it can be ascertained that the company explored reducing the duration of treatment benefit with alectinib from a lifetime to between 3- and 10-years. Beyond these time points, the company appear to set the probabilities of dying on alectinib to be the same as for the comparator arm (i.e. crizotinib). **Note:** TBD was not considered in the comparator arm. The company's submission states (see Section B.3.8.4; page 116) that:

> *"an OS treatment benefit cap provides an arbitrary cut off, not supported by the evidence"*

and on the same page the company's submission states:

> *"Given the extrapolation presented is already deemed significantly conservative towards alectinib, it is not considered appropriate to utilise such a cap"*

No further exploration was conducted by the ERG.

These submissions highlight that case precedence indicates many arbitrary endpoints from which TBD is modelled. In our submission, TBD (treatment waning) starts from week 161 (~3 years) – this is in line with the most conservative TBD point in the alectinib submission and is like the ceritinib submission in terms of the ratio of ToT to the point at which TBD commences (patients are treated for a much shorter duration with ceritinib so you would expect TBD to commence earlier).

Case precedence also highlights that when applying TBD in previous NICE appraisals for ALK inhibitors, the survival rates were reduced to the survival rates seen with the comparator (i.e. survival was waned to crizotinib in the alectinib submission TA536; and was waned to BSC in the ceritinib submission TA395). This is because the primary aim of TBD methods is to address the relative benefit of the intervention vs. the comparator. Subsequent therapy was not considered explicitly in these appraisals; likely due to the lack of data. This is in line with our method of applying TBD in this appraisal, where the survival rate for brigatinib is waned to the survival rate of its comparator ceritinib. The variability in the approach to TBD across ALK inhibitor appraisals highlights the lack of clear guidance as to how this should be modelled.

3. Conclusion

This document contains Takeda's factual accuracy check of the latest combined ERG report and provides our perspective on the approaches now taken by the ERG with respect to the modelling of ToT and TBD (treatment waning). In addition, we highlight the importance of

case precedence and trying to have some consistency across the NICE appraisals of ALK inhibitors for ALK+ NSCLC.

Using the ERG's base case with the following changes:

- For ToT, assuming that patients are treated for 1.53 months beyond progression for both brigatinib and ceritinib (i.e. as agreed at the first committee meeting, and as stated in the ACD).
- Applying TBD (treatment waning) in line with proportional reductions in ToT (this uses the method suggested by the ERG where the proportion of treatment benefit applied is linked to the proportion of patients on treatment, but a scaling factor is applied to the proportion of treatment effect based on the ratio between proportion on treatment in the trial vs. 100% of the estimated average treatment effect).
- Applying a hazard ratio of 1 for BSC (i.e. assuming survival rates for ceritinib)

Making these changes, while maintaining all the ERG's other preferred base case assumptions (including its preferred base case parametric curves and ALTA as a data source across all efficacy inputs) result in an ICER of £67,937/QALY (without PAS) –. This is similar to the company's base case ICER of £67,449/QALY (without PAS).

In the ERG's addendum, the ERG present an alternative method for calculating ToT using a hazard ratio of 0.481 which produces clinically plausible outcomes and an ICER of £70,500. Using this scenario with the following changes:

- Applying TBD (treatment waning) in line with proportional reductions in ToT (this uses the method suggested by the ERG where the proportion of treatment benefit applied is linked to the proportion of patients on treatment, but a scaling factor is applied to the proportion of treatment effect based on the ratio between proportion on treatment in the trial vs. 100% of the estimated average treatment effect).
- Applying a hazard ratio of 1 for BSC (i.e. assuming survival rates for ceritinib)

Making these changes, while maintaining all the ERG's other preferred base case assumptions (including its preferred base case parametric curves, ALTA as a data source across all efficacy inputs and ToT) result in an ICER of £56,034/QALY (without PAS).

Therefore, we consider that three alternative methods of accounting for ToT and TBD now give similar cost effectiveness results, when assumptions are supported by clinical plausibility and case precedence.

4. References

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Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

A Single Technology Appraisal

APPENDIX – No PAS information

ERG Analyses for ACM2

7 November 2018

Contents

1 Commercial information

The list price unit cost of brigatinib is £4,900, this is both the cost of a 28-tablet pack covering 28 days at recommended dose (180mg), and the starter pack for the first month of treatment (7 x 90mg tablets and 21 x 180mg tablets).

2 Issues arising from Company's response and new model

2.1 Correction of minor coding errors in the PFS and AE data

The ERG are not able to verify KM output for the September 2017 data cut (not published), including any changes to it. However, the coding corrections made by the company to the model, in respect to two PFS events and two adverse events, have been adopted by the ERG. The company have shown the impact to be a small increase in the ICER (£317 per QALY gained).

2.2 New price of 30mg and 90mg brigatinib

The company state that these lower prices reduce the ICER by £238 per QALY gained. However, it is only the 90mg tablet size that is included in the model within the confines of the starter pack, which uses 90mg and 180mg tablet sizes. Since the price of the starter pack has not changed we should not expect any change in the ICER as a result of these unit price changes. The ERG has found a coding error in the model leading to the company's finding.

2.3 Duration of treatment benefit after discontinuation

The committee asked the Company to return with a method resembling that of the ERG, but different so that higher long-term survival estimates were attained. The original ERG approach was premised on two components:

(1) a rule determining the time, for each strategy, at which mortality rate changes away from a treatment driven rate; and

(2) a change in mortality rate [at the point(s) determined] to one based on rates observed in patients on BSC.

Whilst the company's new method does establish a time at which the brigatinib driven mortality rate changes, it does not include the same for ceritinib, and the rate does not change to a BSC-based mortality rate. Regarding (1) the company chose the maximum follow-up period of any patient in the ALTA trial, plus a set period, as the point marking the decline from the full brigatinib treatment effect. This was 148 weeks plus 13 weeks, totalling 161 weeks (3.09 years from the commencement of treatment). The company do not state why the observation period in ALTA was chosen, or why the maximum of the range was chosen. Is it that during this period of 148 weeks, when compared to follow-up in ASCEND-2 or ASCEND-5, no decline (or convergence) in the relative effect of brigatinib versus ceritinib is observed? If this is the rationale then the observation period statistics of the included ASCEND trials are relevant. The maximum follow-up in ASCEND-2 is 82 weeks; and the upper quartile follow-up time in

ASCEND-5 is given as 93 weeks (maximum not reported). Visual inspection of the KM plots of OS for the respective trials (Figure 1 and Figure 2), using only the period for which data is available for both strategies, shows clear separation of mortality rate between patients in ALTA and those in both ACSEND-2 and ASCEND-5. No convergence is evident through ~1.5 years versus ASCEND-2; but there may be convergence evident versus ASCEND-5 in the MAIC comparison after about 2 years (Figure 2). Although some caution is necessary since the numbers of patients at risk at this point are low.

Figure 1 Observed OS using Kaplan-Meier; ALTA (brigatinib) plotted against ASCEND-2 (ceritinib). With and without MAIC adjustment of ALTA IPD.

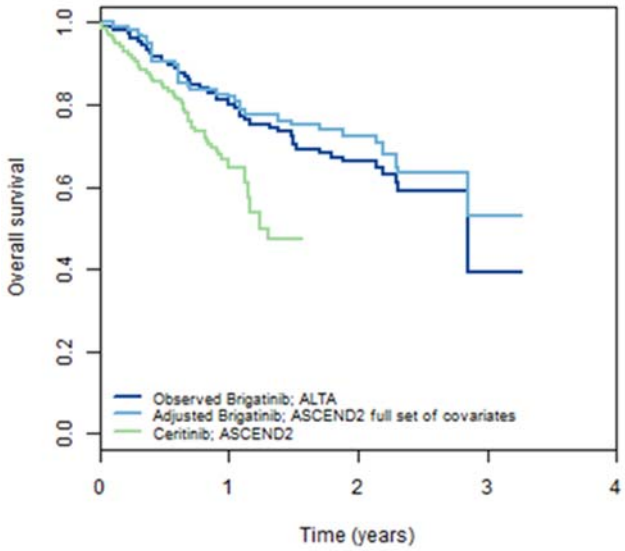
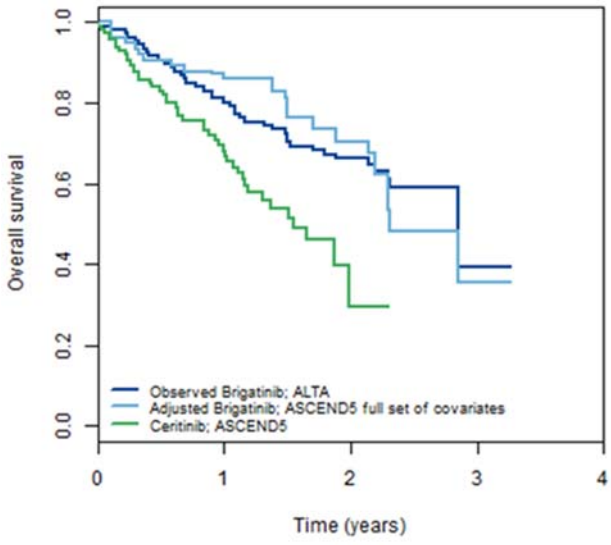


Figure 2 Observed OS using Kaplan-Meier; ALTA (brigatinib) plotted against ASCEND-5 (ceritinib). With and without MAIC adjustment of ALTA IPD.



Source (both): CS Revised, Figure 2 page 4

Regarding (2), the change in mortality rate after full treatment effect is lost, as implemented by the company, is calculated relative to the ceritinib mortality rate. We argue that any loss of effect should be relative to placebo, or BSC in this appraisal. By happenstance the choice of the company to base the subsequent mortality rate on the estimate for ceritinib may be inconsequential, since our targeted review of the literature for a hazard ratio (brigatinib v BSC, or ceritinib v BSC) found only one reliable source (ASCEND-5) and the estimate was 1.0. I.e. ACSEND-5 found there to be no difference in effect on OS between ceritinib and BSC (16 month median follow-up). This means that the ceritinib OS curve in the company approach is in theory also the BSC curve: effectively over-riding the issue with the company choosing to measure declining treatment effect relative to ceritinib rather than BSC. However, a third aspect of the company's approach was the inclusion of a long tapering-off period (4.14 years) in which the ceritinib/BSC mortality rate is used to bring the post 'full effect' brigatinib mortality rate gradually down to that of the ceritinib/BSC rate. Whether or not this is a reasonable assumption compared to, perhaps, the immediate adoption of the ceritinib/BSC rate, is a clinical judgement. It does appear to be a generous interpretation of the committee's requirement. Indeed, the point at which the reduced brigatinib rate equals the ceritinib/BSC rate is 7.23 years from treatment commencement, and 4.14 years after the end of full treatment effect. Further, the company's use of a single time-point of full benefit discontinuation for all patients means that patients who are still on treatment after that time-point may be applied a treatment tapering early; and those whose treatment finishes long before the time point will continue to receive full benefit until that point, and then the tapered benefit afterwards. This is not conservative since a large proportion or patients remain on treatment before 161 weeks, and relatively few afterwards.

In summary, the ERG believe that the method adopted by the company to introduce a loss of treatment effect after the discontinuation of treatment is a generous interpretation of the committee request, leading to an underestimation of the ICER. There is a large amount of uncertainty in aspect of modelling, with strong assumptions likely to introduce inaccuracy in both directions.

In response to the committee's request for another method, the ERG provide here an analysis including various options, as well as a preferred base case option. We have adopted a method which adheres to the two components (1) and (2) described above. I.e. a rule determining a point(s) in time is from which starts a loss of full treatment effect, and this effect is measured relative to BSC, for both brigatinib and ceritinib strategies.

Table 1 describes the differences between the ERG and the company methods. In addition, we have provided a further analysis exploring the way in which ToT is calculated. These scenarios adopt actual ToT event data collected from ALTA, rather than using the PFS+ approach. These scenarios also include a 3 month period following treatment discontinuation of full treatment effect, and apply the mortality rate for BSC (time-varied) after this period ends (unlike the company method which graduates to this rate).

Table 1 ERG and Company methods for estimation of treatment effect after treatment discontinuation

	ERG approach (Cohort)	Company approach (Whole population)
Key parameter underlying method of determination of nature and period of effect	Time on treatment (variable)	Longest follow-up period of a single patient in the ALTA trial (148 weeks)
Measurement of ToT (determining who's on/off treatment)	Proxied by PFS curve + 1.53 months. Method deals with population on/off treatment as it changes over time	Relevant only to estimate the time at which only 1% patients remain alive (marking the time chosen at which mortality rates should equalise [7.2 years from treatment commencement]).
Period of full effect after treatment discontinuation	13 weeks	13 weeks (totalling 161 weeks of full effect)
Fraction of population attributed full effect after treatment discontinuation	Those who progress and discontinue treatment	An average is used to represent all patients
Mortality rate taken by *brigatinib* curve at the point of loss of effect	BSC	Ceritinib
Mortality rate taken by *ceritinib* curve at the point of loss of effect	BSC	N/A. Ceritinib mortality rate remains undiminished
Period of tapering to new mortality rate	No. BSc mortality rate immediately adopted	Yes, tapered to the time when only 1% of patients remain in brigatinib treatment
Curve convergence	Survival curves for strategies converge but will not intercept. The absolute effect of treatment on the population is persistent, albeit reducing with time.	
Parametric curve choices for attainment of plausible long term OS estimate at 5 and 10 years (only	PFS = Exponential OS = Log-Logistic ToT = PFS + 1.53months	PFS = Gompertz OS = Exponential ToT = PFS + 1.53 months

2.4 Use of the evidence base

The company have adopted the ERG's preferred selection of trial results for the PFS ITC. I.e. using the independent review committee datasets and dropping Study 101 (INV only) in favour of ASCEND-5. They have gone further by mirroring this selection for the OS ITC. I.e. they have opted for the meta-analysis of ALTA v ASC-2 MAIC and ALTA v ASC-5 MAIC. This is instead of using the pooled brigatinib data as in their previous base case (MA of the pooled brigatinib versus ASC-2 MAIC, and pooled brigatinib versus ASC-5 MAIC). The justification one of consistency across OS and PFS, otherwise time in pre-progression, and ToT, is increased relative to ceritinib without benefitting survival. This additional change to the studies used for benefit estimation in the model is not fully implemented in the company's revision however, since it is applied to the derivation of the HR (determining the ceritinib curve) but not the baseline strategy (brigatinib), which remains as pooled brigatinib. The ERG agree with the rule of consistency, both in the selection of trials but also in the use of one set of results, the IRC set. Therefore study 101 is excluded from PFS and OS, both in the determination of baseline brigatinib effectiveness, and its relative effectiveness compared to ceritinib. This decreases the company ICER by about £2,500 per QALY gained.

2.5 Post-progression utility

The company quote the ACD (p14) "The Committee concluded that the company's utility value for progressed disease on treatment was reasonable, but considered that a decline in utility was needed for people with progressed disease after treatment had stopped." The ERG interpretation of this conclusion is that the progressed disease utility value could be used to reasonably represent progressed disease on active treatment, but a new yet lower value should be given to progressed disease off active treatment. Previously the utility value 0.643 was given to progressed disease irrespective of active treatment, this was 0.15 less than the pre-progression value of 0.793 (a figure obtained from Chouaid *et al.*). In response t the committee's preference the company use data from the ALTA trial to estimate a new utility value for those progressed but on active treatment (0.732). They apply to this the 'Chouaid' decrement for progression to determine the utility for progressed and off active treatment (0.582). The impact on the ICER of this change versus the previous base case approach is an increase of £1,882. This impact has been verified by the ERG, and we are content that the new set of three utility values meet our interpretation of the committee's view.

2.6 Drug wastage

The company appear to have implemented this committee preference in the same way as the ERG. I.e. 50% recovery of unused product applied through adjustment to MDI. We are happy with this amendment.

2.7 Drug administration cost

The ERG could not source the NHS England estimation of administration cost (£120 per unit, 2017/18). NHS reference coats are currently available for 2016/17 only, published in November 2017. An equivalent figure from 2016/17 might be £164 (Code SB12Z, Deliver exclusively oral chemotherapy, Outpatient). In any case, the company state that a hospital based administration cost, as well as a home delivery administration cost (previously estimated by the ERG to be £42.50) is already included within their cost analysis. Indeed the company do include 1 hour of pharmacist time (£44, band 6 equivalent), which may therefore risk a degree of double counting. The company quote a committee preference for 30% hospital and 70% home, this would provide a weighted average of £79 for administration and delivery. This is £35 more than the company estimate, and more than estimates for administration/delivery of oral chemotherapies in previous TAs. The addition of this cost has minimal impact on the ICER, just an increase of £426 (1%). The ERG would be content for no change to the company's original modelling in respect to this aspect; we have not implemented it in this set of ERG results.

3 Result set for Company method

Table 2 presents the company's result for their revised base case without the application of PAS arrangements.

Table 2 Summary incremental results for revised company base case (without PASs)

Strategy	Total Costs	Total Life Years	Total QALYs	Inc Costs	Inc Life Years	Inc QALYs	ICER
Brigatinib	£123,885	3.29	2.23				
Ceritinib	£48,522	1.71	1.11	£75,364	1.57	1.12	£67,449

4 Result set for ERG method

This method assumes that treatment discontinuation is 1.53 months after progression. Results are presented in Figure 3.

Table 3 Summary results with implementation of a loss of treatment benefit after treatment discontinuation

OS curve choice	PFS curve choice	5 year OS brigatinib	10 year OS brigatinib	ICER (£/QALY) w/o PAS 750mg dose ceritinib	No.
Exponential	Gompertz	13.39%	0.96%	£164,952	1
	Exponential	13.96%	1.05%	£191,848	2
	Gamma	13.63%	1.00%	£178,121	3
	Weibull	13.56%	0.99%	£173,265	4
	Log-logistic	14.30%	1.16%	£193,238	5
Log-logistic	Gompertz	17.39%	4.19%	£142,401	6
	Exponential*	17.90%	4.44%	£169,366	7
	Gamma	17.62%	4.31%	£153,026	8
	Weibull	17.55%	4.27%	£149,090	9
	Log-logistic	18.22%	4.71%	£187,796	10
Gamma	Gompertz	12.13%	0.69%	£169,577	11
	Exponential	12.68%	0.76%	£195,238	12
	Gamma	12.36%	0.72%	£183,629	13
	Weibull	12.28%	0.71%	£178,471	14
	Log-logistic	13.02%	0.85%	£194,739	15
Weibull	Gompertz	11.99%	0.64%	£170,236	16
	Exponential	12.55%	0.70%	£195,400	17
	Gamma	12.22%	0.66%	£184,349	18
	Weibull	12.15%	0.66%	£179,171	19
	Log-logistic	12.88%	0.79%	£194,883	20
Gompertz	Gompertz	12.97%	0.80%	£166,728	21
	Exponential	13.53%	0.88%	£192,880	22
	Gamma	13.21%	0.83%	£180,158	23
	Weibull	13.13%	0.82%	£175,213	24
	Log-logistic	13.88%	0.98%	£193,668	25

*ERG base case in primary analysis

Table 4 Threshold analysis exploring alternative hazard ratios for BSC versus ceritinib (HR = 1.0 in the ERG base case)

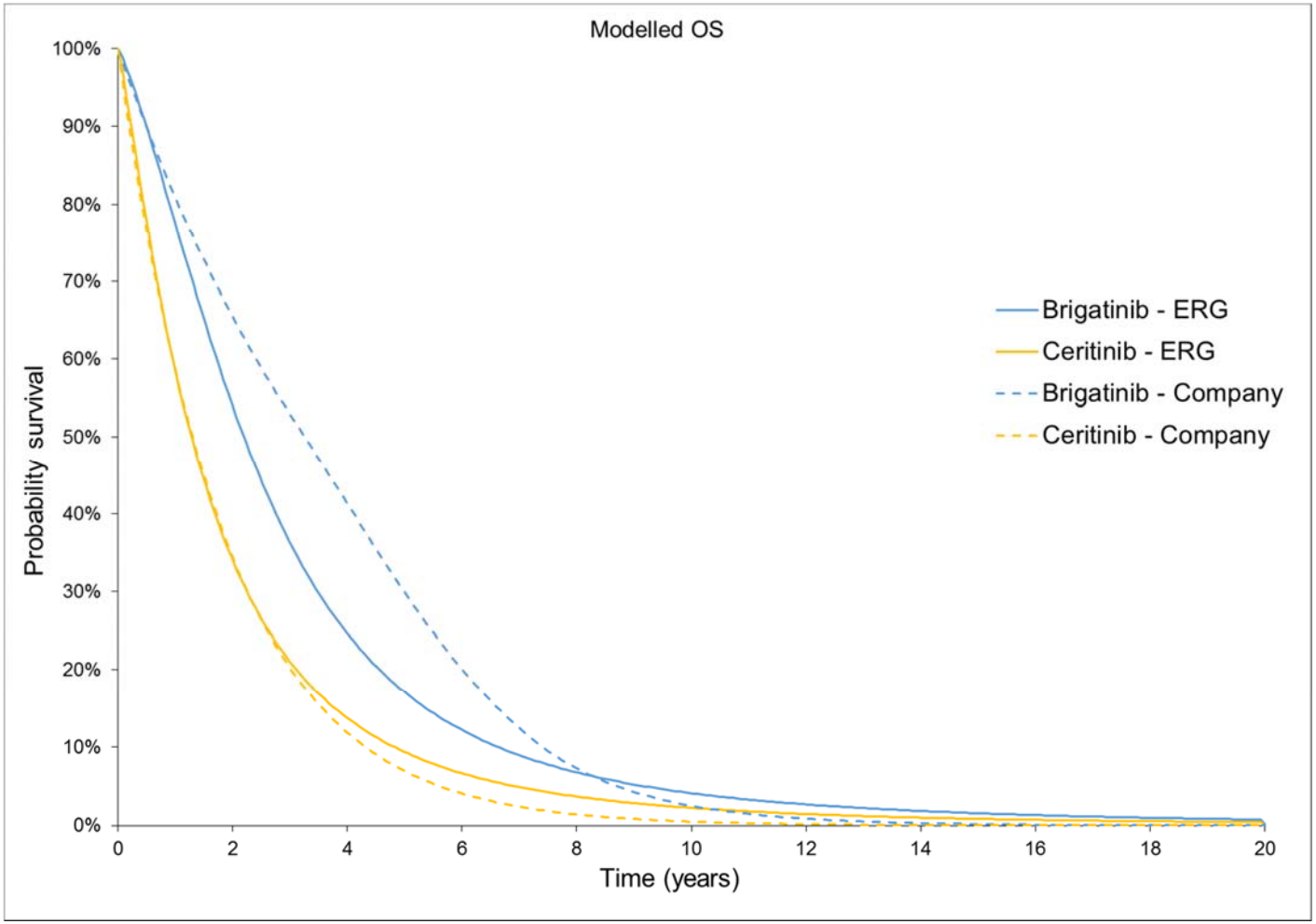
OS curve choice	PFS curve choice	HR ceritinib vs BSC	5 year OS brigatinib	10 year OS brigatinib	ICER (£/QALY) w/o PAS 750mg dose ceritinib	No.
Log-logistic	Exponential	1	17.90%	4.44%	£169,366	1
		0.8	12.94%	2.28%	£166,834	2
		0.6	7.56%	0.75%	£161,100	3
		0.4	2.60%	0.08%	£143,916	4
		0.2	0.11%	<0.01%	£119,233	5
		0.01	<0.01%	<0.01%	£46,561	6
Exponential	Gompertz	1	13.39%	0.96%	£164,952	7
		0.8	9.00%	0.34%	£162,979	8
		0.6	4.65%	0.06%	£155,825	9
		0.4	1.25%	<0.01%	£144,654	10
		0.2	0.03%	<0.01%	£119,048	11
		0.01	<0.01%	<0.01%	£54,623	12

This threshold analysis demonstrates that irrespective of the hazard ratio between BSC and ceritinib, it is unlikely, using the ERG method for loss of treatment effect, that brigatinib is cost-effective at £50,000 per QALY gained.

5 Survival curves

A comparison of company and ERG base case survival curves are presented in Figure 3.

Figure 3 Overall survival curves for brigatinib, ceritinib and BSC, incorporating loss of treatment effect (ERG method)



*The mortality rate of the ERG BSC strategy is the same as the ERG ceritinib strategy (HR BSC v ceritinib = 1.0, ACSEND-5), it cannot be seen.

6 Further ERG scenarios

This method assumes that treatment discontinuation is based on the time on treatment (ToT) endpoint from ALTA rather than the PFS+1.53 months approach.

Table 5 Summary results with implementation of a loss of treatment benefit after treatment discontinuation

OS curve choice	PFS curve choice	ToT option for brigatinib*	5 year OS brigatinib	10 year OS brigatinib	ICER (£/QALY) w/o PAS 750mg dose ceritinib	No.
Log-logistic	Exponential	PFS+1.53 months	17.90%	4.44%	£169,366	1**
		ToT Gamma	17.56%	4.39%	£125,779	2
		ToT Exponential	17.53%	4.31%	£118,299	3
		ToT Weibull	17.62%	4.43%	£125,266	4
		ToT Gen. Gamma	17.37%	4.22%	£124,407	5
		ToT Gompertz	17.65%	4.46%	£120,718	6

*The ToT approach for ceritinib follows that for brigatinib, with the PFS HR for brigatinib vs ceritinib applied. When ToT for brigatinib is equivalent to the fitted PFS curve + 1.53 months, ToT for ceritinib is equivalent to PFS for ceritinib (i.e. the brigatinib PFS curve with the HR applied) + 1.53 months. **This is the ERG base case, given here for reference.

The ERG have also explored scenarios in which treatment benefit discontinuation is based on progression status, rather than on whether the patients are receiving treatment. These give similar ICER results to those in Table 5. As a general point, it is worth noting that even though ToT is not used to determine loss of treatment benefit in these progression status analyses, the choice of approach for ToT (i.e. PFS + 1.53 months, or from the ToT parametric curve) makes a substantial difference to the ICER (though not to the 5 year & 10 year OS estimates) because ToT drives drug costs. This is demonstrated by the difference between ICER 1 and ICERs 2-6 in Table 5.

7 Other relevant issues

End of life qualification

The ERG believe that qualification is met using either the company's revised base case or the ERG's revised base case.

Use of observational data to fit parametric curves

We note to the committee that the portion of the KM data used by the company for the fitting of the brigatinib parametric curve is explicitly specified by the company and we cannot verify that the complete set of observations were used - later potentially unfavourable observations are not apparent in the company model.

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

A Single Technology Appraisal

Erratum to

APPENDIX – No PAS information

ERG Analyses for ACM2

Originally prepared 7 November 2018

Erratum 15 November 2018

- Correction of ERG error in coding of PFS estimates

Ex post note. Errors in the company code for ToT estimation were identified by the ERG after the second appraisal committee meeting. Therefore figures presented in this erratum of data prepared for ACM2 (Tables 4, 5, 6) have subsequently been revised.

Table 1 ERG and Company methods for estimation of treatment effect after treatment discontinuation

	ERG approach (Cohort)	Company approach (Whole population)
Key parameter underlying method of determination of nature and period of effect	Time on treatment (variable)	Longest follow-up period of a single patient in the ALTA trial (148 weeks)
Measurement of ToT (determining who's on/off treatment)	Proxied by PFS curve + 1.53 months. Method deals with population on/off treatment as it changes over time	Relevant only to estimate the time at which only 1% patients remain on-treatment (marking the time chosen at which mortality rates should equalise [7.2 years from treatment commencement]).
Period of full effect after treatment discontinuation	13 weeks	13 weeks (totalling 161 weeks of full effect)
Fraction of population attributed full effect after treatment discontinuation	Those who progress and discontinue treatment	An average is used to represent all patients
Mortality rate taken by *brigatinib* curve at the point of loss of effect	BSC	Ceritinib
Mortality rate taken by *ceritinib* curve at the point of loss of effect	BSC	N/A. Ceritinib mortality rate remains undiminished
Period of tapering to new mortality rate	No. BSc mortality rate immediately adopted	Yes, tapered to the time when only 1% of patients remain in brigatinib treatment
Curve convergence	Survival curves for strategies converge but will not intercept. The absolute effect of treatment on the population is persistent, albeit reducing with time.	
Parametric curve choices for attainment of plausible long term OS estimate at 5 and 10 years (only	PFS = Exponential OS = Log-Logistic ToT = PFS + 1.53months	PFS = Gompertz OS = Exponential ToT = PFS + 1.53 months

3. Result set for ERG method

This method assumes that treatment discontinuation is 1.53 months after progression. Results are presented in **Error! Reference source not found.**.

Table 2 Summary results with implementation of a loss of treatment benefit after treatment discontinuation

OS curve choice	PFS curve choice	5 year OS brigatinib	10 year OS brigatinib	ICER (£/QALY) w/o PAS 750mg dose ceritinib	No.
Exponential	Gompertz	13.39%	0.96%	£109,478	1
	Exponential	13.96%	1.05%	£121,627	2
	Gamma	13.63%	1.00%	£114,628	3
	Weibull	13.56%	0.99%	£112,850	4
	Log-logistic	14.30%	1.16%	£126,879	5
Log-logistic	Gompertz	17.39%	4.19%	£98,732	6
	Exponential*	17.90%	4.44%	£110,342	7
	Gamma	17.62%	4.31%	£103,429	8
	Weibull	17.55%	4.27%	£101,787	9
	Log-logistic	18.22%	4.71%	£124,198	10
Gamma	Gompertz	12.13%	0.69%	£111,063	11
	Exponential	12.68%	0.76%	£123,922	12
	Gamma	12.36%	0.72%	£116,420	13
	Weibull	12.28%	0.71%	£114,572	14
	Log-logistic	13.02%	0.85%	£127,533	15
Weibull	Gompertz	11.99%	0.64%	£111,369	16
	Exponential	12.55%	0.70%	£124,106	17
	Gamma	12.22%	0.66%	£116,731	18
	Weibull	12.15%	0.66%	£114,882	19
	Log-logistic	12.88%	0.79%	£127,576	20
Gompertz	Gompertz	12.97%	0.80%	£110,221	21
	Exponential	13.53%	0.88%	£122,470	22
	Gamma	13.21%	0.83%	£115,421	23
	Weibull	13.13%	0.82%	£113,627	24
	Log-logistic	13.88%	0.98%	£127,060	25

Table 3 Threshold analysis exploring alternative hazard ratios for BSC versus ceritinib (HR = 1.0 in the ERG base case)

OS curve choice	PFS curve choice	HR ceritinib vs BSC	5 year OS brigatinib	10 year OS brigatinib	ICER (£/QALY) w/o PAS 750mg dose ceritinib	No.
Log-logistic	Exponential	1	17.90%	4.44%	£110,342	1
		0.8	12.94%	2.28%	£115,564	2
		0.6	7.56%	0.75%	£122,398	3
		0.4	2.60%	0.08%	£117,633	4
		0.2	0.11%	<0.01%	£105,658	5
		0.01	<0.01%	<0.01%	£48,688	6
Exponential	Gompertz	1	13.39%	0.96%	£109,478	7
		0.8	9.00%	0.34%	£111,918	8
		0.6	4.65%	0.06%	£115,706	9
		0.4	1.25%	<0.01%	£118,157	10
		0.2	0.03%	<0.01%	£106,170	11
		0.01	<0.01%	<0.01%	£56,220	12

This threshold analysis demonstrates that irrespective of the hazard ratio between BSC and ceritinib, it is unlikely, using the ERG method for loss of treatment effect, that brigatinib is cost-effective at £50,000 per QALY gained.

6. Further ERG scenarios

This method assumes that treatment discontinuation is based on the time on treatment (ToT) endpoint from ALTA rather than the PFS+1.53 months approach.

Table 4 Summary results with implementation of a loss of treatment benefit after treatment discontinuation

OS curve choice	PFS curve choice	ToT option for brigatinib*	5 year OS brigatinib	10 year OS brigatinib	ICER (£/QALY) w/o PAS 750mg dose ceritinib	No.
Log-logistic	Exponential	PFS+1.53 months	17.90%	4.44%	£110,342	1**
		ToT Gamma	17.56%	4.39%	£26,383	2
		ToT Exponential	17.53%	4.31%	£20,362	3
		ToT Weibull	17.62%	4.43%	£26,144	4
		ToT Gen. Gamma	17.37%	4.22%	£24,883	5
		ToT Gompertz	17.65%	4.46%	£22,528	6

*The ToT approach for ceritinib follows that for brigatinib, with the PFS HR for brigatinib vs ceritinib applied. When ToT for brigatinib is equivalent to the fitted PFS curve + 1.53 months, ToT for ceritinib is equivalent to PFS for ceritinib (i.e. the brigatinib PFS curve with the HR applied) + 1.53 months. **This is the ERG base case, given here for reference.

The ERG have also explored scenarios in which treatment benefit discontinuation is based on progression status, rather than on whether the patients are receiving treatment. These give similar ICER results to those in Table 4. As a general point, it is worth noting that even though ToT is not used to determine loss of treatment benefit in these progression status analyses, the choice of approach for ToT (i.e. PFS + 1.53 months, or from the ToT parametric curve) makes a substantial difference to the ICER (though not to the 5 year & 10 year OS estimates) because ToT drives drug costs. This is demonstrated by the difference between ICER 1 and ICERs 2-6 in Table 4.

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

A Single Technology Appraisal

ERG Analyses for ACM3

23 November 2018

(amended 30 November 2018 to include section 5)

Contents

1 ERG Comment on Issues Arising

1.1 Overview

The company's model at submission (revised with Sept 2017 ALTA data cut on 14 May 2018) was subsequently adapted by the company in their ACD response to account for treatment benefit discontinuation (TBD). This was done on the request of the committee at ACM1 (12 July) and was supplied to the ERG for review ahead of ACM2 (1 November). The ERG provided a critique of the company's approach and included an alternative approach for implementing loss of treatment benefit. Both the company and ERG incorporate the latest available ALTA trial data-cut (September 2017).

Amidst a lack of clarity regarding the company's method behind their TBD adaptation the ERG, until now, were only able to speculate as to the rationale behind chosen approaches and assumptions. The brigatinib mortality rate is adjusted only during the extrapolated period, and then by a constant linear decrease is applied for 4.14 years, the period in which the remaining ~25% of patients remaining on treatment at the end of follow-up are all predicted to have discontinued brigatinib (<1%). The constant linear decrease in mortality approximates the rate of brigatinib discontinuation through this period. The period of extended post-discontinuation benefit of brigatinib is 3 months, this is included by modelling a delay to the start of mortality rate decline.

The ERG understands the merits of this this approach, which is reasonable, but issues remains.

1) Both TKIs must be treated in the same way. Post discontinuation waning should be modelled for both TKIs, and therefore their respective mortality rates should be adjusted to the rate of no TKI treatment, or BSC.

2) The company's use of an arbitrary decline in mortality rate to simulate the decline in patients alive on treatment in the unobserved period (a constant linear decline) is an approximation which introduces unnecessary inaccuracy. By adjusting mortality rates at each model cycle, there can be a direct link between patients discontinuing treatment (ToT curve), and the time at which loss of effect begins.

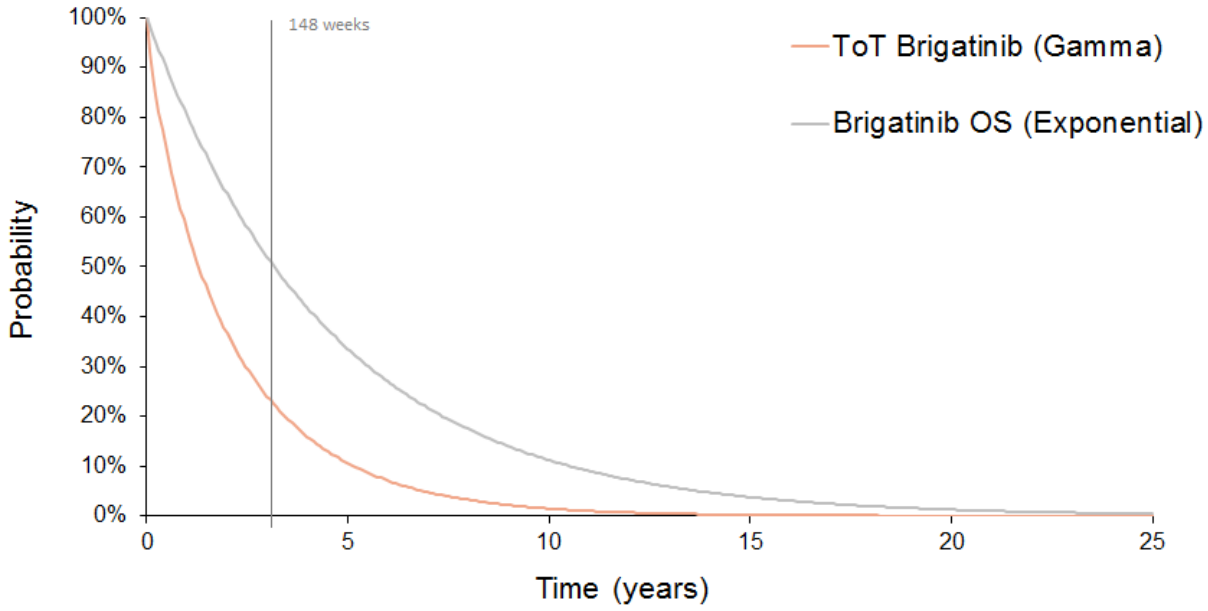
The company and ERG approaches are discussed in more detail in section 1.3.

1.2 Rationale for Treatment benefit discontinuation (TBD)

It is expert clinical opinion that the size of brigatinib effect should be adjusted in this appraisal according to whether patients remain on treatment, such that there is some continuation of treatment effect for a period after treatment discontinuation. Therefore, in modelling the adjustment of post-treatment mortality rate a link between time on treatment and time to event is required. In this case the company, and ERG, consider only the effect on mortality, and exclude consideration of progression, since most patients will progress before treatment discontinuation.

It is reasonable to assume that during a period of observed effect (from here on referring to the within trial observation period), any loss of treatment benefit after the discontinuation of that treatment is inherently captured in the overall survival measure. However, the survival after the trial period is an extrapolation using a parametric distribution, fitted independently of the underlying proportion remaining on treatment. Unfettered, this may introduce imprecision because the treatment-survival relationship during observation continues unchanged from observation into extrapolation, whilst the proportion on-treatment diminishes faster than the proportion alive. Indeed, the ratio of the proportion alive on treatment versus the proportion alive declines (see Figure 1), and this underlies the rationale for adjusting the extrapolated mortality rate for treatment discontinuation.

Figure 1 Time on treatment and OS for brigatinib strategy (company model)



1.3 Contrast of company and revised ERG TBD methods for OS modification

1.3.1 Base case

The company's TBD approach maintains the in-trial/observed brigatinib survival by only adjusting mortality rate for the unobserved/extrapolated phase of the fitted exponential curve. I.e. after week 148. In this period the method adjusts brigatinib mortality rate commensurate with the rate of treatment discontinuation for those remaining on treatment, except that adjustment begins after a three month delay. This is the period of 'extension of effect' post-discontinuation. At 7.23 years the brigatinib mortality rate becomes equal to the rate of the company's reference strategy, the ceritinib strategy. The ToT curve predicts a period of 4.14 years before all but 1% of patients are no longer on treatment. Maintaining mortality rate during the observed period has the benefit of producing a modelled (exponential) median OS close to that of the ALTA trial OS (38.6 versus 34.1 months, respectively); it also implies that observed mortality inherently incorporates any reduced benefit on survival owing to brigatinib discontinuation. However, brigatinib mortality rate for the 54% (interpolated value) of people surviving beyond the observed period is open to much more uncertainty – see rationale in section 1.2. For this period the ERG believes that (1), the new rate should be relative to the biological scenario of no TKI treatment effect, or BSC; and (2), moment of adjustment of mortality rate should be directly linked to the rate of treatment discontinuation. In these key aspects of TBD methodology, the company departs from ERG preference. By adjusting only brigatinib mortality rate the company imply that ceritinib strategy mortality rate does not diminish as a result of discontinuations during the extrapolated period. By calculating the rate of adjustment of the brigatinib mortality rate using the ceritinib mortality rate (unadjusted) – rather than a BSC rate - the company imply that loss of brigatinib effect is limited to its additional effect over ceritinib. The company should not claim that this is a conservative aspect of their method.

The ERG TBD approach does not have the disadvantage of uncoupling the relationship between ToT (when discontinuations occur) and when waning of effect (mortality rate) begins. Neither does it limit the loss of brigatinib effect to only its additional survival benefit over ceritinib. Like the company model, the ERG method delays by 3 months mortality rate loss after discontinuation, but the ERG method maintains the link between ToT and mortality by implementing the loss to at the model cycle in which patients discontinue treatment. This is important given that about half of patients in the brigatinib strategy are predicted to be alive at week 161 (3.09 years), and about a quarter are predicted to remain on-treatment.

Regarding the creation of a BSC mortality curve, there is an absence of high-quality comparative evidence, so a range of BSC versus ceritinib hazard ratios are explored and presented. ASCEND-5 is a relevant RCT but reports an early tentative HR = 1.0 ceritinib versus BSC and chemotherapy. NICE TA395 included an indirect comparison of ceritinib versus BSC and is the preferable source.(1) A hazard ratio is not used in the modelling but the indirect comparison

produces1.35 additional life-years for ceritinib versus BSC, indicating clear survival benefit. This revised ERG base case selects a hazard ratio of 0.75, which is probably conservative.

In respect to the accumulation of costs, specifically the acquisition cost of the TKIs, these were calculated the same general way in both models. That is, TKI costs are accumulated only when patients are on treatment, and this is implemented every model cycle. However, in the company model, ToT is proxied by PFS plus 1.53 months. This additional period represents treatment post-progression and is the difference between the median time on brigatinib treatment in ALTA and the median time to progression in ALTA (Investigator dataset, February 2017 data-cut). In this revised ERG base case the direct observation of ToT (using KM plots based on observation in ALTA) is used to drive TKI costs. PFS is retained to drive utility, concomitant medication and resource use cost estimates. The complete set of differences between the company model and the revised ERG model are bulleted below in section 1.4.

1.3.2 Alternative scenarios

BSC versus ceritinib HR

BSC versus ceritinib hazard ratios ranging from 1.0 to 0.1 are explored and presented in Table 7. The base case value is 0.75.

Period of post-treatment benefit

The period of post-treatment benefit is tested across the range 0 to 12 months and results are presented in Table 9. The base case period is 3 months.

Maximum treatment period

In the company model the time when <1% patients remain on brigatinib treatment is 7.23 years; and on ceritinib treatment is 4.22 years. An ERG scenario analysis explores alternatives to this maximum treatment time. The first alternative scenario limits TKI treatment, and thereby its benefit over BSC, to 1 year after week 161 (week 213). TKI treatment costs are also capped to this point. A second alternative caps TKI treatment to the time at which >99% of patients have progressed, which is strategy specific. Again, TKI treatment costs are capped to these points. See Table 10. The base case has no maximum treatment duration.

1.4 Revised ERG model

This revised ERG model is a combination of company and ERG preferences for the TBD adaptation, along with earlier committee preferences not introduced into the company model. Differences between this and the company base case are described below, and their respective impact is presented sequentially in Table 6.

1. **Brigatinib 90 mg tablet cost**: The ERG base case uses the brigatinib starter pack unit cost of £4,900 for the first treatment cycle (7 x 90mg tablets and 21 x 180mg tablets). It does not reduce the cost of 90mg brigatinib for its use during the initiation of treatment as the company have done. The unit cost of £4,900 was confirmed by the company in their *Response to the ACD* document.
2. **OS and PFS evidence base:** The company responded to the committee request to favour ASCEND-5 over Study 101 for the estimation of the relative PFS effect (ceritinib versus brigatinib hazard ratio). The company went further by mirroring these sources for the estimation of the OS hazard ratio. However, in both cases the company base case retains Study 101 to estimate brigatinib's PFS and OS, as pooled data is used. For consistency, we use only ALTA as the evidence source for brigatinib PFS and OS.
3. **Treatment benefit discontinuation:** The ERG base case adjusts TKI mortality rates during the extrapolated period (plus 13 weeks). This is aligned with the company preference for brigatinib, however we do not use a constant linear decline in mortality rate from week 161 to the point of <1% patients on treatment (4.14 years); instead we retain a direct link between ToT (extrapolated from ALTA KM plot) and the moment the BSC mortality rate is preferred to begin (after 13 weeks). Similar to the company base case 13 weeks of continued brigatinib benefit is awarded to those patients remaining on-treatment, as and when they discontinue treatment. After which the BSC mortality rate is applied. The ERG base case assumes a BSC versus ceritinib hazard ratio of 0.75. This is explored in a scenario analysis.
4. **Exponential distribution fitted to PFS data:** Preferred by the ERG because of its closer fit to both brigatinib and ceritinib observed data. The company preferred the Gompertz distribution.
5. **Log-logistic distribution fitted to OS data:** Preferred by the ERG because it is both a good fit to the observational data and produces 10-year OS estimates closer to committee expectation (4.4% at 10 years). The company use the exponential distribution, but this produces low long-term OS estimates (2.3% at 10 years).
6. **Observed ToT to estimate TKI costs and TBD:** ToT has become an increasingly important parameter given the TBD adaptation; and interpolated/extrapolated observation is

preferred to indirect approximation. Therefore, the ERG uses a gamma distribution on observed ToT to inform TKI costs and TKI discontinuation, rather than PFS + 1.53 months. The PFS curve is retained to inform cohort movement between health states, and therefore drives utility and non-TKI cost estimation (resource use and concomitant medications).

Previously agreed between company, committee and ERG are the following aspects:

a) Modifications to utility approach with the division of the progressed state into progressed on-treatment and progressed off-treatment.

Table 1 Company modification of utility estimation

Previous		**Current**	
Pre-progression	0.793	Pre-progression	0.793
Post-progression	0.643	Post-progression on treatment	0.732
		Post-progression off treatment	0.582

b) Fifty percent recovery of wasted drug (previously 100% recovery).

c) No amendment to company costing of brigatinib administration and delivery cost. Remains the equivalent of 1 hour of band 6 pharmacist time (£44).

1.5 Errors identified in model code

1.5.1 Previous PFS estimates in ERG model

ERG have provided an erratum of corrections to incremental results in the report titled ‘ERG analysis for ACM2’ which relate to coding of the PFS estimate.

1.5.2 Previous ToT estimates in company model (effecting ERG base case only)

The ERG has amended company coding for the estimation of brigatinib and ceritinib ToT, which is relevant to the ERG base case but does not impact the company base case.

1.5.3 Other

The company identified two very small coding issues which have a minimal impact on model results. The first concerns the decrement applied for adverse events; the second concerns the weighting the brigatinib mortality rate. Results in this report are inclusive of these amendments.

2 Company Results

2.1 Summary results (presented previously by the company)

Table 2 Summary incremental results - deterministic

Technology	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
Brigatinib	28.99%	2.28%				
Ceritinib	6.46%	0.42%	£75,364	1.57	1.12	£67,449

Table 3 Summary incremental results - probabilistic

Technology	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
Brigatinib	NR	NR				
Ceritinib	NR	NR	£89,456	-	1.16	£76,855

NR = Not Reported

3 ERG Results

3.1 Summary results ('Compromise model')

Table 4 Summary incremental results - deterministic

Technology	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
Brigatinib	21.13%	3.32%				
Ceritinib	7.17%	1.05%	£97,934	1.36	1.07	£91,123

Table 5 Summary incremental results – probabilistic

Technology	Total costs w/o PAS (£)	Total QALYs PAS (£)	Incremental costs w/o PAS (£)	Incremental QALYs	ICER w/o PAS (£/QALY)
Brigatinib	£136,825	2.14			
Ceritinib	£44,315	1.15	£92,510	0.98	£94,226

Table 6 Cumulative impact of revisions to company base case

Revision	ICER with individual revision w/o PAS	Individual impact w/o PAS	ICER with cumulative revisions w/o PAS	Cumulative impact w/o PAS
None (Company base case)	£67,449		£67,449	-
Starter pack cost	£67,704	£255	£67,704	£255
Data source for OS & PFS distributions	£70,075	£2,626	£70,324	£2,875
TBD method	£75,696	£5,621	£78,987	£11,538
PFS distribution	£75,316	£7,868	£88,446	£20,997
OS distribution	£57,771	-£9,678	£77,767	£10,318
ToT distribution	£86,356	£18,907	£83,350	£15,901
OS HR ceritinib vs BSC	£73,660	£6,211	£91,123	£23,674

3.2 Scenario analyses

3.2.1 Ceritinib versus brigatinib hazard ratio

Table 7 ICERs for alternative hazard ratios for BSC versus ceritinib

OS HR BSC vs Ceritinib	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
1	26.24%	6.50%	£99,302	1.57	1.19	£83,350
0.95	25.36%	5.84%	£99,037	1.53	1.17	£84,738
0.9	24.41%	5.19%	£98,766	1.48	1.15	£86,204
0.85	23.40%	4.55%	£98,492	1.44	1.12	£87,754
0.8	22.30%	3.92%	£98,215	1.40	1.10	£89,393
*0.75**	21.13%	3.32%	£97,934	1.36	1.07	£91,123
0.7	19.86%	2.74%	£97,650	1.32	1.05	£92,951
0.65	18.49%	2.19%	£97,365	1.27	1.03	£94,880
0.6	17.01%	1.69%	£97,078	1.23	1.00	£96,916
0.55	15.42%	1.25%	£96,293	1.19	0.98	£98,668
0.5	13.71%	0.87%	£94,393	1.14	0.95	£99,616
0.4	11.87%	0.55%	£92,082	1.10	0.92	£100,320
0.3	9.92%	0.32%	£89,550	1.06	0.89	£101,011
0.2	5.80%	0.06%	£84,000	0.97	0.82	£102,265
0.1	1.99%	0.00%	£77,988	0.88	0.75	£103,448

*ERG base case – HR of 0.75 is chosen as a best guess estimate.

3.2.2 Period of post-treatment benefit

Table 8 ICERs for alternative periods of post-treatment benefit

Time after trial period at which TBD begins	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
0 months	19.12%	3.00%	£97,362	1.27	1.03	£94,931
3 months (ERG base case)	21.13%	3.32%	£97,934	1.36	1.07	£91,123
6 months	22.77%	3.58%	£98,354	1.42	1.11	£88,541
9 months	24.54%	3.85%	£98,765	1.48	1.15	£86,173
12 months	26.44%	4.15%	£99,166	1.54	1.18	£84,000

3.2.3 Combination of alternative BSC v ceritinib HRs and post-treatment benefit periods

Table 9 ICERs for alternative HRs and periods of post-treatment benefit

OS HR ceritinib vs BSC	Time after trial period at which TBD begins	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
1	0 months	24.61%	6.09%	£98,714	1.48	1.14	£86,529
	3 months	26.24%	6.50%	£99,302	1.57	1.19	£83,350
	12 months	30.33%	7.51%	£100,534	1.75	1.30	£77,510
0.875	0 months	22.08%	4.50%	£98,050	1.38	1.08	£90,433
	3 months	23.91%	4.87%	£98,630	1.46	1.13	£86,969
	12 months	28.59%	5.83%	£99,863	1.65	1.24	£80,541
0.75	0 months	19.12%	3.00%	£97,362	1.27	1.03	£94,931
	3 months	21.13%	3.32%	£97,934	1.36	1.07	£91,123
	12 months	26.44%	4.15%	£99,166	1.54	1.18	£84,000
0.625	0 months	15.63%	1.70%	£96,658	1.17	0.97	£100,114
	3 months	17.77%	1.94%	£97,222	1.25	1.01	£95,884
	12 months	23.70%	2.59%	£98,451	1.44	1.12	£87,930
0.5	0 months	11.56%	0.73%	£92,617	1.06	0.90	£103,273
	3 months	13.71%	0.87%	£94,393	1.14	0.95	£99,616
	12 months	20.11%	1.27%	£97,318	1.33	1.06	£92,060

3.2.4 Maximum treatment duration

Table 10 ICERs for alternative maximum treatment periods

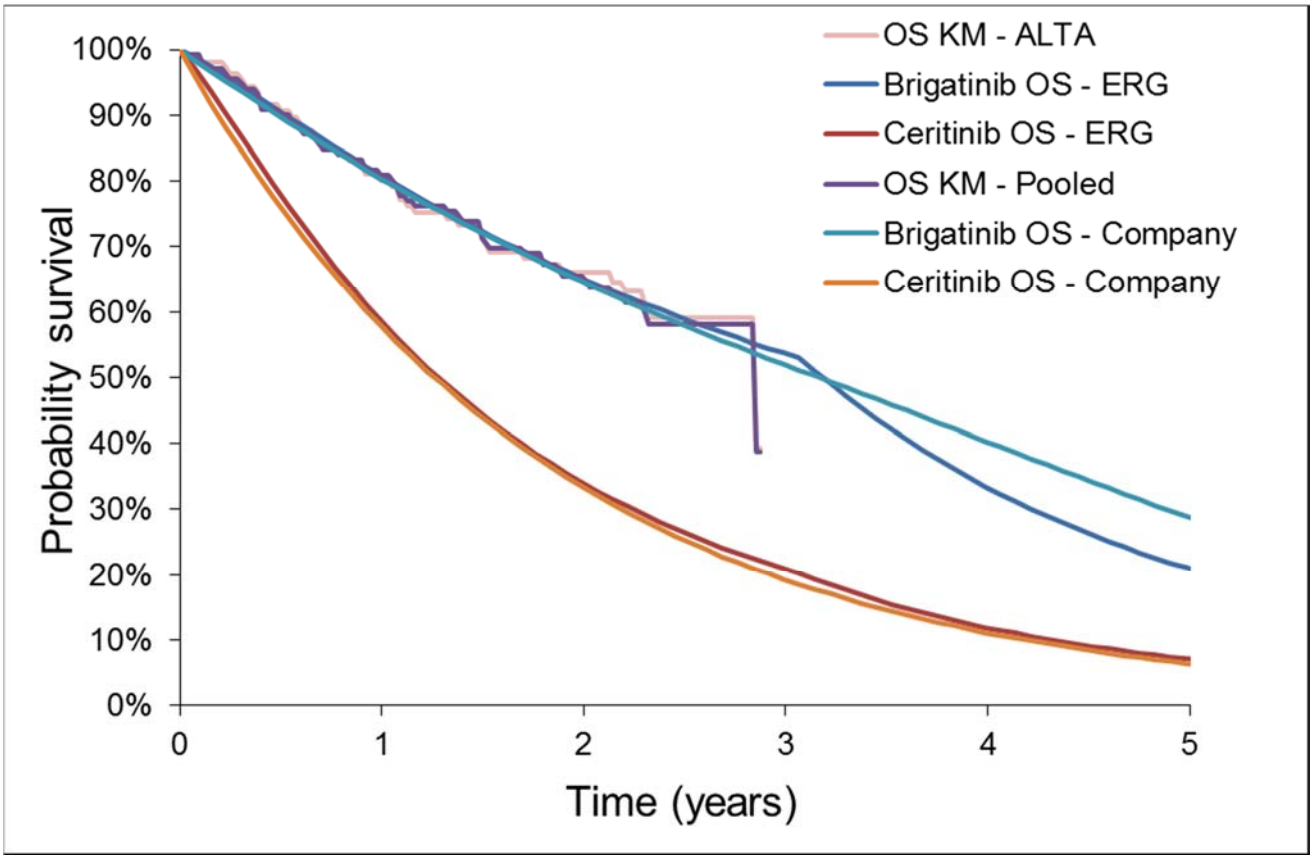
Time point (weeks)	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
None (ERG base case)	21.13%	3.32%	£97,934	1.36	1.07	£91,123
572 [a]	21.13%	3.32%	£96,925	1.36	1.07	£90,321
480 [b]	21.13%	3.31%	£95,791	1.36	1.07	£89,399
377	21.13%	3.26%	£92,920	1.36	1.07	£87,038
213 [c]	20.25%	2.98%	£78,494	1.32	1.04	£75,471

[a] Time at which <1% of patients remain on treatment, [b] Time at which >99% of patients have progressed, [c] 161 weeks + 1 year.

4 Comparative Survival Curves

A comparison of company and ERG base case survival curves are presented in Figure 2.

Figure 2 Overall survival curves for brigatinib, ceritinib and BSC, incorporating loss of treatment effect (Company and ERG base cases)



5 Additional scenario added on 30th November 2018

The scenarios presented in Table 11 give ERG model ICERs for a range of brigatinib versus ceritinib hazard ratios. Scenario 1 is for reference and represents the ERG model base case. In each scenario the specified hazard ratio is applied to the KM fitted brigatinib ToT curve (gamma) to produce the ceritinib ToT curve. In the ERG model the ToT curves inform mean per person total TKI cost, and the treatment benefit discontinuation adaptation.

Table 11 ToT HR brigatinib vs ceritinib

ToT curve choice	ToT HR brigatinib vs ceritinib	Median ceritinib ToT (months)	ICER w/o PAS (£/QALY)	No.
Gamma	0.282*	3.68	£91,123	1 (BC)
	0.312	4.60	£87,912	2
	0.366	5.52	£82,391	3
	0.424	6.44	£76,475	4
	0.481	7.36	£70,500	5
	0.537	8.28	£64,423	6
	0.592	9.20	£58,237	7

*HR used in ERG base case (ACM3)

An exact match of modelled and observed medians is not achievable due to the cycle length of 4 weeks, but since the modelled estimates of OS and PFS medians (both company and ERG) tend to be lower than trial medians, and the company's modelled ToT median is only 5.52 months, the Gamma based HR of 0.481 may represent reasonable alternative to the base case HR of 0.282. Table 12 presents trial and modelled medians for the outcome measures used in the modelling.

Table 12 Trial and modelled medians for the outcome measures

	Median OS (months)	Median PFS (months)	Median ToT (months)
ASCEND-2[2] (INV)	14.9 (95% CI: 13.5-not evaluable)	5.7 (95% CI: 5.4-7.6)	8.8
ASCEND-5[3] (INV)	18.1 (95% CI: 13.4-23.9)	5.4 (95% CI: 4.1-6.9)	6.99
Company BC	15.64	4.60	5.52
ERG BC	15.64	5.52	3.68

References: 2. Crino L, Ahn MJ, De Marinis F, Groen HJ, Wakelee H, Hida T, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. J Clin Oncol. 2016;34(24):2866-73.; 3. Shaw AT, Kim TM, Crinò L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK -rearranged non-small-cell lung cancer previously given chemotherapy and

crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. The Lancet Oncology. 2017;18(7):874-86.

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2. Crino L, Ahn MJ, De Marinis F, Groen HJ, Wakelee H, Hida T, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. J Clin Oncol. 2016;34(24):2866-73.
3. Shaw AT, Kim TM, Crinò L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK -rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. The Lancet Oncology. 2017;18(7):874-86.

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

A Single Technology Appraisal

ERG Analyses for ACM3

23 November 2018

(amended 30 November 2018 to include section 5)

Erratum – 8 Jan 2019

3 ERG Results

3.1 Summary results ('Compromise model')

Table 1 Summary incremental results - deterministic

Technology	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
Brigatinib	21.13%	3.32%				
Ceritinib	7.17%	1.05%	£100,255	1.36	1.07	£93,283

Table 2 Summary incremental results – probabilistic

Technology	Total costs w/o PAS (£)	Total QALYs PAS (£)	Incremental costs w/o PAS (£)	Incremental QALYs	ICER w/o PAS (£/QALY)
Brigatinib	£136,772	2.14			
Ceritinib	£41,854	1.15	£94,918	0.98	£97,053

Table 3 Cumulative impact of revisions to company base case

Revision	ICER with individual revision w/o PAS	Individual impact w/o PAS	ICER with cumulative revisions w/o PAS	Cumulative impact w/o PAS
None (Company base case)	£67,449	-	£67,449	-
Starter pack cost	£67,704	£255	£67,704	£255
Data source for OS & PFS distributions	£70,075	£2,626	£70,324	£2,875
TBD method	£78,979	£11,530	£82,274	£14,825
PFS distribution	£75,316	£7,868	£91,531	£24,082
OS distribution	£57,771	-£9,678	£80,478	£13,029
ToT distribution	£86,356	£18,907	£85,299	£17,850
OS HR ceritinib vs BSC	£73,660	£6,211	£93,283	£25,834

3.2 Scenario analyses

3.2.1 Ceritinib versus brigatinib hazard ratio

Table 4 ICERs for alternative hazard ratios for BSC versus ceritinib

OS HR BSC vs Ceritinib	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
1	26.24%	6.50%	£101,624	1.57	1.19	£85,299
0.95	25.36%	5.84%	£101,358	1.53	1.17	£86,724
0.9	24.41%	5.19%	£101,088	1.48	1.15	£88,231
0.85	23.40%	4.55%	£100,814	1.44	1.12	£89,823
0.8	22.30%	3.92%	£100,536	1.40	1.10	£91,506
*0.75**	21.13%	3.32%	£100,255	1.36	1.07	£93,283
0.7	19.86%	2.74%	£99,972	1.32	1.05	£95,161
0.65	18.49%	2.19%	£99,687	1.27	1.03	£97,142
0.6	17.01%	1.69%	£99,400	1.23	1.00	£99,233
0.55	15.42%	1.25%	£98,615	1.19	0.98	£101,047
0.5	13.71%	0.87%	£96,714	1.14	0.95	£102,066
0.4	9.92%	0.32%	£91,871	1.10	0.92	£103,629
0.3	5.80%	0.06%	£86,320	1.06	0.89	£105,089
0.2	1.99%	0.00%	£80,305	0.97	0.82	£106,521
0.1	0.09%	0.00%	£73,901	0.88	0.75	£108,034

*ERG base case – HR of 0.75 is chosen as a best guess estimate.

3.2.2 Period of post-treatment benefit

Table 5 ICERs for alternative periods of post-treatment benefit

Time after trial period at which TBD begins	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
0 months	19.12%	3.00%	£99,684	1.27	1.03	£97,195
3 months (ERG base case)	21.13%	3.32%	£100,255	1.36	1.07	£93,283
6 months	22.77%	3.58%	£100,675	1.42	1.11	£90,631
9 months	24.54%	3.85%	£101,086	1.48	1.15	£88,199
12 months	26.44%	4.15%	£101,487	1.54	1.18	£85,966

3.2.3 Combination of alternative BSC v ceritinib HRs and post-treatment benefit periods

Table 6 ICERs for alternative HRs and periods of post-treatment benefit

OS HR ceritinib vs BSC	Time after trial period at which TBD begins	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
1	0 months	24.61%	6.09%	£101,035	1.48	1.14	£88,564
	3 months	26.24%	6.50%	£101,624	1.57	1.19	£85,299
	12 months	30.33%	7.51%	£102,855	1.75	1.30	£79,300
0.875	0 months	22.08%	4.50%	£100,371	1.38	1.08	£92,574
	3 months	23.91%	4.87%	£100,951	1.46	1.13	£89,016
	12 months	28.59%	5.83%	£102,184	1.65	1.24	£82,413
0.75	0 months	19.12%	3.00%	£99,684	1.27	1.03	£97,195
	3 months	21.13%	3.32%	£100,255	1.36	1.07	£93,283
	12 months	26.44%	4.15%	£101,487	1.54	1.18	£85,966
0.625	0 months	15.63%	1.70%	£98,980	1.17	0.97	£102,518
	3 months	17.77%	1.94%	£99,543	1.25	1.01	£98,174
	12 months	23.70%	2.59%	£100,773	1.44	1.12	£90,004
0.5	0 months	11.56%	0.73%	£94,938	1.06	0.90	£105,862
	3 months	13.71%	0.87%	£96,714	1.14	0.95	£102,066
	12 months	20.11%	1.27%	£99,640	1.33	1.06	£94,256

3.2.4 Maximum treatment duration

Table 7 ICERs for alternative maximum treatment periods

Time point (weeks)	5-year OS brigatinib (%)	10-year OS brigatinib (%)	Incremental costs w/o PAS (£)	Incremental LYG	Incremental QALYs	ICER w/o PAS (£/QALY)
None (ERG base case)	21.13%	3.32%	£100,255	1.36	1.07	£93,283
572 [a]	21.13%	3.32%	£99,247	1.36	1.07	£92,484
480 [b]	21.13%	3.31%	£98,112	1.36	1.07	£91,566
377	21.13%	3.26%	£95,242	1.36	1.07	£89,213
213 [c]	20.25%	2.98%	£80,812	1.32	1.04	£77,700

[a] Time at which <1% of patients remain on treatment, [b] Time at which >99% of patients have progressed, [c] 161 weeks + 1 year.

5 Additional scenario added on 30th November 2018

The scenarios presented in Table 8 give ERG model ICERs for a range of brigatinib versus ceritinib hazard ratios. Scenario 1 is for reference and represents the ERG model base case. In each scenario the specified hazard ratio is applied to the KM fitted brigatinib ToT curve (gamma) to produce the ceritinib ToT curve. In the ERG model the ToT curves inform mean per person total TKI cost, and the treatment benefit discontinuation adaptation.

Table 8 ToT HR brigatinib vs ceritinib

ToT curve choice	ToT HR brigatinib vs ceritinib	Median ceritinib ToT (months)	ICER w/o PAS (£/QALY)	No.
Gamma	0.282*	3.68	£93,283	1 (BC)
	0.312	4.60	£90,354	2
	0.366	5.52	£85,358	3
	0.424	6.44	£80,037	4
	0.481	7.36	£74,676	5
	0.537	8.28	£69,225	6
	0.592	9.20	£63,679	7

*HR used in ERG base case (ACM3)

An exact match of modelled and observed medians is not achievable due to the cycle length of 4 weeks, but since the modelled estimates of OS and PFS medians (both company and ERG) tend to be lower than trial medians, and the company's modelled ToT median is only 5.52 months, the Gamma based HR of 0.481 may represent reasonable alternative to the base case HR of 0.282. Table 9 presents trial and modelled medians for the outcome measures used in the modelling.

Table 9 Trial and modelled medians for the outcome measures

	Median OS (months)	Median PFS (months)	Median ToT (months)
ASCEND-2[2] (INV)	14.9 (95% CI: 13.5-not evaluable)	5.7 (95% CI: 5.4-7.6)	8.8
ASCEND-5[3] (INV)	18.1 (95% CI: 13.4-23.9)	5.4 (95% CI: 4.1-6.9)	6.99
Company BC	15.64	4.60	5.52
ERG BC	15.64	5.52	3.68

References: 2. Crino L, Ahn MJ, De Marinis F, Groen HJ, Wakelee H, Hida T, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. J Clin Oncol. 2016;34(24):2866-73.; 3. Shaw AT, Kim TM, Crinò L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK -rearranged non-small-cell lung cancer previously given chemotherapy and