NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer [865]

The following documents are made available to the consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document** from Pfizer
   - Comments on the Appraisal Consultation Document
   - New Information Included within Pfizer's Response to the ACD

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roy Castle Lung Cancer Foundation
   - British Thoracic Oncology Group
   - RCP on behalf of the NCRI-ACP-RCP-RCR
   - NHS England

     The Department of Health stated that they had no comments

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

5. **ERG critique of new information following ACD consultation** prepared by Centre for Reviews and Dissemination,York

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non small cell lung cancer

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment [sic]	Response
Pfizer Ltd	Thank you for giving us the opportunity to comment on the Appraisal Consultation Document for the above appraisal. We are disappointed with the Committee's draft recommendation, and indeed believe that the several assumptions which underpin this decision are flawed and lack the necessary clinical validity. We believe that the information included within this response will provide the Committee with sufficient evidence and clinical opinion to reconsider a number of their currently preferred assumptions (especially with respect to overall survival), and therefore allow the Committee to recommend crizotinib within its licensed indication as a clinically and cost-effective use of NHS resources. As part of our response (and as agreed with the NICE secretariat), we have included new evidence from PROFILE 1014 and PROFILE 1007 to address some of the Committee's comments noted in the ACD. This is specifically in relation to the time on treatment with crizotinib, the utility when continuing to treat beyond progression with crizotinib, and the survival benefit associated with crizotinib. All revised cost-effectiveness analyses provided as part of this response also include a revision to the Patient Access Scheme (PAS). The data regarding overall survival unequivocally demonstrate that crizotinib leads to at least a 7.1 month survival benefit versus current therapy, with an upper bound of the resulting ICER range which sits below £50,000 per QALY, bearing in mind the Committee's conclusion that crizotinib meets the criteria to be considered as an End of Life therapy. We believe, based on conservative estimates of overall survival, that crizotinib is cost-effective. Further maturation of trial data would only serve to confirm that the assumptions we have made are conservative, as the clinical reality – which we have observed in the second-line setting – is that the survival gain is far greater than the minimum necessary to prove crizotinib is cost-effective. The revisions to the Patient Access Scheme guarantee that crizotinib provides value of money to the NHS and aims to ensure that ALK-positive patients receive timely access to treatment. We present a compelling case within our response and strongly believe crizotinib is both a clinically- and cost-effective treatment option that should be made available for patients within England and Wales.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended crizotinib as specified in section 1 of the FAD. The committee's full considerations for each issue are outlined in section 4 of the FAD.
Pfizer Ltd	<u>Executive Summary</u> Pfizer do not consider the provisional recommendations to be a sound or a suitable basis for guidance to	Comment noted. The committee's considerations for each issue are outlined in

Consultee	Comment [sic]	Response
	the NHS. While we welcome the conclusion of the Committee that crizotinib is a clinically effective treatment, it is disappointing that crizotinib's cost-effectiveness has not been recognised. We understand that the ICER the Committee considers most closely reflects its preferred assumptions is £130,364 per QALY. This ICER is underpinned by the ERG's independent parametric curves analysis, which relaxes the proportional hazards assumption ('separate curve' selection) and independently stratifies covariates to extrapolate survival data. It results in a modelled mean overall survival (OS) of 21.6 months for crizotinib and 20.8 months for pemetrexed, equating to a 0.8 month mean survival gain. Pfizer believe that this analysis **vastly over-inflates crizotinib's true ICER**, most notably because of the clinically implausible assumptions pertaining to this OS associated with pemetrexed. These flawed assumptions serve to produce an unrepresentative ICER, which should not form the basis for decision making. The modelled OS gain associated with the Committee's preferred ICER (0.8 months) is less than that concluded by the Committee in the second-line appraisal of crizotinib for NSCLC (7.1 months), less than that considered clinically plausible by clinicians with experience using crizotinib (7.1-13 months), and most notably is contradictory to the OS gain for crizotinib noted elsewhere in the ACD where the Committee agree that crizotinib is associated with sufficient survival benefit to satisfy the End of Life criteria (>3 months mean gain). In our response below, we first present the ICER which represents the Committee's preferred set of assumptions, as described in the ACD. This ICER includes a correction to the survival extrapolation for crizotinib used by the ERG in their independent parametric curves analysis, and brings the assumed OS gain for crizotinib in line with what would be expected clinically (this correction to survival alone halves the Committee's preferred ICER). The absolute minimum survival advantage which should be considered to be afforded by crizotinib in the first-line setting is that accepted by the Committee in the second-line appraisal, which has since been demonstrated to be a very conservative estimate, even in the second line. As long as this minimum survival advantage is assumed, the deterministic ICER for crizotinib is no greater than £49,186 (pertaining to a probabilistic ICER of £49,354 per QALY). In reality, consensus from multiple clinical experts with experience in using crizotinib have all indicated they would expect crizotinib's crossover-adjusted OS gain to fall between 7.1 (established at the second-line appraisal) and 13 months, as the first-line OS gain is expected to be greater than the second-line OS gain. Maturation of the first-line trial data would only serve to confirm that the assumptions we have made in the first-line are conservative. The upper bound of the crizotinib ICER drops to £40,851 when the treatment duration is stopped at progression to reflect the recent NICE approval of ceritinib as a treatment to follow crizotinib. In our revisions to the ERG preferred economic modelling approach, we have [redacted] the Patient Access Scheme (PAS) to [redacted]%. We are confident, based on these new analyses, that the most credible, plausible ICER for crizotinib sits below the £50,000 per QALY threshold and we believe that the information presented in this response should satisfy the Committee to recommend crizotinib for use within its licensed indication, and that ALK-positive NSCLC patients in England and Wales are given access to this	section 4 of the FAD and below.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>targeted medicine.</td><td></td></tr>
<tr><td>Pfizer Ltd</td><td>
1. <u>The Committee's Preferred ICER</u>
The ACD notes that the ICER which the Committee considered most reflective of its preferred assumptions is £130,064 per QALY. This is referred to as the ERG's independent parametric curves analysis. The ACD also notes the ICER is necessarily an over-estimate, as it does not reflect all of the Committee's preferred assumptions. Key assumptions which comprise this ICER (and the Committee's preferred alternatives, where changes are required) are listed in the table below.

Table 1: Summary of the key assumptions in the Committee's preferred ICER at ACD
<table>
<tr><th>Assumption included in the chosen ICER</th><th>Preferred by the Committee?</th><th>Considerations</th></tr>
<tr><td>(A) Higher utility values for pre-progression pemetrexed patients (once off treatment) than those in Pfizer's base case</td><td>Yes</td><td>A higher utility value is preferred by the Committee; however, the utility value selected for pemetrexed patients is that of crizotinib patients, which contradicts clinical rationale supporting differences in utility between treatment arms. [See Section 3]</td></tr>
<tr><td>(B) Use of unadjusted parametric survival curve to estimate time on treatment with crizotinib</td><td>No.
Paragraph 4.12 notes that the Committee would prefer to see an adjusted parametric survival curve for time on treatment.</td><td>With PFS and OS curves adjusted for a real-world cohort, the Committee's preference is to also have time on treatment adjusted in the same manner. [See Section 4 and Appendix C]</td></tr>
<tr><td>(C) Inclusion of crizotinib administration costs</td><td>Yes</td><td>The inclusion of administration costs is preferred by the Committee; however, the costs included in the chosen ICER are those for chemotherapy, not a targeted inhibitor. [See Section 3]</td></tr>
<tr><td>(D) Increased cost of ALK testing beyond that assumed in the Pfizer base case</td><td>Yes.
However, the Committee believed the figure included in the chosen ICER</td><td>The Committee heard from a clinical expert
that the cost of immunohistochemistry (IHC) was between £50 and £100 (excluding laboratory costs) and so agreed that the ERG may have overestimated</td></tr>
</table>
</td><td>After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended crizotinib as specified in section 1 of the FAD.

The committee's considerations about the survival curves and ICERs are outlined in the FAD. (see section 4.19 of the FAD).</td></tr>
</table>

Consultee	Comment [sic]			Response
		may be an overestimate (paragraph 4.15).	the cost (paragraph 4.15). *[See Section 3]*	
	(E) Higher post-progression utilities for crizotinib patients when still on treatment	Yes. However, the values used in the chosen ICER were noted as an area of uncertainty.	The Committee cited uncertainty as the values used in the Pfizer base case for post-progression utility were not evidence-based. New analyses *[see Section 4 and Appendix D]* included in this response now provide in-trial values for these utilities removing the need for assumptions to be made.	
	(F) Relaxation of the proportional hazards assumption in the extrapolation of overall survival	Yes	The ACD indicates that the Committee preferred to not assume proportional hazards due to the availability of patient level data, and because the two treatment regimens are administered differently. *[See Section 2 and Appendix B]*	
	(G) Survival extrapolations in which the baseline prognostic factors are stratified independently for each treatment group	Yes	Although the ACD reflects the Committee's thoughts behind proportional hazards, it does not does not state why the Committee considered separate curve modelling with independent covariate stratification. *[See Section 2 and Appendix B]*	
	Taking into account the changes to the Patient Access Scheme, the ICER which presents the Committee's preferred assumptions (i.e., changes to [B], [D], & [E] above) is £51,945 per QALY. This ICER has also incorporated a correction to the parametric curve selected for the extrapolation of crizotinib survival with respect to assumption [F] in Table 1. This correction is described below in Section 2 and explained in more detail in Appendix B. This ICER of £51,945 per QALY reflects no changes to [A] or [C], however the company believes revised assumptions should be considered for both in Section 3 which would lower the Committee's preferred ICER to £47,921 per QALY. This ICER is £49,186 per QALY in a proportional hazards model using the same stratification covariates for PFS and OS. All other modelling adjustments made by the ERG in their critique, with which the Committee did not express a preference, have been accepted by Pfizer and are incorporated into this ICER for the sake of simplicity. Neither these, nor those assumptions from the Pfizer base case with which the Committee agreed, are listed in Table 1.			

<table>
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2. <u>Clinical Plausibility of the Survival Assumed in the Committee's Preferred ICER</u>
We do not consider the assumptions which underpin the ICER informing the basis for the negative recommendation in the ACD (£130,364 per QALY) to accurately reflect clinical reality, most notably the assumptions which influence the assumed months of survival.
The ICER of £130,364 per QALY represents less than a one-month mean survival gain with crizotinib, which is much less than that deemed plausible by clinical experts, suggested by the data, and indeed accepted in the second-line appraisal where the PFS benefit was more conservative. Multiple clinical experts with experience in using crizotinib have indicated the expected OS gain for crizotinib in the first-line, in the absence of crossover, would fall between 7.1 and 13 months (i.e. at least that accepted by NICE in the second-line). Regardless of the statistical framework used to extrapolate and model overall survival, every analysis which adheres to the End-of-Life Criteria (mean life expectancy with current therapy <24 months), and assumes the mean and median survival gain attributed to crizotinib by the Committee is, at a minimum, at least that accepted in the second-line appraisal (7.1 months), produces an ICER of between £31,708 and £49,186 per QALY (see Table B1 in Appendix B). These ICERs include revised assumptions as set out in Table A1 in Appendix A.
For ease of consideration, Table 2 below presents the mean and median survival times associated with each of the modelled ICERs that were considered by the Committee at the ACD meeting. Note that the Committee's preferred ICER is underpinned by the ERG's independent parametric curves analysis, which uses separate curve modelling with independent covariate stratification to extrapolate survival data (seen in row 3).
Table 2: Mean and median OS that pertains to the ICERs considered by the Committee at ACD
<table>
<tr><th>Model considered by the Committee</th><th>ICER (cost per QALY)</th><th>OS crizotinib</th><th>OS pemetrexed</th><th>OS gain with crizotinib</th></tr>
<tr><td>(1) Company's base case (proportional hazards)</td><td>£47,620</td><td rowspan="2">28.5 months mean
21.7 months median</td><td rowspan="2">17.4 months mean
13.8 months median</td><td rowspan="2">11.1 mean gain
7.9 median gain</td></tr>
<tr><td>(2) ERG's preferred base case (proportional hazards)</td><td>£74,792</td></tr>
<tr><td>(3) ERG's separate curve modelling (non-proportional hazards) with independent covariate stratification</td><td>£130,364</td><td>21.6 months mean
21.7 months median</td><td>20.8 months mean
14.8 months median</td><td>0.8 mean gain
6.9 median gain</td></tr>
</table>
</td><td>
The committee acknowledged there was uncertainty about the size of the average gain in overall survival. The committee's full considerations about the average gain in overall survival are outlined in FAD (see section 4.14 of the FAD).

The committee's considerations about the survival curves and ICERs are outlined in the FAD. (see section 4.19 of the FAD).

The committee noted that the hazard ratios were likely to change over time and that the assumption of proportional hazards was unlikely to hold. It agreed that it was appropriate to adjust each treatment for the population separately. The committee's full considerations about the average gain in overall survival are outlined in FAD (see sections 4.12 and 4.13 of the FAD).
</td></tr>
</table>

Consultee	Comment [sic]	Response

(3b) ERG's separate curve modelling with independent covariate stratification, **but with lowest AIC/BIC curve selected**	£68,741	33.9 months mean 24.6 months median	20.8 months mean 14.8 months median	13.1 mean gain 9.9 median gain

Note: *These ICERs relate to the ACD-meeting, and above do not include any of the proposed revisions to the modelling that are detailed in this response.*

As noted above in Section 1, the ICER of £130,364 per QALY is not based on the most appropriate curve to extrapolate crizotinib survival. The ERG report cites the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) as rationale for the curve selection; the crizotinib curve with the lowest cumulative AIC and BIC score is the exponential (Table 50, ERG report; also in Table B2 in Appendix B of this document). However, contrary to this stated rationale, the ERG selected the generalised gamma. Accordingly, the ICER associated with the ERG's independent parametric curves analysis should have been £68,741 per QALY (changing no other variables; this ICER does not reflect the revision to the PAS). Importantly, the exponential curve models survival which is more clinically plausible than that generated by the generalised gamma (see Appendix B for rationale). This 'corrected' model is presented in row (3b) in Table 2.

Most importantly, the generalised gamma curve selected to inform the ICER of £130,634 per QALY is inappropriate because it fundamentally lacks clinical plausibility. From Table 2, it can be seen that the Appraisal Committee's chosen ICER *without* the correction to the crizotinib survival curve (row 3), is associated with assumed mean OS of 21.6 months for crizotinib and 20.8 months for pemetrexed, which results in a 0.8 month benefit. This is directly at odds with the conclusion that crizotinib meets the End of Life criteria, for which the ACD states the Committee were confident that crizotinib met at least the required 3-month mean survival gain. We believe that the statistical models which best represent the clinical reality of using first-line crizotinib are those which demonstrate **at least** the survival benefit assumed in the second-line appraisal (TA296), and this is supported as such:

- Prior to the submission, clinical expert opinion was consulted to test the validity of the modelled estimates of **7.9 months median** and **11.1 months mean OS gain** with crizotinib. The experts stated that these were clinically plausible and would be expected to be observed in clinical practice.
- Real world expertise from multiple clinical experts with experience treating with both crizotinib and pemetrexed consulted since the publication of the ACD have confirmed that it is appropriate to assume a mean and median of **7.1 to 13 months of OS gain** with crizotinib.
- During the second-line NICE appraisal of crizotinib (TA296), the experts advised that an estimated OS benefit of 8 to 9 months would be expected, with NICE concluding that an estimate of 7.1 months was sufficiently plausible (crossover adjusted HR of 0.79 [0.45, 1.40]).[1] The OS

Consultee	Comment [sic]	Response
	data from the pivotal trial for second-line use of crizotinib has subsequently matured, with the RPSFT crossover-adjusted hazard ratio now showing a much greater benefit to crizotinib (HR=0.38 (0.28, 0.52), Appendix C)[2]. As the PFS gain with crizotinib is greater at first-line than at second-line [3,4], and the second-line OS hazard ratio has vastly improved once data have matured, it can be reasonably expected that crizotinib in the first-line would, at an absolute minimum, be expected to have an **OS gain of greater than the 7.1 months accepted in the second-line appraisal.** • A naïve comparison across studies of published real-world data estimates of OS for both crizotinib and pemetrexed shows an **OS gain of over 12 months** with crizotinib (Tables 68 and 69 in the company's submission). As noted at the start of this section, **even when the ERG's separate curve modelling with independent covariate stratification is used (as preferred by the Committee), all parametric extrapolations which produce at least this minimum benefit (and which do not assume a life-expectancy with pemetrexed >24 months, in line with the End of Life criteria) are associated with ICERs less than £51,946 per QALY, should only assumptions [B],[D], and [E] from Table 1 be modified to reflect the Committee's preferences**. Pfizer strongly believes revisions should be also made to assumptions [A] and [C] from Table 1, with rationale for these revisions presented in Section 3 following. **When [A] and [C] are also amended, the ICERs fall to under £49,186 per QALY (Table B1, Appendix B).** In addition to the estimates of survival considered as clinically plausible by the Committee, two other issues influencing the model choice for the extrapolation of OS data (assumptions [F] and [G] in Table 1) warrant re-consideration by the Committee • **The use of proportional hazards** **Pfizer do not believe that there is sufficient clinical or statistical rationale to relax the assumption of proportional hazards with respect to modelling progression-free and overall survival**. The ACD states that the Committee prefers not to assume proportional hazards (paragraph 4.11). The ERG have provided the following rationale for why the assumption of proportional hazards may not be appropriate: 1. Independent curves should be selected because individual patient data were available 2. Proportional hazards may not be valid because the two treatment regimens are administered differently (chemotherapy is capped; crizotinib is not) With respect to point 1, regardless of the availability of patient level data, **the recommended checks were performed to test if the proportional hazards assumption held**, in line with NICE DSU guidance [5]. This included an inspection of the log-cumulative hazard plots (figure 18, company submission), validation of the assumption with clinical expert opinion (response to clarification question B11), and face validation of the resulting OS estimates with clinical experts and other published estimates (Tables 68 & 69, company submission). **These all indicate the proportional hazards assumption is appropriate.**	

Consultee	Comment [sic]	Response
	With respect to point 2, clinical expert opinion received during consultation on the ACD suggests there is no reason to assume that the different treatment regimens would impact the proportional treatment effect on either PFS or OS. Indeed, in the appraisal of pemetrexed maintenance (TA190), two pemetrexed regimens were compared (one capped at 4 cycles, and one given until progression). **It was accepted by the Committee that the assumption of proportional hazards was appropriate, irrespective of the differing treatment regimens**. It is important to note that even **if the Committee are not persuaded by the above rationale and retain their preference for the relaxation of the proportional hazards assumption in the survival analysis, crizotinib is still cost-effective when the independent model is used and clinically plausible estimates of survival are considered.** Appendix B details the parametric functions that can be considered plausible, with Table B4 showing the most suitable ICER in an independently fit model is **£47,921 per QALY**. • **The use of independent covariate stratification** Pfizer's base case assumption was to use a model using the same covariates for stratification, implying that covariates (such as age, gender, etc) have the same prognostic effects on patients, regardless of treatment, with the only covariate that affects patients differently between treatment arms being treatment itself. The independent covariate stratification model preferred by the Committee implies that not only is treatment effect non-proportional (see above), but that the influence of other covariates are similarly non-proportional between the two treatment arms. In other words, each covariate (such as patient's age or gender, etc.) influences that patient's outcome to different proportions, depending on the treatment he or she receives. **There is no evidence to suggest that there should be a difference in prognosis for PFS or OS outcomes between groups** included in the PROFILE 1014 clinical trial, where baseline characteristics were well matched. The only factor influencing clinical outcomes was the treatment offered to patients in each arm. Indeed, clinical expert opinion sought during consultation on the ACD agrees with this conclusion. While one's age, performance status, smoking status, etc. may influence one's overall prognosis, it will not influence the prognosis while receiving treatment with crizotinib to any different degree than it would whilst receiving pemetrexed. **Therefore, we maintain the approach to survival modelling used in our base case whereby baseline covariates have the same prognostic effect on patients in either treatment arm, with treatment being the only variable driving the differences in outcomes between arms; this method uses the same set of covariates for stratifying both treatment arms.** This is more appropriate and clinically valid than the use of an independent covariate stratification model, with respect to OS and PFS. Although independent covariate stratification is not suitable for the outcomes PFS and OS, **Pfizer accept that it is reasonable to assume this approach for time on treatment** given that covariates may affect treatment duration differently, and especially given the Committee's preference for the calculation of treatment duration (see Section 4). For example, an older patient may typically have a different number of	

Consultee	Comment [sic]	Response
	treatment cycles with IV chemotherapy, or may be less likely to complete the planned number of cycles in the course, than would be expected with a younger, fitter patient who is able to tolerate the treatment-related toxicities better, thereby facilitating delivery of the planned treatment course. However, the difference in treatment duration may not differ to the same degree when the same patients are given an oral therapy with a more favourable side effect profile. In this instance, the age covariate may impact the duration of treatment differently due to the inherent differences in the regimens (side effect profile, mode of delivery, need for supportive medication, requirement to attend the hospital for treatment, and time spent in the hospital receiving treatment). Similarly, it stands to reason that the treatment duration curves for crizotinib and pemetrexed may not be the same shape, as crizotinib is used until progression yet pemetrexed is used for a fixed number of cycles. This is in contrast to the evidence for the efficacy of the treatments, which suggests the PFS and OS curves retain proportionality regardless of differences in treatment regimens. Pfizer's preferred model stratifies PFS and OS using the same covariates, but uses independent covariate stratification for treatment duration where it is more appropriate. When modelled, this is associated with survival of 21.7 months median (28.5 months mean) for crizotinib, 13.8 months median (17.4 months mean) for pemetrexed, **resulting in a 7.9 month median (11.1 month mean) OS gain for crizotinib**. This model produces results with the requisite face validity, as they fall within the established range of expected survival benefit. This relationship between mean and median OS – the mean being the greater than the median – is supported by clinical expert opinion as it indicates that the OS curves, particularly crizotinib's, are expected to have right hand "tails" that cause the mean to be higher than the median. Considerations to other assumptions that impact the ICER further are presented in the next sections.	
Pfizer Ltd	3. <u>Accuracy of the preferred assumptions regarding administration costs and pemetrexed utility values</u> • **Administration costs for crizotinib** The Committee heard from clinical experts that there would be some administration costs associated with crizotinib and preferred these to be included in the economic analysis. At the time of the second-line appraisal for crizotinib (TA296), the preference for this cost inclusion saw the cost of oral chemotherapy applied to crizotinib in the absence of a more suitable value. As crizotinib is not a chemotherapy, we suggest that it is not appropriate to apply the cost of oral chemotherapy administration to a targeted inhibitor such as crizotinib. As we presented in the submission, NICE has recently appraised a similar targeted oral inhibitor (nintedanib, also in NSCLC), in which no administration costs were assumed (TA347). Setting aside this inconsistency, Pfizer acknowledge the Committee's preference to include an administration cost, and recall the expert at the ACD meeting stating pharmacy dispensing costs would be incurred. The inclusion of a pharmacy dispensing cost is echoed by the approach taken within ceritinib's recent NICE appraisal [ID729] in which the Committee accepted that this was a valid proxy for administration costs. Due to the similarities between crizotinib and ceritinib, **it would be appropriate to include the**	The committee agreed that the lowest administration cost was more appropriate. It considered that the considered that the cost of ALK mutation testing was between £2,380 and £4,500. The committee's full considerations about costs are outlined in FAD (see section 4.18 of the FAD). The committee agreed that the pre-progression-yet-off-treatment utility value was closer to 0.75 than 0.81 and that the company's revised

Consultee	Comment [sic]	Response
	same administration cost for crizotinib that was accepted by NICE for ceritinib. From the ceritinib appraisal, a dispensing cost of £13.60 was assumed to be associated with each prescription, based on the cost of 12 minutes of hospital pharmacists time.[6] The cost included for crizotinib should therefore be £14.40 to reflect an update of the PSSRU (hourly rate of a hospital pharmacist, £72÷5=£14.40).[7] This administration cost is included in every cycle for crizotinib, **and reduces the ICER by £3,425 per QALY** in the proportional hazards model compared to the inclusion of cost of oral chemotherapy administration. • **Pre-progression-yet-off-treatment utility values for pemetrexed** The Pfizer base case assumed the on-treatment utility value for pemetrexed (0.72) for the duration of time pemetrexed patients spent in the PFS health state. The Committee felt a higher utility value than this is appropriate for pemetrexed patients when they have completed their treatment but are still pre-progression to reflect fewer treatment-related toxicities (paragraph 4.14). The value used in the ERG's analysis to reflect this off-treatment rebound in utility was the PFS value for crizotinib (0.81; derived from EQ-5D data collected within PROFILE 1014). Pfizer accept the rationale provided that the proposed utility value may underestimate the utility of patients who are still pre-progression but have completed the treatment cycle. However, there are the following key issues with using the PFS value for crizotinib: The rationale for using this value implies that the difference between the two arms is driven solely by adverse events, and the effect of adverse events on utility is -0.09 (=0.81-0.72). This is not correct because: - The differences in health-related quality of life between crizotinib and chemotherapy are not just a factor of crizotinib's more favourable toxicity profile, but also a result of statistically significant improvements in symptom burden with crizotinib that arise as a result of the reduction in tumour burden (company submission, figures 12 & 13). Removing disutility from pemetrexed's adverse events does not, therefore, increase the utility to that of crizotinib patients, as pemetrexed patients experience no such reduction in tumour burden and consequently no such symptom improvement. - The assumption of a 0.09 rebound is not evidence based. The disutility from pemetrexed's adverse events had in fact previously been established as -0.03 in the Pfizer submission (page 148). This was used in scenario analysis 17 in Table 74 in the original submission. Removal of disutility from adverse events in the pemetrexed arm should thus only increase utility by 0.03. The change in the utility value is assumed to be immediate, after the last cycle of treatment is administered. However, treatment side effects do not immediately 'disappear' after treatment has finished. Clinical experts have confirmed that patients may take a month to recover from the cumulative side effects of chemotherapy delivered for advanced NSCLC, and indeed recommend a phased return to work, where appropriate. For example, cumulative toxicities such as fatigue are associated with chemotherapy (any grade fatigue was seen in 38% of chemotherapy patients in PROFILE 1014 [3]). Consequently, the impact	utility was appropriate. The committee's full considerations about utilities are outlined in FAD (see section 4.17 of the FAD).

Consultee	Comment [sic]	Response
	on utility from no adverse events may not occur immediately. Based on the rationale provided above, we have reduced the assumption of a 0.09 rebound in utility to a value of 0.03, which we believe is a more clinically appropriate estimate to denote adverse events alleviation (but itself may be an over-estimate for pemetrexed patients as it assumes all adverse events immediately disappear). As a consequence, increasing pemetrexed utility from 0.72 to 0.75 after treatment completion has the effect of **reducing the ICER by £982 per QALY** in the proportional hazards model compared to when increasing it to a value of 0.81 as suggested by the ERG (= crizotinib's utility). • **ALK test costs** The Committee's chosen ICER includes a cost of £4,500 for ALK testing per positively identified patient. The Committee noted that their ICER contained some assumptions they did not prefer, of which this was one. The Committee believed the true cost of ALK-testing to be between the company's suggestion (£[redacted]) and the ERG's (£4,500). The Committee heard from the pathologist at the meeting that an IHC test would likely cost £50-£100; this compares to a cost of £[redacted] assumed in the company's calculations. To provide the Committee with an estimate between Pfizer's original and the ERG's, we have assumed an increase IHC testing cost to the middle of this range, £75. This now estimates the cost per positively identified patient at £2,380 and provides a value in between the original two estimates, which was where the Committee felt the true value lied. This **reduces the ICER by £3,167 per QALY** compared to when using a testing cost of £4,500.	
Pfizer Ltd	4. <u>New data incorporated in the above analyses: time on treatment and treating beyond progression</u> • **Adjusted time on treatment with crizotinib (Assumption (B) in Table 1)** In the ACD, the Committee indicated its preference for a parametric survival curve for time on treatment, and for this to be adjusted for real-world patient characteristics, in line with the adjustments for PFS and OS. The ERG previously incorporated time on treatment curves into the model through 'digitizing' screenshots of the Kaplan-Meier curves, but were unable to adjust these without further data. To address the Committee's request, we have re-analysed the patient-level data to provide precise Kaplan-Meier plots for time on treatment for each treatment arm. In the Pfizer submission, Appendix 15 details the evaluation of the absolute effect of several selected covariates by fitting a Cox regression models. These analyses enabled the real-world cohort adjustment for PFS and OS outcomes. This same regression analysis has now been conducted for time on treatment. For reasons stated in Section 2, separate curve modelling with independent covariate stratification model is appropriate for treatment duration. • Crizotinib's mean extrapolated treatment duration, when adjusted for a real-world cohort, is 15.8 months. This adjustment reflects the Committee's preferences, and is in line with how PFS and	Comment noted. The committee agreed that the company's adjusted time on treatment was appropriate. The committee's full considerations about time on treatment are outlined in FAD (see section 4.15 of the FAD). The committee concluded that the utility value for the period after a patient's disease has progressed but the patient continues to take crizotinib was uncertain. The committee's full considerations about utilities are outlined in FAD (see

Consultee	Comment [sic]	Response
	OS are also adjusted. • In the revised Pfizer base case model (which assumes proportional hazards for PFS and OS, but uses separate curves with independent covariate stratification to extrapolate treatment duration) the adjusted treatment duration results in a **mean of 4.1 months treatment beyond progression for a real-world cohort**. • Clinical experts with experience in treating patients with crizotinib have advised that if a patient were treated beyond progression in practice, the likely additional treatment duration would have ranged between **1 and 6 months**, however this is **now extremely unlikely due to the recent NICE approval of ceritinib** for use following crizotinib. The ceritinib FAD was not published at the time of the first crizotinib Committee meeting, meaning that the use of ceritinib and its impact on treatment practices could not be previously considered. However, in light of this new addition to the ALK-positive NSCLC treatment pathway, it is reasonable to assume that treatment with crizotinib would be unlikely to continue beyond progression. **Analyses in which crizotinib treatment is stopped at progression are likely to be most reflective of UK clinical practice moving forward.** In the model which assumes proportional hazards for PFS and OS, stopping treatment at progression reduces the ICER to **£40,851 per QALY,** and down to £45,574 to in the separate curve with independent covariate stratification model. • **New post-progression utility values for crizotinib, isolated from the in-trial utility data (Assumption (E) in Table 1)** The economic model allows treatment beyond progression with crizotinib to reflect the PROFILE 1014 clinical trial, where 73% of patients continued treatment past progression. In the Pfizer base case, we assumed that there would be a decrease in utility for these patients compared to pre-progression, but that utility would still be maintained (to an extent), as a treating clinician would only continue to treat if they perceived some benefit to a patient. The Committee accepted the approach, though cited an absence of health-related quality-of- life data for these patients to inform the selection of the most appropriate utility value. To address this uncertainty, **all ICERs within this response now use EQ-5D trial data isolated from this specific treatment-beyond-progression group of patients for this value in the model**. The EQ-5D data collected in the trial were collected for patients on treatment. This includes those crizotinib patients treated past the point of progression, as they were still on treatment. Applying the value of 0.81 to the pre-progression state only (as in the Pfizer base case) is therefore conservative. Nevertheless, to address the uncertainty cited by the Committee with regard to the post-progression-but-on-treatment utility value, we have analysed the patient level EQ-5D data to identify the true extent to which the utility scores from the pre-progression period differed from the post-progression- but-on-treatment period (in the crizotinib arm). The mean change in utility in the treatment beyond progression period is -0.03 compared to pre-progression. The value used pre-progression is 0.81, thus the value used when treating beyond progression is 0.78. This is higher than the previously assumed 0.74, which was used as it was the mid-	section 4.17 of the FAD).

Consultee	Comment [sic]	Response
	point between first-line crizotinib utility and second-line docetaxel utility. All ICERs within this response now use this more accurate value.	
Pfizer Ltd	5. Factual inaccuracies We include below a summary of factual inaccuracies contained within the ACD which will need to be amended in the FAD: • The ACD states that most [not all] of the crossover in PROFILE 1014 occurred at or after disease progression. The PROFILE 1014 trial protocol sets out that crossover was permitted but only upon disease progression, not before. • The ACD states (page 7) that two methods for crossover were presented by the company. Indeed two methods were modelled (two stage and RPSFT), but three methods (including the IPE) were presented in the submission. All three showed similar results. • The ACD states that: "the ERG was unable to identify any particular curve as being clinically the most appropriate…." The ERG report does not state that the curves were considered for clinical appropriateness during selection. • The ACD states that: "the ERG … therefore selected curves using the lowest AIC." The ERG stated that both the AIC and the BIC were considered when choosing curves, not solely the AIC. 6. References 7. Appendices *The consultee submitted several appendices and references in its response to consultation and have not been reproduced here. Please see Committee papers for the full response.*	Comment noted. The FAD has been amended accordingly in response to the summary of technical comments/corrections on the ACD.
Roy Castle Lung Cancer Foundation	• We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Crizotinib in this indication. We do, however, welcome the ongoing nature of the appraisal process and hope that the Appraisal Committee will re-consider their decision and ensure that this important new technology is made available within the NHS at the earliest opportunity. • We note the adverse implications of a negative decision, not only in denying access to appropriate lung cancer patients but also, the deleterious effect on the wider cancer/cancer research community, which has a current focus on developing such targeted/personalised medicines. We are very concerned that this decision is contrary to the direction of the international community, in which widespread ALK testing and appropriate Crizotinib use, has become the standard. Clearly, we do not wish to see the NHS in England deprive lung cancer patients of therapies routinely available elsewhere	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended crizotinib as specified in section 1 of the FAD.

Consultee	Comment [sic]	Response

	• We welcome several of the conclusions reached by the Appraisal Committee in this ACD
	  o Crizotinib is clinically effective and increases progression free survival, as compared with conventional chemotherapy, in ALK-positive patients. (section 4.6, 4.8)
	  o Crizotinib meets the criteria of a life extending, end of life treatment (section 4.17, 4.18)
	• We would remind the Appraisal Committee that patients with advanced lung cancer generally have a poor outlook. Crizotinib is an oral therapy and has a good side effect profile, as compared with conventional chemotherapy for nsclc. It is reported that ALK rearrangements are found in only 3% to 5% of patients. This therapy therefore represents a targeted treatment option, providing benefit to a clearly defined small segment of non small cell lung cancer patients.
	• We note the uncertainty in assumptions in the inputs to the economic modelling. High levels of crossover, in particular, means the overall survival benefit is uncertain. This has obvious implication for cost effectiveness calculation.
	• With the complication of crossover, a lack of clarity on overall survival data, and uncertainty about what the correct value of the ICER should be, we feel very concerned that such a negative decision is being taken by NICE, thus depriving patients of a therapy, which the Committee acknowledges in paragraph 4.8, increases overall survival, as compared with standard chemotherapy.
	• **On behalf of the many lung cancer patients who would derive benefit from this therapy, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure that areas of uncertainty and cost issues are addressed.** Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement on price can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.	

Consultee	Comment [sic]	Response
NHS England	Please find NHS England's response to the ACD – Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer which has been reviewed by the Chemotherapy CRG **Has all of the relevant evidence been taken into account?** Yes **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes **Any other comments** We disagree with the comment in section 4.4 that platinum-based chemotherapy with pemetrexed followed by pemetrexed maintenance therapy alone could be a relevant comparator because it is often used in clinical practice. This use of pemetrexed is currently only available via the CDF and so cannot be considered a comparator.	Thank you for your comment. The committee was aware of the NICE statement on handling comparators and treatments in the Cancer Drugs Fund and agreed that it could consider pemetrexed maintenance a relevant comparator as specified in section 4.3 of the FAD.
Department of Health	No comment	Noted.
British Thoracic Oncology Group	Thank you for the opportunity to comment on the ACD. I note that NICE have accepted that end of life criteria apply and that the drug is clinically effective in the first line setting. Therefore, on behalf of BTOG, I would like to submit the comment that BTOG is disappointed that crizotinib is not being made available in the first-line setting. BTOG would encourage that the pharmaceutical company, NHS England and NICE continue to explore all avenues to make this clinically effective treatment available to NHS patients. With regard to cost effectiveness, within the assessment there was an assumption that crizotinib treatment would continue beyond progression in some patients and debate about how many and how long for. A recent NICE appraisal approved a drug (ceritinib) for treatment *after* crizotinib progression and the availability of this drug will greatly reduce the use of crizotinib beyond progression and probably have enough of an effect to influence the health economic calculations that were done for this STA.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended crizotinib as specified in section 1 of the FAD.

Consultee	Comment [sic]	Response
NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation. We note that NICE have accepted that end of life criteria apply and that the drug is clinically effective in the first line setting. Therefore, the final decision comes down to the cost effective analysis and low likelihood that it will meet thresholds. Within the assessment there was an assumption that crizotinib treatment would continue beyond progression in some patients, and debate about how many and how long for. A recent NICE appraisal approved a drug for treatment after crizotinib progression and the availability of this drug will greatly reduce the use of crizotinib beyond progression and probably have enough of an effect to influence the health economic calculations that were done for this STA. We would like to note our disappointment that crizotinib is not being made available in the first line setting, and encourage the company and NHS England/NICE to continue to explore all avenues to make these clinically effective treatments available to NHS patients.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended crizotinib as specified in section 1 of the FAD.

Comments received from members of the public

Role*	Comment [sic]	Response
Health professional (within NHS) – consultant clinical oncologist	I understand that the use of Crizotinib in the second line setting is currently being subjected to a separate NICE review. I disagree with this approach, and would have preferred the use of Crizotinib in both first and second line setting to be considered at the same time. The two questions that should be considered are 1. Does the use of Crizotinib among ALK positive lung cancer patients alter their overall survival? 2. Does it matter at which line Crizotnib is used among these patients to optimise its benefit? My response to the first questions is definitely yes, and a conditional yes to the second one. Let me explain further. I shall start by answering the second	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended crizotinib as specified in section 1 of the FAD.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Comment [sic]	Response
	question first. A direct interpretation of both PROFILE 1007 and 1014 trials is that, given the high proportion of patients on the control chemotherapy arms in both studies who subsequently crossed over to the Crizotinib arm, the absence of an overall survival difference would suggest that provided these patients receive Crizotinib at some stage of their cancer journey, they would probably benefit from it. The purists among the statisticians would no doubt be aghast by my conclusion, given that neither trial was designed to establish the optimal sequencing of chemotherapy and Crizotinib, and the null and alternate hypotheses were centred around the progression free survival benefit. We know that among as much as 20% of these patients are not fit for chemotheray based on our recent audit. The caveat to the above assumption is that we have to select our patients carefully. There are patients who are too unwell to receive chemotherapy as first line treatment, yet might be of a borderline fitness to be challenged with Crizotinib. These are the people I think will benefit most from first line Crizotinib. The current CDF guidelines stipulated that only patients who have received a platinum containing chemotherapy will be eligible to receive Crizotinib as their second line treatment. Hence patients of borderline performance status are denied what can potentially be quite an effective drug. To answer the first question, apart from ALK inhibitors treatment, the treatment options for these patients are very limited. Based on the limited clinical evidence so far immunotherapy do not work well among these patients. Hence if ALK inhibitors are not available their choices are limited to platinum containing chemotherapy doublet, docetaxel (+/- Nintedanib) or single agent vinorelbine. Clinical practice has changed substantially since Crizotinib received its license. For patients with ALK positive disease the best practice would be to start them on an ALK inhibitor. What we are exploring in the clinical practice is the optimal sequence in which we should be using these second generation (Alectinib; Brigatininb; Ceritinib) and possibly even third generation ALK inhibitors (Lorlatinib) and really keep chemotherapy to when we have simply run out of ALK inhibitors option.	

Pfizer Limited
Walton Oaks
Dorking Road
Tadworth
KT20 7NS
22nd June 2016

Dear Dr Adler,

Re: Lung cancer (non-small-cell, untreated, ALK positive) - crizotinib [ID865] ACD

Thank you for giving us the opportunity to comment on the Appraisal Consultation Document for the above appraisal. We are disappointed with the Committee's draft recommendation, and indeed believe that the several assumptions which underpin this decision are flawed and lack the necessary clinical validity. We believe that the information included within this response will provide the Committee with sufficient evidence and clinical opinion to reconsider a number of their currently preferred assumptions (especially with respect to overall survival), and therefore allow the Committee to recommend crizotinib within its licensed indication as a clinically and cost-effective use of NHS resources.

As part of our response (and as agreed with the NICE secretariat), we have included new evidence from PROFILE 1014 and PROFILE 1007 to address some of the Committee's comments noted in the ACD. This is specifically in relation to the time on treatment with crizotinib, the utility when continuing to treat beyond progression with crizotinib, and the survival benefit associated with crizotinib. All revised cost-effectiveness analyses provided as part of this response also include a revision to the Patient Access Scheme (PAS).

The data regarding overall survival unequivocally demonstrate that crizotinib leads to at least a 7.1 month survival benefit versus current therapy, with an upper bound of the resulting ICER range which sits below £50,000 per QALY, bearing in mind the Committee's conclusion that crizotinib meets the criteria to be considered as an End of Life therapy. We believe, based on conservative estimates of overall survival, that crizotinib is cost-effective. Further maturation of trial data would only serve to confirm that the assumptions we have made are conservative, as the clinical reality – which we have observed in the second-line setting – is that the survival gain is far greater than the minimum necessary to prove crizotinib is cost-effective. The revisions to the Patient Access Scheme guarantee that crizotinib provides value of money to the NHS and aims to ensure that ALK-positive patients receive timely access to treatment.

We present a compelling case within our response and strongly believe crizotinib is both a clinically- and cost-effective treatment option that should be made available for patients within England and Wales.

Yours sincerely,

[Commercial in confidence information removed]
For and on behalf of Pfizer UK

Executive Summary

Pfizer do not consider the provisional recommendations to be a sound or a suitable basis for guidance to the NHS. While we welcome the conclusion of the Committee that crizotinib is a clinically effective treatment, it is disappointing that crizotinib's cost-effectiveness has not been recognised.

We understand that the ICER the Committee considers most closely reflects its preferred assumptions is £130,364 per QALY. This ICER is underpinned by the ERG's independent parametric curves analysis, which relaxes the proportional hazards assumption ('separate curve' selection) and independently stratifies covariates to extrapolate survival data. It results in a modelled mean overall survival (OS) of 21.6 months for crizotinib and 20.8 months for pemetrexed, equating to a 0.8 month mean survival gain.

Pfizer believe that this analysis **vastly over-inflates crizotinib's true ICER**, most notably because of the clinically implausible assumptions pertaining to this OS associated with pemetrexed. These flawed assumptions serve to produce an unrepresentative ICER, which should not form the basis for decision making. The modelled OS gain associated with the Committee's preferred ICER (0.8 months) is less than that concluded by the Committee in the second-line appraisal of crizotinib for NSCLC (7.1 months), less than that considered clinically plausible by clinicians with experience using crizotinib (7.1-13 months), and most notably is contradictory to the OS gain for crizotinib noted elsewhere in the ACD where the Committee agree that crizotinib is associated with sufficient survival benefit to satisfy the End of Life criteria (>3 months mean gain).

In our response below, we first present the ICER which represents the Committee's preferred set of assumptions, as described in the ACD. This ICER includes a correction to the survival extrapolation for crizotinib used by the ERG in their independent parametric curves analysis, and brings the assumed OS gain for crizotinib in line with what would be expected clinically (this correction to survival alone halves the Committee's preferred ICER).

The absolute minimum survival advantage which should be considered to be afforded by crizotinib in the first-line setting is that accepted by the Committee in the second-line appraisal, which has since been demonstrated to be a very conservative estimate, even in the second line. As long as this minimum survival advantage is assumed, the deterministic **ICER for crizotinib is no greater than £49,186** (pertaining to a probabilistic ICER of £49,354 per QALY). In reality, consensus from multiple clinical experts with experience in using crizotinib have all indicated they would expect crizotinib's crossover-adjusted OS gain to fall between 7.1 (established at the second-line appraisal) and 13 months, as the first-line OS gain is expected to be greater than the second-line OS gain. Maturation of the first-line trial data would only serve to confirm that the assumptions we have made in the first-line are conservative. The upper bound of the crizotinib **ICER drops to £40,851 when the treatment duration is stopped at progression** to reflect the recent NICE approval of ceritinib as a treatment to follow crizotinib.

In our revisions to the ERG preferred economic modelling approach, we have *[Commercial in confidence information removed]* the Patient Access Scheme (PAS) to *[Commercial in confidence information removed].* We are confident, based on these new analyses, that the most credible, plausible ICER for crizotinib sits below the £50,000 per QALY threshold and we believe that the information presented in this response should satisfy the Committee to recommend crizotinib for use within its licensed indication, and that ALK-positive NSCLC patients in England and Wales are given access to this targeted medicine.

1. The Committee's Preferred ICER

The ACD notes that the ICER which the Committee considered most reflective of its preferred assumptions is £130,064 per QALY. This is referred to as the ERG's independent parametric curves analysis. The ACD also notes the ICER is necessarily an over-estimate, as it does not reflect all of the Committee's preferred assumptions. Key assumptions which comprise this ICER (and the Committee's preferred alternatives, where changes are required) are listed in the table below.

Table 1: Summary of the key assumptions in the Committee's preferred ICER at ACD

Assumption included in the chosen ICER	Preferred by the Committee?	Considerations
(A) Higher utility values for pre-progression pemetrexed patients (once off treatment) than those in Pfizer's base case	Yes	A higher utility value is preferred by the Committee; however, the utility value selected for pemetrexed patients is that of crizotinib patients, which contradicts clinical rationale supporting differences in utility between treatment arms. *[See Section 3]*
(B) Use of unadjusted parametric survival curve to estimate time on treatment with crizotinib	No. Paragraph 4.12 notes that the Committee would prefer to see an adjusted parametric survival curve for time on treatment.	With PFS and OS curves adjusted for a real-world cohort, the Committee's preference is to also have time on treatment adjusted in the same manner. *[See Section 4 and Appendix C]*
(C) Inclusion of crizotinib administration costs	Yes	The inclusion of administration costs is preferred by the Committee; however, the costs included in the chosen ICER are those for chemotherapy, not a targeted inhibitor. *[See Section 3]*
(D) Increased cost of ALK testing beyond that assumed in the Pfizer base case	Yes. However, the Committee believed the figure included in the chosen ICER may be an overestimate (paragraph 4.15).	The Committee heard from a clinical expert that the cost of immunohistochemistry (IHC) was between £50 and £100 (excluding laboratory costs) and so agreed that the ERG may have overestimated the cost (paragraph 4.15). *[See Section 3]*
(E) Higher post-progression utilities for crizotinib patients when still on treatment	Yes. However, the values used in the chosen ICER were noted as an area of uncertainty.	The Committee cited uncertainty as the values used in the Pfizer base case for post-progression utility were not evidence-based. New analyses *[see Section 4 and Appendix D]* included in this response now provide in-trial values for these utilities removing the need for assumptions to be made.
(F) Relaxation of the proportional hazards assumption in the extrapolation of overall survival	Yes	The ACD indicates that the Committee preferred to not assume proportional hazards due to the availability of patient level data, and because the two treatment regimens are administered differently. *[See Section 2 and Appendix B]*
(G) Survival extrapolations in which the baseline prognostic factors are stratified independently for each treatment group	Yes	Although the ACD reflects the Committee's thoughts behind proportional hazards, it does not does not state why the Committee considered separate curve modelling with independent covariate stratification. *[See Section 2 and Appendix B]*

Taking into account the changes to the Patient Access Scheme, the ICER which presents the Committee's preferred assumptions (i.e., changes to [B], [D], & [E] above) is £51,945 per QALY. This ICER has also incorporated a correction to the parametric curve selected for the extrapolation of crizotinib survival with respect to assumption [F] in Table 1. This correction is described below in Section 2 and explained in more detail in Appendix B. This ICER of £51,945 per QALY reflects no changes

to [A] or [C], however the company believes revised assumptions should be considered for both in Section 3 which would lower the Committee's preferred ICER to £47,921 per QALY. This ICER is £49,186 per QALY in a proportional hazards model using the same stratification covariates for PFS and OS.

All other modelling adjustments made by the ERG in their critique, with which the Committee did not express a preference, have been accepted by Pfizer and are incorporated into this ICER for the sake of simplicity. Neither these, nor those assumptions from the Pfizer base case with which the Committee agreed, are listed in Table 1.

2. Clinical Plausibility of the Survival Assumed in the Committee's Preferred ICER

We do not consider the assumptions which underpin the ICER informing the basis for the negative recommendation in the ACD (£130,364 per QALY) to accurately reflect clinical reality, most notably the assumptions which influence the assumed months of survival.

The ICER of £130,364 per QALY represents less than a one-month mean survival gain with crizotinib, which is much less than that deemed plausible by clinical experts, suggested by the data, and indeed accepted in the second-line appraisal where the PFS benefit was more conservative. Multiple clinical experts with experience in using crizotinib have indicated the expected OS gain for crizotinib in the first-line, in the absence of crossover, would fall between 7.1 and 13 months (i.e. at least that accepted by NICE in the second-line). Regardless of the statistical framework used to extrapolate and model overall survival, **every analysis which adheres to the End-of-Life Criteria (mean life expectancy with current therapy <24 months), and assumes the mean and median survival gain attributed to crizotinib by the Committee is, at a minimum, at least that accepted in the second-line appraisal (7.1 months), produces an ICER of between £31,708 and £49,186 per QALY** (see Table B1 in Appendix B). These ICERs include revised assumptions as set out in Table A1 in Appendix A.

For ease of consideration, Table 2 below presents the mean and median survival times associated with each of the modelled ICERs that were considered by the Committee at the ACD meeting. Note that the Committee's preferred ICER is underpinned by the ERG's independent parametric curves analysis, which uses separate curve modelling with independent covariate stratification to extrapolate survival data (seen in row 3).

Table 2: Mean and median OS that pertains to the ICERs considered by the Committee at ACD

Model considered by the Committee	ICER (cost per QALY)	OS crizotinib	OS pemetrexed	OS gain with crizotinib
(1) Company's base case (proportional hazards)	£47,620	28.5 months mean 21.7 months median	17.4 months mean 13.8 months median	11.1 mean gain 7.9 median gain
(2) ERG's preferred base case (proportional hazards)	£74,792			
(3) ERG's separate curve modelling (non-proportional hazards) with independent covariate stratification	£130,364	21.6 months mean 21.7 months median	20.8 months mean 14.8 months median	**0.8 mean** gain 6.9 median gain
(3b) ERG's separate curve modelling with independent covariate stratification, **but with lowest AIC/BIC curve selected**	£68,741	33.9 months mean 24.6 months median	20.8 months mean 14.8 months median	13.1 mean gain 9.9 median gain

Note: *These ICERs relate to the ACD-meeting, and above do not include any of the proposed revisions to the modelling that are detailed in this response.*

As noted above in Section 1, the ICER of £130,364 per QALY is not based on the most appropriate curve to extrapolate crizotinib survival. The ERG report cites the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) as rationale for the curve selection; the crizotinib curve with the lowest cumulative AIC and BIC score is the exponential (Table 50, ERG report; also in Table B2 in Appendix B of this document). However, contrary to this stated rationale, the ERG selected the generalised gamma. Accordingly, the ICER associated with the ERG's independent parametric curves analysis should have been £68,741 per QALY (changing no other variables; this ICER does not reflect the revision to the PAS). Importantly, the exponential curve models survival which is more clinically plausible than that generated by the generalised gamma (see Appendix B for rationale). This 'corrected' model is presented in row (3b) in Table 2.

Most importantly, the generalised gamma curve selected to inform the ICER of £130,634 per QALY is inappropriate because it fundamentally lacks clinical plausibility. From Table 2, it can be seen that the Appraisal Committee's chosen ICER *without* the correction to the crizotinib survival curve (row 3), is associated with assumed mean OS of 21.6 months for crizotinib and 20.8 months for pemetrexed, which results in a 0.8 month benefit. This is directly at odds with the conclusion that crizotinib meets the End of Life criteria, for which the ACD states the Committee were confident that crizotinib met at least the required 3-month mean survival gain. We believe that the statistical models which best represent the clinical reality of using first-line crizotinib are those which demonstrate **at least** the survival benefit assumed in the second-line appraisal (TA296), and this is supported as such:

- Prior to the submission, clinical expert opinion was consulted to test the validity of the modelled estimates of **7.9 months median** and **11.1 months mean OS gain** with crizotinib. The experts stated that these were clinically plausible and would be expected to be observed in clinical practice.

- Real world expertise from multiple clinical experts with experience treating with both crizotinib and pemetrexed consulted since the publication of the ACD have confirmed that it is appropriate to assume a mean and median of **7.1 to 13 months of OS gain** with crizotinib.

- During the second-line NICE appraisal of crizotinib (TA296), the experts advised that an estimated OS benefit of 8 to 9 months would be expected, with NICE concluding that an estimate of 7.1 months was sufficiently plausible (crossover adjusted HR of 0.79 [0.45, 1.40]).[1] The OS data from the pivotal trial for second-line use of crizotinib has subsequently matured, with the RPSFT crossover-adjusted hazard ratio now showing a much greater benefit to crizotinib (HR=0.38 (0.28, 0.52), Appendix C)[2]. As the PFS gain with crizotinib is greater at first-line than at second-line [3,4], and the second-line OS hazard ratio has vastly improved once data have matured, it can be reasonably expected that crizotinib in the first-line would, at an absolute minimum, be expected to have an **OS gain of greater than the 7.1 months accepted in the second-line appraisal.**

- A naïve comparison across studies of published real-world data estimates of OS for both crizotinib and pemetrexed shows an **OS gain of over 12 months** with crizotinib (Tables 68 and 69 in the company's submission).

As noted at the start of this section, **even when the ERG's separate curve modelling with independent covariate stratification is used (as preferred by the Committee), all parametric extrapolations which produce at least this minimum benefit (and which do not assume a life-expectancy with pemetrexed**

>24 months, in line with the End of Life criteria) are associated with ICERs less than £51,946 per QALY, should only assumptions [B],[D], and [E] from Table 1 be modified to reflect the Committee's preferences. Pfizer strongly believes revisions should be also made to assumptions [A] and [C] from Table 1, with rationale for these revisions presented in Section 3 following. **When [A] and [C] are also amended, the ICERs fall to under £49,186 per QALY (Table B1, Appendix B).**

In addition to the estimates of survival considered as clinically plausible by the Committee, two other issues influencing the model choice for the extrapolation of OS data (assumptions [F] and [G] in Table 1) warrant re-consideration by the Committee

- **The use of proportional hazards**

Pfizer do not believe that there is sufficient clinical or statistical rationale to relax the assumption of proportional hazards with respect to modelling progression-free and overall survival.

The ACD states that the Committee prefers not to assume proportional hazards (paragraph 4.11). The ERG have provided the following rationale for why the assumption of proportional hazards may not be appropriate:

1. Independent curves should be selected because individual patient data were available

2. Proportional hazards may not be valid because the two treatment regimens are administered differently (chemotherapy is capped; crizotinib is not)

With respect to point 1, regardless of the availability of patient level data, **the recommended checks were performed to test if the proportional hazards assumption held**, in line with NICE DSU guidance [5]. This included an inspection of the log-cumulative hazard plots (figure 18, company submission), validation of the assumption with clinical expert opinion (response to clarification question B11), and face validation of the resulting OS estimates with clinical experts and other published estimates (Tables 68 & 69, company submission). **These all indicate the proportional hazards assumption is appropriate.**

With respect to point 2, clinical expert opinion received during consultation on the ACD suggests there is no reason to assume that the different treatment regimens would impact the proportional treatment effect on either PFS or OS. Indeed, in the appraisal of pemetrexed maintenance (TA190), two pemetrexed regimens were compared (one capped at 4 cycles, and one given until progression). **It was accepted by the Committee that the assumption of proportional hazards was appropriate, irrespective of the differing treatment regimens**.

It is important to note that even **if the Committee are not persuaded by the above rationale and retain their preference for the relaxation of the proportional hazards assumption in the survival analysis, crizotinib is still cost-effective when the independent model is used and clinically plausible estimates of survival are considered.** Appendix B details the parametric functions that can be considered plausible, with Table B4 showing the most suitable ICER in an independently fit model is **£47,921 per QALY**.

- **The use of independent covariate stratification**

Pfizer's base case assumption was to use a model using the same covariates for stratification, implying that covariates (such as age, gender, etc) have the same prognostic effects on patients, regardless of treatment, with the only covariate that affects patients differently between treatment arms being

treatment itself. The independent covariate stratification model preferred by the Committee implies that not only is treatment effect non-proportional (see above), but that the influence of other covariates are similarly non-proportional between the two treatment arms. In other words, each covariate (such as patient's age or gender, etc.) influences that patient's outcome to different proportions, depending on the treatment he or she receives.

There is no evidence to suggest that there should be a difference in prognosis for PFS or OS outcomes between groups included in the PROFILE 1014 clinical trial, where baseline characteristics were well matched. The only factor influencing clinical outcomes was the treatment offered to patients in each arm. Indeed, clinical expert opinion sought during consultation on the ACD agrees with this conclusion. While one's age, performance status, smoking status, etc. may influence one's overall prognosis, it will not influence the prognosis while receiving treatment with crizotinib to any different degree than it would whilst receiving pemetrexed. **Therefore, we maintain the approach to survival modelling used in our base case whereby baseline covariates have the same prognostic effect on patients in either treatment arm, with treatment being the only variable driving the differences in outcomes between arms; this method uses the same set of covariates for stratifying both treatment arms.** This is more appropriate and clinically valid than the use of an independent covariate stratification model, with respect to OS and PFS.

Although independent covariate stratification is not suitable for the outcomes PFS and OS, **Pfizer accept that it is reasonable to assume this approach for time on treatment** given that covariates may affect treatment duration differently, and especially given the Committee's preference for the calculation of treatment duration (see Section 4). For example, an older patient may typically have a different number of treatment cycles with IV chemotherapy, or may be less likely to complete the planned number of cycles in the course, than would be expected with a younger, fitter patient who is able to tolerate the treatment-related toxicities better, thereby facilitating delivery of the planned treatment course. However, the difference in treatment duration may not differ to the same degree when the same patients are given an oral therapy with a more favourable side effect profile. In this instance, the age covariate may impact the duration of treatment differently due to the inherent differences in the regimens (side effect profile, mode of delivery, need for supportive medication, requirement to attend the hospital for treatment, and time spent in the hospital receiving treatment). Similarly, it stands to reason that the treatment duration curves for crizotinib and pemetrexed may not be the same shape, as crizotinib is used until progression yet pemetrexed is used for a fixed number of cycles. This is in contrast to the evidence for the efficacy of the treatments, which suggests the PFS and OS curves retain proportionality regardless of differences in treatment regimens.

Pfizer's preferred model stratifies PFS and OS using the same covariates, but uses independent covariate stratification for treatment duration where it is more appropriate. When modelled, this is associated with survival of 21.7 months median (28.5 months mean) for crizotinib, 13.8 months median (17.4 months mean) for pemetrexed, **resulting in a 7.9 month median (11.1 month mean) OS gain for crizotinib**. This model produces results with the requisite face validity, as they fall within the established range of expected survival benefit. This relationship between mean and median OS – the mean being the greater than the median – is supported by clinical expert opinion as it indicates that the OS curves, particularly crizotinib's, are expected to have right hand "tails" that cause the mean to be higher than the median.

Considerations to other assumptions that impact the ICER further are presented in the next sections.

3. Accuracy of the preferred assumptions regarding administration costs and pemetrexed utility values

- **Administration costs for crizotinib**

The Committee heard from clinical experts that there would be some administration costs associated with crizotinib and preferred these to be included in the economic analysis. At the time of the second-line appraisal for crizotinib (TA296), the preference for this cost inclusion saw the cost of oral chemotherapy applied to crizotinib in the absence of a more suitable value.

As crizotinib is not a chemotherapy, we suggest that it is not appropriate to apply the cost of oral chemotherapy administration to a targeted inhibitor such as crizotinib. As we presented in the submission, NICE has recently appraised a similar targeted oral inhibitor (nintedanib, also in NSCLC), in which no administration costs were assumed (TA347). Setting aside this inconsistency, Pfizer acknowledge the Committee's preference to include an administration cost, and recall the expert at the ACD meeting stating pharmacy dispensing costs would be incurred.

The inclusion of a pharmacy dispensing cost is echoed by the approach taken within ceritinib's recent NICE appraisal [ID729] in which the Committee accepted that this was a valid proxy for administration costs. Due to the similarities between crizotinib and ceritinib, **it would be appropriate to include the same administration cost for crizotinib that was accepted by NICE for ceritinib**. From the ceritinib appraisal, a dispensing cost of £13.60 was assumed to be associated with each prescription, based on the cost of 12 minutes of hospital pharmacists time.[6] The cost included for crizotinib should therefore be £14.40 to reflect an update of the PSSRU (hourly rate of a hospital pharmacist, £72÷5=£14.40).[7] This administration cost is included in every cycle for crizotinib, **and reduces the ICER by £3,425 per QALY** in the proportional hazards model compared to the inclusion of cost of oral chemotherapy administration.

- **Pre-progression-yet-off-treatment utility values for pemetrexed**

The Pfizer base case assumed the on-treatment utility value for pemetrexed (0.72) for the duration of time pemetrexed patients spent in the PFS health state. The Committee felt a higher utility value than this is appropriate for pemetrexed patients when they have completed their treatment but are still pre-progression to reflect fewer treatment-related toxicities (paragraph 4.14). The value used in the ERG's analysis to reflect this off-treatment rebound in utility was the PFS value for crizotinib (0.81; derived from EQ-5D data collected within PROFILE 1014).

Pfizer accept the rationale provided that the proposed utility value may underestimate the utility of patients who are still pre-progression but have completed the treatment cycle. However, there are the following key issues with using the PFS value for crizotinib:

- The rationale for using this value implies that the difference between the two arms is driven solely by adverse events, and the effect of adverse events on utility is -0.09 (=0.81-0.72). This is not correct because:
    - The differences in health-related quality of life between crizotinib and chemotherapy are not just a factor of crizotinib's more favourable toxicity profile, but also a result of statistically significant improvements in symptom burden with crizotinib that arise as a result of the reduction in tumour burden (company submission, figures 12 & 13).

Removing disutility from pemetrexed's adverse events does not, therefore, increase the utility to that of crizotinib patients, as pemetrexed patients experience no such reduction in tumour burden and consequently no such symptom improvement.

- The assumption of a 0.09 rebound is not evidence based. The disutility from pemetrexed's adverse events had in fact previously been established as -0.03 in the Pfizer submission (page 148). This was used in scenario analysis 17 in Table 74 in the original submission. Removal of disutility from adverse events in the pemetrexed arm should thus only increase utility by 0.03.

- The change in the utility value is assumed to be immediate, after the last cycle of treatment is administered. However, treatment side effects do not immediately 'disappear' after treatment has finished. Clinical experts have confirmed that patients may take a month to recover from the cumulative side effects of chemotherapy delivered for advanced NSCLC, and indeed recommend a phased return to work, where appropriate. For example, cumulative toxicities such as fatigue are associated with chemotherapy (any grade fatigue was seen in 38% of chemotherapy patients in PROFILE 1014 [3]). Consequently, the impact on utility from no adverse events may not occur immediately.

Based on the rationale provided above, we have reduced the assumption of a 0.09 rebound in utility to a value of 0.03, which we believe is a more clinically appropriate estimate to denote adverse events alleviation (but itself may be an over-estimate for pemetrexed patients as it assumes all adverse events immediately disappear).

As a consequence, increasing pemetrexed utility from 0.72 to 0.75 after treatment completion has the effect of **reducing the ICER by £982 per QALY** in the proportional hazards model compared to when increasing it to a value of 0.81 as suggested by the ERG (= crizotinib's utility).

- **ALK test costs**

The Committee's chosen ICER includes a cost of £4,500 for ALK testing per positively identified patient. The Committee noted that their ICER contained some assumptions they did not prefer, of which this was one. The Committee believed the true cost of ALK-testing to be between the company's suggestion (*[Commercial in confidence information removed]*) and the ERG's (£4,500).

The Committee heard from the pathologist at the meeting that an IHC test would likely cost £50-£100; this compares to a cost of *[Commercial in confidence information removed]* assumed in the company's calculations. To provide the Committee with an estimate between Pfizer's original and the ERG's, we have assumed an increase IHC testing cost to the middle of this range, £75. This now estimates the cost per positively identified patient at £2,380 and provides a value in between the original two estimates, which was where the Committee felt the true value lied. This **reduces the ICER by £3,167 per QALY** compared to when using a testing cost of £4,500.

4. <u>New data incorporated in the above analyses: time on treatment and treating beyond progression</u>

- **Adjusted time on treatment with crizotinib (Assumption (B) in Table 1)**

In the ACD, the Committee indicated its preference for a parametric survival curve for time on treatment, and for this to be adjusted for real-world patient characteristics, in line with the adjustments for PFS and OS. The ERG previously incorporated time on treatment curves into the model through 'digitizing' screenshots of the Kaplan-Meier curves, but were unable to adjust these without further data.

To address the Committee's request, we have re-analysed the patient-level data to provide precise Kaplan-Meier plots for time on treatment for each treatment arm. In the Pfizer submission, Appendix 15 details the evaluation of the absolute effect of several selected covariates by fitting a Cox regression models. These analyses enabled the real-world cohort adjustment for PFS and OS outcomes. This same regression analysis has now been conducted for time on treatment. For reasons stated in Section 2, separate curve modelling with independent covariate stratification model is appropriate for treatment duration.

- Crizotinib's mean extrapolated treatment duration, when adjusted for a real-world cohort, is 15.8 months. This adjustment reflects the Committee's preferences, and is in line with how PFS and OS are also adjusted.

- In the revised Pfizer base case model (which assumes proportional hazards for PFS and OS, but uses separate curves with independent covariate stratification to extrapolate treatment duration) the adjusted treatment duration results in a **mean of 4.1 months treatment beyond progression for a real-world cohort**.

- Clinical experts with experience in treating patients with crizotinib have advised that if a patient were treated beyond progression in practice, the likely additional treatment duration would have ranged between **1 and 6 months**, however this is **now extremely unlikely due to the recent NICE approval of ceritinib** for use following crizotinib.

The ceritinib FAD was not published at the time of the first crizotinib Committee meeting, meaning that the use of ceritinib and its impact on treatment practices could not be previously considered. However, in light of this new addition to the ALK-positive NSCLC treatment pathway, it is reasonable to assume that treatment with crizotinib would be unlikely to continue beyond progression. **Analyses in which crizotinib treatment is stopped at progression are likely to be most reflective of UK clinical practice moving forward.** In the model which assumes proportional hazards for PFS and OS, stopping treatment at progression reduces the ICER to **£40,851 per QALY,** and down to £45,574 to in the separate curve with independent covariate stratification model.

- **New post-progression utility values for crizotinib, isolated from the in-trial utility data (Assumption (E) in Table 1)**

The economic model allows treatment beyond progression with crizotinib to reflect the PROFILE 1014 clinical trial, where 73% of patients continued treatment past progression. In the Pfizer base case, we assumed that there would be a decrease in utility for these patients compared to pre-progression, but that utility would still be maintained (to an extent), as a treating clinician would only continue to treat if

they perceived some benefit to a patient. The Committee accepted the approach, though cited an absence of health-related quality-of- life data for these patients to inform the selection of the most appropriate utility value. To address this uncertainty, **all ICERs within this response now use EQ-5D trial data isolated from this specific treatment-beyond-progression group of patients for this value in the model**.

The EQ-5D data collected in the trial were collected for patients on treatment. This includes those crizotinib patients treated past the point of progression, as they were still on treatment. Applying the value of 0.81 to the pre-progression state only (as in the Pfizer base case) is therefore conservative. Nevertheless, to address the uncertainty cited by the Committee with regard to the post-progression-but-on-treatment utility value, we have analysed the patient level EQ-5D data to identify the true extent to which the utility scores from the pre-progression period differed from the post-progression-but-on-treatment period (in the crizotinib arm).

The mean change in utility in the treatment beyond progression period is -0.03 compared to pre-progression. The value used pre-progression is 0.81, thus the value used when treating beyond progression is 0.78. This is higher than the previously assumed 0.74, which was used as it was the mid-point between first-line crizotinib utility and second-line docetaxel utility. All ICERs within this response now use this more accurate value.

5. Factual inaccuracies

We include below a summary of factual inaccuracies contained within the ACD which will need to be amended in the FAD:

- The ACD states that most [not all] of the crossover in PROFILE 1014 occurred at or after disease progression. The PROFILE 1014 trial protocol sets out that crossover was permitted but only upon disease progression, not before.

- The ACD states (page 7) that two methods for crossover were presented by the company. Indeed two methods were modelled (two stage and RPSFT), but three methods (including the IPE) were presented in the submission. All three showed similar results.

- The ACD states that: "the ERG was unable to identify any particular curve as being clinically the most appropriate…." The ERG report does not state that the curves were considered for clinical appropriateness during selection.

- The ACD states that: "the ERG … therefore selected curves using the lowest AIC." The ERG stated that both the AIC and the BIC were considered when choosing curves, not solely the AIC.

6. References

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[3] Solomon, B.J., et al., First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. New England Journal of Medicine, 2014. 371(23): p. 2167-2177.

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7. Appendices

Appendix A: Summary of data behind key assumptions

Table A1 sets out the Committee's preferences for certain assumptions, and summarises the data used for each of these assumptions that have been presented in Sections 3 and 4 of this document. These changes in input data have been implemented into the version of the economic model which included the adaptations made by the ERG (shared with Pfizer by request on 22nd April 2016).

Table A1: Summary of the differing key assumptions between the ERG's base case (the Committee's preferred ICER), the company's base case, and the proposed revised base case

Assumption	**Pfizer Submission**	**ERG analysis informing preferred ICER**	**Revised: Pfizer ACD response**	**Comment on data in revised ACD response** *(see Sections 3 and 4 for details)*
(A) Utility values for pre-progression pemetrexed patients once off treatment	0.72	0.81	0.75	0.81 was not evidence-based; new 0.75 reflects the accurate removal of disutility from grade 3/4 AEs
(B) Adjusted time on treatment with crizotinib (and resulting treatment beyond progression [TBP])	Not included (=2.2 months mean TBP)	Not included (=11.7 months mean TBP)	Included (=4.1 months mean TBP)	Time on treatment has now been adjusted using patient level data, as per Committee's preference.
(C) Crizotinib administration costs	£0	£163.85	£14.40	In line with what NICE accepted for the other oral ALK inhibitor, ceritinib.
(D) Increased cost of ALK testing beyond that assumed in the Pfizer base case	[redacted] per ALK-positive patient	£4,500 per ALK-positive patient	£3,115 per ALK-positive patient	Reflects an increase of IHC to middle of expert's range (£75)
(E) Post-progression utilities for crizotinib patients treating beyond progression	0.74	0.74	0.78	EQ-5D elicited data from pivotal trial to replace assumption

The deterministic ICERs, once the above five revised assumptions are included, are:

- **£49,186 per QALY** in the company's model of proportional hazards using the same stratification covariates for PFS and OS.
- **£47,921 per QALY** if the alternative model using separate curves with independent covariate stratification.

Appendix B: Curves with credible overall survival estimates

Testing the plausibility of modelled survival is an important part of model validation and should be used to rule out which parametric models are not appropriate for consideration.

1) Survival models with an OS gain of greater than 7.1 months

Section 2 set out that the minimum expected OS gain is 7.1 months, with models not meeting this rule considered not clinically valid. There is a choice of 6 possible parametric curve pairings in the Pfizer's basecase proportional hazards model, and 36 different pairings in the Committee's preferred non-proportional model. From all these 42 possible models, Table B1 presents those which meet the threshold of a minimum of 7.1 months mean and median survival gain. All others are ruled out as not clinically plausible. These 18 models have ICERs that range from £31,708 to £57,035 per QALY.

The Committee has concluded that crizotinib meets the End of Life criteria, in part because the life expectancy with current standard of care is <24 months. Therefore, no model choice in which the comparator has a mean OS of >24 months is appropriate for consideration. When both of these considerations are taken into account, there are 11 possible choices, with ICERs that range from **£31,708 to £49,186 per QALY**.

Table B1. ICERs when a minimum of 7.1 months mean & median OS gain with crizotinib is assumed

Crizotinib curve	Pemetrexed curve	Median OS gain	Mean OS gain	ICER (£ per QALY)
Proportional hazards with the same covariates for stratification *(company's preferred model)*				
Gamma		7.9	12.7	46,485
Exponential		8.9	13.0	45,945
Weibull		7.9	11.1	49,186
Log-normal*		10.8	15.9	42,403*
Log-logistic*		9.9	15.0	43,139*
Gompertz		8.9	11.5	48,622
Separate curve modelling with independent covariate stratification *(Committee's preferred model)*				
Exponential	Gamma*	9.9	8.8	57,035*
Exponential	Exponential	9.9	13.0	47,921
Exponential	Weibull	9.9	14.1	46,004
Log−normal	Gamma*	9.9	22.9	36,126*
Log−normal	Exponential	9.9	27.2	32,529
Log−normal	Weibull	9.9	28.3	31,708
Log−normal	Log−normal*	9.9	14.4	46,656*
Log−normal	Log−logistic*	10.8	18.4	40,729*
Log−logistic	Gamma	7.9	15.5	44,817
Log−logistic	Exponential	7.9	19.8	39,181
Log−logistic	Weibull	7.9	20.9	37,939
Log−logistic	Log−logistic*	8.9	11.0	52,505*

** Asterisks indicate models in which pemetrexed's mean OS is greater than 24 months, contradicting End of Life criteria.*

Note that the ICERs include the "revised" input data for assumptions [A] through [E] in Table A1, Appendix A.

2) <u>Clinical plausibility of individual survival curves</u>

As set out in Table B1, only 4 of the proportional hazard parametric models and 11 of separate curve with independent covariate stratification models have the requisite face validity. However, some of these can be further ruled out when the estimates of individual mean and median OS for each curve are considered, either because of the OS gain attributed to crizotinib or because of the relationship between the mean and median (with clinical expert opinion stating it is implausible to assume mean<median). Table B2 presents these estimates, along with AIC and BIC.

Table B2. Individual independent curve estimates of mean and median OS for crizotinib

Curve	Crizotinib				Pemetrexed plus platinum			
	Mean OS	Median OS	AIC	BIC	Mean OS	Median OS	AIC	BIC
Gamma	21.6§	21.7§	433.05	464.53	25.1*	14.8	409.45	440.87
Exponential	33.9	24.6	433.88	459.06	20.8	14.8	406.78	431.91
Weibull	26.4	21.7	433.34	461.66	19.8	14.8	408.65	436.93
Log–normal	48.0†	24.6	440.43	468.76	33.6*	14.8	408.40	436.67
Log–logistic	40.6†	22.7	436.79	465.12	29.6*	13.8	407.49	435.76
Gompertz	23.8	21.7	434.12	462.44	48.8*	15.8	407.57	435.84

** Asterisks indicate models in which pemetrexed's mean OS is greater than 24 months, which is at odds with the Committee' conclusion that the End of Life criteria are met.*

† Daggers indicate crizotinib models which are less likely to be plausible due to high mean OS.

§ Symbol indicates implausible model due to mean OS < median OS. This contradicts clinical expert opinion that stated this should not be expected as it implies no "tail" in the survival curve, which crizotinib's curve would be expected to have.

Bringing together plausible parametric model pairings from Table B1 with plausible curves selections in Table B2 indicates that only 2 possible curve pairings are clinically plausible in a separate curve with independent covariate stratification model:

- Exponential – Exponential (ICER of **£47,921 per QALY**)
- Exponential – Weibull (ICER of **£46,004 per QALY**)

It is important to note that the Exponential-Exponential model is also the best statistical pairing, as this model renders the lowest cumulative AIC and BIC criteria across both crizotinib curves and the pemetrexed curves.

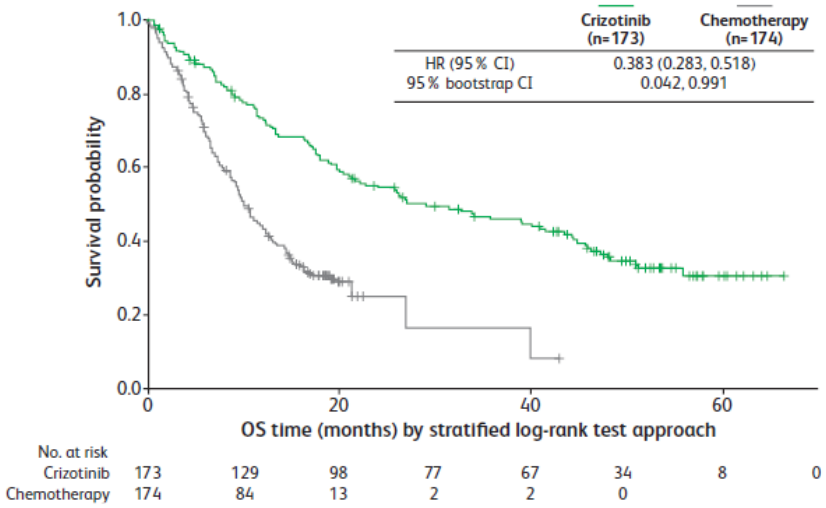
In the proportional hazards model with the same covariates for stratification for PFS and OS (but with independent covariates for treatment duration), which Pfizer believe is the most justifiable modelling approach, all 4 models from Table B1 produce plausible estimates with median OS for crizotinib ranging from 21.7 to 22.7 months, while mean is 28.5 to 32.3 months. For pemetrexed, median OS is 13.8 months, while mean ranges from 17.4 to 19.4 months. The ICER range for 4 models is **£45,945 to £49,186 per QALY.**

Appendix C: Crizotinib's mature survival data from the second-line trial

Below are the crossover adjusted OS curves from the PROFILE 1007 second-line study of crizotinib versus pooled chemotherapy (pemetrexed and docetaxel).

- RPSFT stratified log-rank test: HR = 0.383 (0.042, 0.991) [2]
- RPSFT stratified Wilcoxon test: HR = 0.402 (0.069,0.971) [2]
- RPSFT stratified Cox model based Wald test: HR = 0.352 (0.037, 0.853) [2]

Figure C1: Crossover adjusted OS curves (RPSFT log-rank) from PROFILE 1007 [2]



[a]After adjusting for crossover by RPSFTM, all Kaplan-Meier plots were similar (based on the stratified log-rank test, Wilcoxon test, or Cox model based Wald test). The plot based on the stratified log-rank test was selected for inclusion as this was the method used to compare survival curves between treatment arms in the unadjusted analysis of OS.

New Information Included within Pfizer's Response to the ACD for ID865

To accompany Pfizer's formal response to the ACD, this supplementary document details the new data presented and referred to within the response. These data and analyses include:

(1) A re-calculation of the time on treatment with crizotinib (and include details of this recalculation).

Reference to ACD paragraph 4.12

(2) Post-progression utility values for crizotinib, isolated from the in-trial utility data.

Reference to ACD paragraph 4.14

(3) Hazard ratios for recently published for mature overall survival from crizotinib's second-line trial.

Newly cited data to support model validation

(4) Cost-effectiveness estimates which incorporate an alternate parametric fit for the crizotinib survival data to that which was put forward by the ERG.

Re-examination of the Akaike information and the Bayesian information criterion (AIC and BIC).

(5) An amendment to the simple Patient Access Scheme (PAS) and new results

Details of [Commercial in confidence information removed].

(6) List of changes to the model

Guide to which cells have been amended to reflect changes

1) New data: Time on treatment

In the ACD, the Committee indicated its preference for a parametric survival curve for time on treatment, adjusted for real-world patient characteristics, in line with the adjustments for PFS and OS. The ERG previously incorporated time on treatment curves into the model through 'digitizing' screenshots of the Kaplan-Meier curves, but were unable to adjust these without further data.

To address the Committee's request, we have re-analysed the patient level data to provide precise Kaplan-Meier plots for time on treatment for each treatment arm. In the company's submission, Appendix 15 details the evaluation of the absolute effect of several selected covariates by fitting a Cox regression models. These analyses enabled the real-world cohort adjustment for PFS and OS outcomes. This same regression analysis has now been conducted for time on treatment.

Although we present the rationale in the ACD response as to why we feel the Pfizer base case (i.e., a proportional hazards model with the same covariates for stratification) is more suitable for the outcomes PFS and OS, we accept that it is reasonable to assume that separate curve modelling with independent covariate stratification for time on treatment is more suitable, given that covariates may affect treatment duration differently. For example, an older patient may typically have a different number of treatment cycles with IV chemotherapy than would be expected with a younger, fitter patient who is able to tolerate the treatment-related toxicities better. However, the difference in treatment duration may not differ to the same degree when the same patient is given an oral therapy with a more favourable side effect profile, with a different number of cycles in the regimen. In the example of the age covariate, this may impact the duration of treatment differently due to the inherent differences in the regimens (side effect profile, mode of delivery, need for supportive medication, requirement to attend the hospital for treatment and time spent in the hospital receiving treatment). Similarly, it stands to reason that the treatment duration curves for crizotinib and pemetrexed may not be the same shape, as crizotinib is used until progression yet pemetrexed is used for a fixed number of cycles.

Table 1 presents the statistics for separate curve modelling with independently stratified covariates for both treatment arms. Figures 1 and 2 display the curve fits, with Figures 3 and 4 being adjusted for real-world patient characteristics. The stratification covariates are included in the model, sheet "TTD_Model_Estimates".

It appears the most favourable curve fits are the exponential curve for crizotinib and the Gompertz curve for pemetrexed. Although the generalized Gamma has low AIC and BIC for crizotinib, it does not fit the data correctly (see the curve 'kinks' in Figures C1 and C2) so should not be considered.

Crizotinib's mean extrapolated treatment duration, when adjusted for a real-world cohort, is 15.8 months. This adjustment reflects the Committee's preference, and is in line with how PFS and OS are also adjusted. In the revised company base case model (which assumes proportional hazards for PFS and OS, but uses separate curves with independent covariate stratification to extrapolate treatment duration) the adjusted treatment duration results in a mean of 4.1 months treatment beyond progression for a real-world cohort. Clinical opinion indicates this would be between 1 and 6 months in practice, but likely 0-1 months following the introduction of ceritinib.

Figure 1. Time on treatment extrapolations (crizotinib); PROFILE 1014 data not adjusted for real-world patient characteristics

[Academic in confidence information removed]

Figure 2. Time on treatment extrapolations (crizotinib); extrapolations adjusted for real-world (KM not adjusted)

[Academic in confidence information removed]

Figure 3. Time on treatment extrapolations (pemetrexed plus platinum); PROFILE 1014 data not adjusted

[Academic in confidence information removed]

Figure 4. Time on treatment extrapolations (pemetrexed plus platinum); extrapolations adjusted for real-world patients (KM not adjusted)

[Academic in confidence information removed]

Table 1. Time on treatment AIC and BIC (separate curves with independently stratified covariates)

Model	Pemetrexed + platinum		Crizotinib	
	AIC	BIC	AIC	BIC
Exponential	782.230	807.269	751.691	776.825
Generalised Gamma	547.264	578.563	747.222	778.639
Gompertz	533.165	561.334	753.679	781.954
Log-logistic	637.175	665.344	758.295	786.570
Log-normal	660.708	688.877	759.849	788.124
Weibull	582.311	610.480	753.314	781.589

2) New data: Utility when continuing to treat beyond progression

In the ACD response, we put forward a revised utility value of 0.78 when treating beyond progression with crizotinib. This reflects a -0.03 utility change in the treatment beyond progression phase.

The EQ-5D data collected in the trial were collected for patients whilst on treatment; this includes those crizotinib patients treated past the point of progression (as they were still on treatment). Therefore, the utility value of 0.81 could be considered applicable to crizotinib patients at all times (pre- and post-progression), so any decrease from 0.81 is conservative. Nevertheless, to address the uncertainty cited by the Committee with regard to the post-progression-but-on-treatment utility value, we have analysed the patient level EQ-5D data to identify the true extent to which the utility scores from the pre-progression period differed from the post-progression- but-on-treatment period (in the crizotinib arm).

There are EQ-5D data available for *[Academic in confidence information removed]* patients who treated beyond progression. A 'baseline' was established for each individual patient using their last recorded utility pre-progression; the closest EQ-5D score available before the point of progression was used. How the patient's utility changes in the post-progression phase from this baseline can be evaluated in a similar manner to how a patient's utility changes from their original baseline. By using the last recorded score pre-progression as the baseline, the changes seen post-progression due to both symptom worsening, and any negative psychological impacts that might be expected when a patient is informed that they have progressed, are captured.

Table 2. Post-progression utility change compared to pre-progression whilst remaining on crizotinib [8]

Cycle (post-progression)	n	Utility change from baseline	Cycle (post-progression)	n	Utility change from baseline
1	*[Academic in confidence information removed]*		19	*[Academic in confidence information removed]*	
2			20		
3			21		
4			22		
5			23		
6			24		
7			25		
8			26		
9			27		
10			28		
11			29		
12			30		
13			31		
14			32		
15			33		
16			34		
17			35		
18			36		

Cycle numbers refer to cycles starting from the point of progression

In the cycles beyond progression, the change from this pre-progression baseline was analysed and the mean change from this baseline was calculated for all patients for whom there were data available. Although utility changes over time, the economic model considers one utility value that represents the

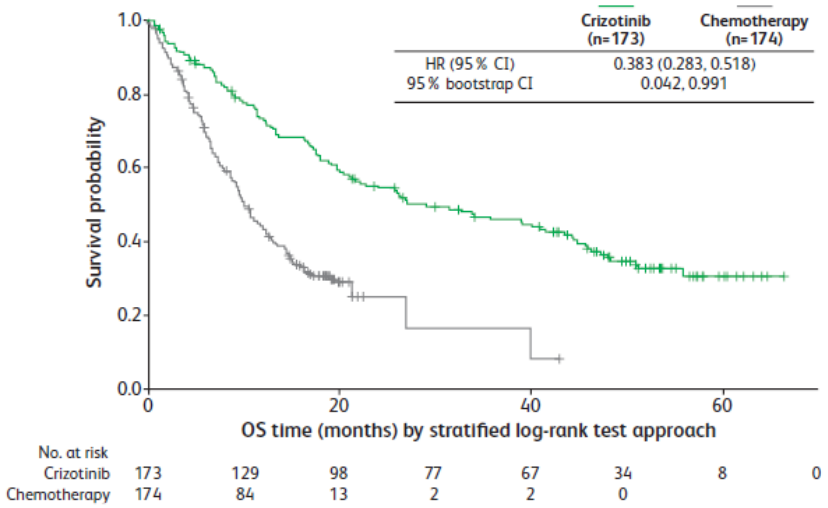
average experienced in that state. In the ERG report (p90), the ERG point out that our assumption of transitional utilities was not appropriate due to double counting and a single average should be used for all patients; we accept the ERG's rationale, and therefore for the same reasons use the average recorded utility score post-progression from all the recorded scores, to reflect a mean change from the pre-progression state. Accordingly, the mean change from baseline in the post-progression state is -0.03. Deducted from value of 0.81, this suggests a 0.78 utility for patients treating beyond progression. This mean value was calculated from the clinical trial data in Table 2 as: SUM(n*utility) / total n.[8]

3) Hazard ratios for recently published for mature overall survival from crizotinib's second-line trial.

In June 2016, mature survival data became available from crizotinib's second-line trial (PROFILE 1007), with updates to the crossover adjusted hazard ratios for overall survival now available for consideration. The results from the trial update are presented below to aid the face validation of the model (Appendix C in the ACD response).

- RPSFT stratified log-rank test: HR = 0.383 (0.042, 0.991) [2]
- RPSFT stratified Wilcoxon test: HR = 0.402 (0.069,0.971) [2]
- RPSFT stratified Cox model based Wald test: HR = 0.352 (0.037, 0.853) [2]

Figure 5: Crossover adjusted OS curves (RPSFT log-rank) from PROFILE 1007 [2]



[a]After adjusting for crossover by RPSFTM, all Kaplan-Meier plots were similar (based on the stratified log-rank test, Wilcoxon test, or Cox model based Wald test). The plot based on the stratified log-rank test was selected for inclusion as this was the method used to compare survival curves between treatment arms in the unadjusted analysis of OS.

During the second-line NICE appraisal of crizotinib (TA296), the experts advised that an estimated OS benefit of 8 to 9 months would be expected, with NICE concluding that an estimate of 7.1 months was sufficiently plausible (crossover adjusted HR of 0.79 [0.45, 1.40]).[1]

The overall survival data from the pivotal trial for second-line use of crizotinib has subsequently matured, with the RPSFT crossover-adjusted hazard ratio now showing a much greater benefit to crizotinib (HR=0.38 (0.28, 0.52))[2]. As the PFS gain with crizotinib is greater at first-line than at second-line [3,4], and the second-line OS hazard ratio has vastly improved once data have matured, it can be reasonably expected that crizotinib in the first-line would, at an absolute minimum, be expected to have an OS gain of greater than the 7.1 months accepted in the second-line appraisal.

4) **Parametric curve selection in the ERG's independent parametric curves analysis**

In our ACD response we discuss the clinical validity of overall survival curves and accordingly the most appropriate models. In this, we note that the ERG's selected curves in the Committee's preferred ICER of £130,364 per QALY were based upon inspection of the lowest AIC and BIC table (ERG report, p117 and p118). This resulted in the Gamma curve selected for crizotinib's OS.

However, Table 49 in the ERG report shows that from the lowest AIC and BIC values it is the exponential curve that should be chosen for crizotinib. In fact, the exponential curve was not even considered in the top three to include as exploratory analyses: "…the generalised Gamma, Gompertz and Weibull curves had the lower AIC and BIC values and visually more plausible for crizotinib." The exponential curve for crizotinib is also visually plausible and Pfizer have now sought clinical expert opinion which deemed its estimates plausible.

In Table 2 (row 3B) in our ACD response (Table 3 below), we present the alternative ICER that we believe should have been considered at the ACD stage. We estimate the ICER with this change would have been £68,741per QALY; this ICER was taken directly from the ERG's model (version dated 04.04.2016) by changing the crizotinib curve choice to "exponential". No other changes were made, and ICER reflects the PAS which was considered by the Committee at the first appraisal meeting.

Table 3 *(Table 2 in ACD response)***: Mean and median OS that pertains to the ICERs considered by the Committee at ACD**

Model considered by the Committee	**ICER (cost per QALY)**	**OS crizotinib**	**OS pemetrexed**	**OS gain with crizotinib**
(1) Company's base case (proportional hazards)	£47,620	28.5 months mean 21.7 months median	17.4 months mean 13.8 months median	11.1 mean gain 7.9 median gain
(2) ERG's preferred base case (proportional hazards)	£74,792			
(3) ERG's separate curve modelling (non-proportional hazards) with independent covariate stratification	£130,364	21.6 months mean 21.7 months median	20.8 months mean 14.8 months median	**0.8 mean** gain 6.9 median gain
(3b) ERG's separate curve modelling with independent covariate stratification, **but with lowest AIC/BIC curve selected**	£68,741	33.9 months mean 24.6 months median	20.8 months mean 14.8 months median	13.1 mean gain 9.9 median gain

Note: *These ICERs do not include any of the proposed revisions to the modelling that are detailed in the ACD response.*

5) An amendment to the simple Patient Access Scheme (PAS) and new results

The PAS *[Commercial in confidence information removed].* The ICERs relating to this new PAS are presented in our ACD response. The new results that contain the amended PAS that we present in our ACD response as follows:

a) New base case that also includes revised data for the five key assumptions summarised in Table 6 in this document

- **£49,186 per QALY** in the company's preferred model of proportional hazards using the same stratification covariates for PFS and OS (probabilistic ICER of £49,354 per QALY).

- **£47,921 per QALY** in the alternative separate curve modelling with independent covariate stratification (referred to as "fully stratified" in the economic model).

    - Includes choosing exponential OS curve for crizotinib; see section (b) below for clinical validity and Section 4 above for statistical consideration

b) Assessment of survival curves with credible overall survival estimates

The ACD sets out, based the estimated OS from the second-line appraisal (see Section 3) and consultation with clinical experts, that the minimum expected OS gain in the first line would be 7.1 months, and that this minimum threshold is indeed conservative. All OS curve choices that meet have a median and mean gain of 7.1 months are considered in Table 4. The ICERs included here contain the "revised" input data (see Table 6).

Table 4. ICERs when a minimum of 7.1 months mean & median OS gain is assumed

Crizotinib curve	Pemetrexed curve	Median OS gain	Mean OS gain	ICER
Proportional hazards with the same covariates for stratification *(company's preferred model)*				
Gamma		7.9	12.7	46,485
Exponential		8.9	13.0	45,945
Weibull		7.9	11.1	49,186
Log-normal*		10.8	15.9	42,403*
Log-logistic*		9.9	15.0	43,139*
Gompertz		8.9	11.5	48,622
Separate curve modelling with independent covariate stratification *(Committee's preferred)*				
Exponential	Gamma*	9.9	8.8	57,035*
Exponential	Exponential	9.9	13.0	47,921
Exponential	Weibull	9.9	14.1	46,004
Log−normal	Gamma*	9.9	22.9	36,126*
Log−normal	Exponential	9.9	27.2	32,529
Log−normal	Weibull	9.9	28.3	31,708
Log−normal	Log−normal*	9.9	14.4	46,656*
Log−normal	Log−logistic*	10.8	18.4	40,729*
Log−logistic	Gamma	7.9	15.5	44,817
Log−logistic	Exponential	7.9	19.8	39,181
Log−logistic	Weibull	7.9	20.9	37,939
Log−logistic	Log−logistic*	8.9	11.0	52,505*

** Asterisks indicate models in which pemetrexed's mean OS is > 24 months, which to do align to the conclusion that critzotinib meets the End of Life criteria.*

The validity of the individual curves is considered in Table 5, with reference to the OS attributed or the relationship between the mean and median. Clinical expert opinion has indicated to the company that a "tail" on the OS curve would be expected for crizotinib and that relatedly the mean would be expectedly higher than the median OS.

Table 5. Individual independent curve estimates of mean and median OS for crizotinib

Curve	Crizotinib				Pemetrexed plus platinum			
	Mean OS	Median OS	AIC	BIC	Mean OS	Median OS	AIC	BIC
Gamma	21.6§	21.7§	433.05	464.53	25.1*	14.8	409.45	440.87
Exponential	33.9	24.6	433.88	459.06	20.8	14.8	406.78	431.91
Weibull	26.4	21.7	433.34	461.66	19.8	14.8	408.65	436.93
Log–normal	48.0†	24.6	440.43	468.76	33.6*	14.8	408.40	436.67
Log–logistic	40.6†	22.7	436.79	465.12	29.6*	13.8	407.49	435.76
Gompertz	23.8	21.7	434.12	462.44	48.8*	15.8	407.57	435.84

** Asterisks indicate models in which pemetrexed's mean OS is > 24 months, which to do align to the conclusion that critzotinib meets the End of Life criteria.*

† Daggers indicate crizotinib models which are less likely to be plausible due to high mean OS.

§ Symbol indicates implausible model due to mean OS < median OS. This contradicts clinical expert opinion that stated this should not be expected as it implies no "tail" in the survival curve, which crizotinib's curve would be expected to have.

The conclusion from Tables 4 and 5 is that only the following curve pairings are plausible in a model with separate curve with independent covariate stratification model:

- Exponential – Exponential (ICER of £47,921 per QALY)
- Exponential – Weibull (ICER of £46,004 per QALY)

It is important to note that the Exponential-Exponential model also has the lowest AIC/BIC criteria, suggesting it this is the optimal curve choice in this model.

In the proportional hazards model with the same covariates for stratification for PFS and OS (but with independent covariates for treatment duration), the 4 curve choices from Table 4 produce median OS for crizotinib ranging from 21.7 to 22.7 months, while mean is 28.5 to 32.3 months. For pemetrexed, median OS is 13.8 months, while mean ranges from 17.4 to 19.4 months. The ICER range for 4 models is £45,945 to £49,186 per QALY.

c) ICERs when treatment with crizotinib is stopped at progression

Clinical expert opinion has indicated it unlikely treatment beyond progression will occur with the recent approval of ceritinib. The ICERs when treatment is stopped at progression should therefore be considered extremely relevant to decision making (relates to ICERs in Section a):

- £40,851 per QALY in the company's preferred model of proportional hazards using the same stratification covariates for PFS and OS.

- £45,574 per QALY in the alternative separate curve modelling with independent covariate stratification (referred to as "fully stratified" in the economic model).

6) List of changes to the economic model

Table 6 below summarises the key assumptions addressed within the ACD response. All other modelling adjustments made by the ERG in their critique, with which the Committee did not express a preference, have been accepted by Pfizer and are incorporated into this ICER for the sake of simplicity.

Table 6: Summary of the differing key assumptions between the ERG's base case (the Committee's preferred ICER), the company's base case, and the proposed revised base case

Assumption	**Pfizer Submission**	**ERG analysis informing preferred ICER**	**Revised: Pfizer ACD response**	**Comment on data in revised ACD response** *(details in ACD response)*
(A) Utility values for pre-progression pemetrexed patients once off treatment	0.72	0.81	0.75	0.81 was not evidence-based; new 0.75 reflects the accurate removal of disutility from grade 3/4 AEs
(B) Adjusted time on treatment with crizotinib (and resulting treatment beyond progression [TBP])	Not included (=2.2 months mean TBP)	Not included (=11.7 months mean TBP)	Included (=4.1 months mean TBP)	Time on treatment has now been adjusted using patient level data, as per Committee's preference.
(C) Crizotinib administration costs	£0	£163.85	£14.40	In line with what NICE accepted for the other oral ALK inhibitor, ceritinib.
(D) Increased cost of ALK testing beyond that assumed in the Pfizer base case	*[Commercial in confidence information removed]*	£4,500 per ALK-positive patient	£3,115 per ALK-positive patient	Reflects an increase of IHC to top of expert's range (£75)
(E) Post-progression utilities for crizotinib patients treating beyond progression	0.74	0.74	0.78	New EQ-5D elicited data from pivotal trial to replace weaker assumption

- In the model with separate curves and independent covariate stratification, once the exponential is chosen, the ICER falls to £51,946 per QALY, should only assumptions [B],[D], and [E] from Table 6 be modified to reflect the Committee's preferences with the proposed revisions.

- The amendment of the IHC testing cost to £75 (middle of the expert's range in the ACD) estimates the cost per positively identified patient at £2,380. This reduces the ICER by **£3,167 per QALY** compared to when using a testing cost of £4,500, in the company's proportional hazards basecase.

- Increasing pemetrexed's utility from 0.72 to 0.75 after treatment completion reduces the ICER by **£982 per QALY** in the proportional hazards model compared to when increasing it to a value of 0.81 as suggested by the ERG (= crizotinib's utility).

- Including an administration cost for crizotinib of 12 mins of pharmacy time, as was accepted in ceritinib's basecase,[6] is £14.40 (hourly rate of a hospital pharmacist, £72÷5=£14.40).[7] This cost included in every cycle for crizotinib reduces the ICER by **£3,425 per QALY** in the proportional hazards model compared to the inclusion of the cost of oral chemotherapy.

All revisions to the model have made to the ERG's version (dated 4th April) which NICE provided to us on 26th April 2016. A detailed list of changes made to the model is presented below in Table 7.

Table 7: Summary of changes to the model since ERG's version "04.04.2016"

Sheet	Range	Change
ERG_Controls	J26	Switch changed to 'No' to reflect revised assumption
	J34	Switch included in order to choose type of TTD model employed (unstratified, partially stratified and fully stratified)
	J36	Switch included in order to choose parametric model by which Criz TTD is extrapolated
	J38	Switch included in order to choose parametric model by which Pem TTD is extrapolated
	J42	Switch moved to accommodate TTD switches above. Switch also changed to static 'data validation' switch
	J44	
	J48	
	J50	
	J55	Switch added to cap crizotinib treatment at progression
Tx admin cost	D15	Admin cost of Criz has been updated to reflect that of ceritinib
Testing cost	H58	Reflects an update in IHC cost
Utilities	C20	Reflects an update to the utility applied for pemetrexed off-treatment but pre-progression
	C42	Reflects an update to the utility following crizotinib (treatment beyond progression)
TTD	Entire sheet	Inclusion of TTD calculations for all types of models and curves
Calc_tx1	O	Inclusion of TTD calculations, and capping of Criz
Calc_tx2	O	Inclusion of TTD calculations
	AH	Correction of equation to account for instances where TTD and PFS curves cross
Parameters	B312:R377	Inclusion of TTD parameter information
Lists	A60:P70	Inclusion of unstratified and fully stratified inputs for TTD
TTD_Model_Estimates	Entire sheet	Inclusion of TTD parameter information - unstratified
Fully_stratified_TTD		Inclusion of TTD parameter information - fully stratified
VBA correction required due to new *ERG Controls* sheet		
Visual basic code	Macro 2	Updated references in deterministic scenario analysis code to change cells in ERG controls sheet rather than Model controls sheet (scenarios 8-13) as switches had been moved and code no longer functioned correctly
Visual basic code	Macro 4	Updated references in probabilistic scenario analysis code to change cells in ERG controls sheet rather than Model controls sheet (scenarios 8-13) as switches had been moved and code no longer functioned correctly
Identified at during factual accuracy check of the ERG's model (second factual accuracy check 28.04.2016)and acknowledged by the ERG (response to second factual accuracy check 29.04.2016)		
Calc_tx1	Column AI	Ensure that the proportion of patients in TBP is bounded by 0 (noted in factual accuracy check of ERG model)
Calc_Tx2	Column AN	Ensure that for pemetrexed the proportion of patients off treatment and in PFS is bounded by 0, and remove double-counting of QALYs for patients in progressed disease receiving BSC (noted in factual accuracy check of ERG model)
	Column AH	
Calc_Tx2	Column AQ	Amended cost of pemetrexed remove additional costs which should not be included (noted in factual accuracy check of ERG model)

References

[1] NICE. Crizotinib for previously treated non-small cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. Final Appraisal Determination (FAD). August 2013. Available at: https://www.nice.org.uk/guidance/TA296/documents/lung-cancer-nonsmallcell-anaplastic-lymphoma-kinase-fusion-gene-previously-treated-crizotinib-final-appraisal-determination3 Accessed: 21st June 2016

[2] Shaw, A. Janne, P. Solomon, B. et al. Crizotinib vs chemotherapy in ALK+ advanced non-small cell lung cancer (NSCLC): final survival results from PROFILE 1007. ASCO 2016 Abstract 9066. Jun 2016

[3] Solomon, B.J., et al., First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. New England Journal of Medicine, 2014. 371(23): p. 2167-2177.

[4] Shaw, A.T., et al., Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med, 2013. 368(25): p. 2385-94.

[5] Latimer, N., NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011 (Updated: March 2013). Available at: *http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf* Accessed: 21st June 2016

[6] NICE. Ceritinib for previously treated anaplastic lymphoma kinase-positive non small-cell lung cancer [ID729]. Committee Papers 2. 20th May 2016. Available at: https://www.nice.org.uk/guidance/GID-TAG478/documents/committee-papers-2 Accessed: 21st June 2016

[7] Curtis, L. Unit costs of health and social care 2015. Available at: *http://www.pssru.ac.uk/project-pages/unit-costs/2015/* Accessed: 21st June 2016

[8] Pfizer Ltd, PROFILE 1014: Clinical Study Report. *Additional Analyses May 2016*.

Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Crizotinib for untreated anaplastic lymphoma kinase~positive, advanced non small cell lung cancer.

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Crizotinib in this indication. We do, however, welcome the ongoing nature of the appraisal process and hope that the Appraisal Committee will re-consider their decision and ensure that this important new technology is made available within the NHS at the earliest opportunity.

- We note the adverse implications of a negative decision, not only in denying access to appropriate lung cancer patients but also, the deleterious effect on the wider cancer/cancer research community, which has a current focus on developing such targeted/personalised medicines. We are very concerned that this decision is contrary to the direction of the international community, in which widespread ALK testing and appropriate Crizotinib use, has become the standard. Clearly, we do not wish to see the NHS in England deprive lung cancer patients of therapies routinely available elsewhere

- We welcome several of the conclusions reached by the Appraisal Committee in this ACD
    - Crizotinib is clinically effective and increases progression free survival, as compared with conventional chemotherapy, in ALK-positive patients. (section 4.6, 4.8)
    - Crizotinib meets the criteria of a life extending, end of life treatment (section 4.17, 4.18)

- We would remind the Appraisal Committee that patients with advanced lung cancer generally have a poor outlook. Crizotinib is an oral therapy and has a good side effect profile, as compared with conventional chemotherapy for nsclc. It is reported that ALK rearrangements are found in only 3% to 5% of patients. This therapy therefore represents a targeted treatment option, providing benefit to a clearly defined small segment of non small cell lung cancer patients.

- We note the uncertainty in assumptions in the inputs to the economic modelling. High levels of crossover, in particular, means the overall survival benefit is uncertain. This has obvious implication for cost effectiveness calculation.
  With the complication of crossover, a lack of clarity on overall survival data, and uncertainty about what the correct value of the ICER should be, we feel very concerned that such a negative decision is being taken by NICE, thus depriving patients of a therapy, which the Committee acknowledges in paragraph 4.8, increases overall survival, as compared with standard chemotherapy.

- **On behalf of the many lung cancer patients who would derive benefit from this therapy, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure that areas of uncertainty and cost issues are addressed**. Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement on price can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.

[redacted]
Roy Castle Lung Cancer Foundation
June 2016

British Thoracic Oncology Group
Glenfield Hospital
Groby Road
Leicester
LE3 9QP England

☎ Direct Line [redacted]

NICE
1st Floor
10 Spring Gardens
London
SW1A 2BU

8 June 2016

Dear Sirs

ACD - Consultees & Commentators: Lung cancer (non-small-cell, untreated, ALK positive) - crizotinib [865]

Thank you for the opportunity to comment on the ACD.

I note that NICE have accepted that end of life criteria apply and that the drug is clinically effective in the first line setting. Therefore, on behalf of BTOG, I would like to submit the comment that BTOG is disappointed that crizotinib is not being made available in the first-line setting. BTOG would encourage that the pharmaceutical company, NHS England and NICE continue to explore all avenues to make this clinically effective treatment available to NHS patients.

With regard to cost effectiveness, within the assessment there was an assumption that crizotinib treatment would continue beyond progression in some patients and debate about how many and how long for. A recent NICE appraisal approved a drug (ceritinib) for treatment *after* crizotinib progression and the availability of this drug will greatly reduce the use of crizotinib beyond progression and probably have enough of an effect to influence the health economic calculations that were done for this STA.

Yours faithfully
For and on behalf of BTOG

[redacted]
Weston Park Hospital, Sheffield

[redacted]
Royal Marsden Hospital, London

British Thoracic Oncology Group - Company Number 9816385
The Registrar of Companies for England and Wales
Registered Charity number 1166012
Registered address: Adam Longley Accountants Limited, The Old Barn, 1815 Melton Road, Rearsby, Leicestershire LE7 4YS
VAT Registration 228 9445 75

Comments from the NCRI-ACP-RCP-RCR

[redacted]

The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation.

We note that NICE have accepted that end of life criteria apply and that the drug is clinically effective in the first line setting. Therefore, the final decision comes down to the cost effective analysis and low likelihood that it will meet thresholds.

Within the assessment there was an assumption that crizotinib treatment would continue beyond progression in some patients, and debate about how many and how long for. A recent NICE appraisal approved a drug for treatment after crizotinib progression and the availability of this drug will greatly reduce the use of crizotinib beyond progression and probably have enough of an effect to influence the health economic calculations that were done for this STA.

We would like to note our disappointment that crizotinib is not being made available in the first line setting, and encourage the company and NHS England/NICE to continue to explore all avenues to make these clinically effective treatments available to NHS patients.

I would be grateful if you could confirm receipt.

Best wishes

[redacted]
Membership Support and Global Engagement Department| Royal College of Physicians
11 St Andrews Place | Regent's Park | London NW1 4LE

Direct line +44 (0)[redacted] | www.rcplondon.ac.uk | facebook | twitter | linkedin

NHS England Response to NICE ACD – Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer

Please find NHS England's response to the ACD – Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer which has been reviewed by the Chemotherapy CRG

Has all of the relevant evidence been taken into account?
Yes
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Yes
Any other comments
We disagree with the comment in section 4.4 that platinum-based chemotherapy with pemetrexed followed by pemetrexed maintenance therapy alone could be a relevant comparator because it is often used in clinical practice. This use of pemetrexed is currently only available via the CDF and so cannot be considered a comparator.

Contact details

Title (e.g. Dr, Mr, Ms, Prof)	[redacted]
Name	[redacted]
Job title or role	[redacted]
Email address	[redacted]

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

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	
Location	England
Conflict	I have received honoraria from Pfizer and Bristol Myers Squibb for attendance at advisory board meetings and as speaker for promotional events.

Comments the ACD:

I understand that the use of Crizotinib in the second line setting is currently being subjected to a separate NICE review. I disagree with this approach, and would have preferred the use of Crizotinib in both first and second line setting to be considered at the same time.

The two questions that should be considered are

1. Does the use of Crizotinib among ALK positive lung cancer patients alter their overall survival?

2. Does it matter at which line Crizotnib is used among these patients to optimise its benefit?

My response to the first questions is definitely yes, and a conditional yes to the second one. Let me explain further. I shall start by answering the second question first.

A direct interpretation of both PROFILE 1007 and 1014 trials is that, given the high proportion of patients on the control chemotherapy arms in both studies who subsequently crossed over to the Crizotinib arm, the absence of an overall survival difference would suggest that provided these patients receive Crizotinib at some stage of their cancer journey, they would probably benefit from it. The purists among the statisticians would no doubt be aghast by my conclusion, given that neither trial was designed to establish the optimal sequencing of chemotherapy and Crizotinib, and the null and alternate hypotheses were centred around the progression free survival benefit. We know that among as much as 20% of these patients are not fit for chemotheray based on our recent audit.

The caveat to the above assumption is that we have to select our patients carefully. There are patients who are too unwell to receive chemotherapy as first line treatment, yet might be of a borderline fitness to be challenged with Crizotinib. These are the people I think will benefit most from first line Crizotinib. The current CDF guidelines stipulated that only patients who have received a platinum containing chemotherapy will be eligible to receive Crizotinib as their second line treatment. Hence patients of borderline performance status are denied what can potentially be quite an effective drug.

To answer the first question, apart from ALK inhibitors treatment, the treatment options for these patients are very limited. Based on the limited clinical evidence so far immunotherapy do not work well among these patients. Hence if ALK inhibitors are not available their choices are limited to platinum containing chemotherapy doublet, docetaxel (+/- Nintedanib) or single agent vinorelbine.

Clinical practice has changed substantially since Crizotinib received its license. For patients with ALK positive disease the best practice would be to start them on an ALK inhibitor. What we are exploring in the clinical practice is the optimal sequence in which we should be using these second generation (Alectinib; Brigatininb; Ceritinib) and possibly even third generation ALK inhibitors (Lorlatinib) and really keep chemotherapy to when we have simply run out of ALK inhibitors option. □

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Crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer [ID865]

ERG commentary on the additional information submitted by the company in response to the ACD

Produced by	**CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**
Date	**30/06/2016**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Introduction

The evidence review group (ERG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the appraisal consultation document (ACD) and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and ensured replication of the results presented by the company. In addition, the ERG has also undertaken additional scenario analysis to address any remaining issues or areas of uncertainty that it considered was not reflected in the company's response.

The company's response to the ACD included:

A. A revised patient access scheme (PAS);
B. Additional evidence from the clinical trials PROFILE 1007 and PROFILE 1014 in support of the assumptions relating to time on treatment; utility when treated beyond progression; and, estimated overall survival benefits associated with crizotinib;
C. Cost-effectiveness results from an amended version of the model which includes a revised company base-case.

The revised model incorporates a number of adjustments to the economic model presented in the original company submission (CS). These adjustments reflect the additional ERG analyses presented in the original evaluation report; the Committee's considerations of the issues in considering the most plausible incremental cost effectiveness ratio (ICER) for crizotinib; and a number of alternative assumptions based on new evidence presented by the company. The changes made to the economic model are summarised in Table 1 below and are discussed in more detail in the following sections.

Table 1 Summary of the key changes to model

Parameter	Assumption in CS base-case	Assumption in ERG base case	Assumption in revised company model
Utility values for pre-progression pemetrexed patients (once off treatment)	Assumes constant utility score of 0.72 for pre-pre-progressed pemtrexed patients	Assumes a utility score of 0.81 for pemetrexed patients who have completed treatment, but not progressed.	Assumes a utility score of 0.75 for pemetrexed patients who have completed treatment, but not progressed.
Time on treatment with crizotinib	Assumes patients receive crizotinib beyond pre-progression for maximum of 4 cycles (mean 2.2)	Time on treatment is estimated from unadjusted parametric curve based on time on treatment in the PROFILE 1014 study.	Time on treatment is estimated from parametric curve adjusted using real world data.
Crizotinib administration costs	No administration costs included	Administration costs of £163.85 per month included.	Administration costs of £14.40 per month included.
ALK testing costs	Cost of ALK testing based on file data. Cost of testing per ALK patient is [redacted].	Cost of ALK testing based on Cancer Research UK survey. Cost of testing per ALK patient is £4500.	Cost of ALK testing based on expert testimony. Cost of testing per ALK patient is £2379.89.
Post-progression utility score for crizotinib patients when still on treatment	Assumes a utility score of 0.74 based on improved symptom control and lower toxicity	Assumes a utility score of 0.74.	Assumes a utility score of 0.78 based on analysis of HRQoL data from PROFILE 1014.
PFS and OS extrapolation	Assumes proportional hazard and a common covariates for prognostic factors in each treatment group.	Scenario analysis presented using separate curves and assuming prognostic factors are stratified independently for each treatment group	Assumes proportional hazard and a common covariates for prognostic factors in each treatment group.

The ERG considers that the documentation submitted in the company's response largely reflects amendments and corrections intended to address the NICE Appraisal Committee's considerations raised within the ACD and ERG report. The company's revised base-case, however, assumes proportional hazards in the modelling of progression free survival (PFS) and overall survival (OS), though additional scenario analysis in which separate parametric curves are used are also presented. The revised base-case ICER presented by the company, which assumes proportional hazards, is £49,186 per quality adjusted life year (QALY). Where separate parametric curves are used the ICER falls to £47, 921 based on the company's preferred curve selection.

2 Revised Patient Access Scheme (PAS)

The company has proposed a revised PAS which is now incorporated into a revised base-case. The PAS consists of a [redacted] crizotinib. This is an increase from the original PAS of [redacted].

With the revised PAS, crizotinib is now priced at [redacted] (list price 4689.00) per pack of 200mg or 250mg tablets. The ERG has checked the revised economic model and is satisfied that the revised PAS has been correctly implemented by the company.

3 Amended economic model and revised base-case

As described above the company's revised base case makes a number of amendments to the economic model. This section presents a detail description of the changes made by the company and critique of the revised assumptions and the data they are based upon.

3.1 Post treatment, pre-progression utility in pemetrexed patients

In the ERG's report on the CS we noted an inconsistency in the health related quality of life (HRQoL) data collected in the PROFILE 1014 trial. This issue specifically related to the fact that HRQoL data collected in PROFILE 1014 trial was collected only while on treatment. As such, the utility input assigned to chemotherapy patients in the PFS state represented that of patients while on treatment. Chemotherapy treatment is associated with a number of adverse events including, neutropenia, anaemia, leukopenia, thrombocytopenia, fatigue, nausea and vomiting. The impact of these adverse events on HRQoL is likely to be significant and as such the ERG highlighted that estimating HRQoL life while on treatment is likely to underestimate the HRQoL of patients who have completed chemotherapy treatment, but have not progressed. In the ERG's base-case analysis it was therefore assumed that the HRQoL of chemotherapy patients post treatment and prior to progression was 0.81, the same utility score used for pre-progressed crizotinib patients.

The company's response accepts the rationale, the company, however, raises the following issues with regard to the magnitude of the QALY increment assumed in the ERG's base-case:

- That the difference in HRQoL between crizotinib and chemotherapy is the product of both better symptom burden and a more favourable toxicity profile associated with crizotinib. The company in particular make reference to Figures 13 and 14 in the CS which show a statistically significantly reduction in symptom burden;
- That it is unrealistic to assume that treatment side-effects associated with chemotherapy are resolved immediately following treatment and that advice from clinical experts suggests that the toxicity effects may persist for up to a month following completion of treatment.

On the basis of these two arguments the revised base-case presented by the company includes a reduced utility value of 0.75 for chemotherapy patients that have completed treatment, but are yet to progress. This value is based on the disutility value of -0.03 associated with the grade 3 and 4 adverse events experienced by chemotherapy patients. The company highlight that they consider this value to be conservative in light of the second point regarding the resolution of side effects following completion of treatment.

With regards to the first issue raised the ERG notes the following points. Firstly, the evidence put forward by the company evidencing the reduction in symptom burden is likely to suffer from the same issues that the HRQoL data does i.e. that it was collected only while patients were on treatment. This is particularly relevant as many of the symptoms capture in the EORTC QLQ-C30 and EORTC QLQ-LC13 measures relate to adverse events associated with treatment. The statistically significant difference the company refers to for example include differences in fatigue, nausea and vomiting, alopecia, constipation and appetite loss, all of which are adverse events associated with chemotherapy treatment. The statistically significant differences in these measures therefore appear to largely reflect differences in the toxicity profile of crizotinib and chemotherapy rather than a reduction in symptoms associated with lung cancer. As such, the ERG considers it likely that many of these differences would disappear following completion of chemotherapy treatment. Secondly, the ERG note that the increment in utility based on the grade 3 and 4 adverse events does not account for the cumulative effect of more minor grade 1 and 2 adverse events and is therefore likely that the 0.03 increment underestimates the total adverse event burden experienced by chemotherapy patients. Finally, the ERG note that the clinical advisor to the ERG considered that chemotherapy patients who have completed treatment, but are yet to progress would experience a higher quality of life than pre-progressed patients receiving crizotinib.

With regards to the second point the ERG concedes that the increase in utility following completion of treatment may not occur immediately, however, the ERG note that the impact of this effect on total QALYs is likely to be very small and definitely no larger than a 0.03 difference in incremental QALYs in the company's revised base-case and 0.09 QALYs in the ERG's base-case.

The ERG therefore does not consider that the evidence put forward by the company justifies the reduction in the utility value for chemotherapy patients and while acknowledging that there is some uncertainty regarding the appropriate value, the 0.81 value used in the ERG base-case is considered to be more plausible than the 0.75 value used by the company in its revised model.

3.2 Adjustment of time on treatment using "real life" data

One of the central issues raised by the ERG report was the estimated time crizotinib patients spent on treatment post progression. The ERG specifically considered the approach taken by the company to be

inappropriate and to significantly underestimate the time crizotinib patients spent on treatment post progression. The ERG therefore made significant changes to the economic model and incorporated time on treatment curves into the model based on Kaplan -Meier data supplied by the company. The ERG was however, not able to adjust the time on treatment curves using the 'real life' data used to adjust both PFS and OS. Consequently the ERG's base-case reflected the time patients spent on treatment in PROFILE 1014 trial which may not reflect the time patients would spend on treatment in the NHS.

To resolve this inconsistency in the ERG base-case model the company's revised base-case include time on treatment curves adjusted using the 'real life' data used to adjust PFS and OS. This adjustment reduces the total estimated time on crizotinib from [redacted] months to 15.8 months and consequently significantly reduces the ICER. The ERG considers this modification of the model to be appropriate and that the selection of the parametric curves to be reasonable.

3.3 Treatment beyond progression

Ceritinib is target therapy similar to crizotinib and has been approved by the European Medicines Agency (EMA) for the treatment of ALK positive metastatic non-small cell lung cancer (NSCLC) who have previously been treated with crizotinib. The NICE final appraisal document (FAD) had not been published at the time of first appraisal meeting, but has since been published recommending ceritinib as potential second-line treatment for NSCLC patients who are ALK positive.[1] The company highlight that the availability of ceritinib has the effect of changing the care path-way of ALK positive NSCLC patients and that it is now unlikely that an ALK positive NSCLCS patient in England would be treated with crizotinib beyond progression. The company therefore presents an additional scenario analysis in which patients are assumed to discontinue therapy at progression. The impact of this assumption is to reduce the ICER from £49,186 to £40,851 per QALY.

The ERG considers the company's reasoning regards the use of crizotinib beyond progression reasonable and that a scenario which crizotinib is discontinued at progression is likely to be more representative of how patients in England will now be treated. The ERG, however, have significant concerns regarding the scenario analysis carried out by the company and do not consider is representative of the counterfactual scenario where patients do not receive crizotinib post progression. This is because the scenario presented by the company considers only the implication of stopping treatment beyond progression on costs and not on OS. As the company have noted in their response, crizotinib has been demonstrated to be an effective second-line therapy extending life by at 7.1 months when compared to docetaxel. The OS benefit observed in the PROFILE 1014 trial is therefore at least partially attributable to differences in treatment received by crizotinib and chemotherapy patients post progression. We would therefore not expect to realise the same OS benefits were

treatment with crizotinib stopped at progression as predicted by the model. This scenario is therefore likely to significantly overestimate the OS of crizotinib patients and hence underestimate the ICER.

3.4 Treatment beyond progression utilities for crizotinib patients

The base-case model submitted by the company assumed that patients who received crizotinib would experience higher HRQoL while they remained on crizotinib treatment. The rationale being that these patients would continue to experience better disease control and a better toxicity profile than patients receiving docetaxel (see CS pg. 145). In the absence of evidence on the utility of these patients the company made the simplifying assumption that patients treated beyond progression with crizotinib have a utility score that is the midpoint between first-line and second-line utility. The ERG noted in their critique that they felt this figure was somewhat arbitrary and questioned the clinical plausibility of the utility score as it implies that crizotinib patients being treated beyond progression have higher than that of pre-progressed patients receiving chemotherapy.

Noting the uncertainty highlighted in the ERG's report the company carried out additional analysis of the HRQoL data collected in PROFILE 1014. This analysis was used to estimate the mean change in utility following progression of those patients who continued with crizotinib therapy. This analysis estimated the difference between pre-progressed and post progressed crizotinib patients to be -0.03. The company revised base-case therefore assumes that crizotinib patients being treated beyond progression receive a utility of 0.78. This compares with 0.74 in the original company base-case.

The ERG has significant concerns regarding the new analysis carried out by the company and the clinical plausibility of the 0.78 utility score used in the company's revised base. Firstly, the data upon which this decrement in utility is calculated from suffers from extensive loss to follow up. As such there is significant risk of attrition bias. This bias is likely to act to reduce the magnitude of any obverted difference in the HRQoL of progressed patients. This is because the patients who are lost to follow up are likely to consist of sicker patients with lower HRQoL. Evidence of the impact of this loss to follow up on post-progression utility is seen in the data used in the company's new analysis, as patients' utility actually appears to increase when we would expect to fall as patients continue to progress. Secondly, one must consider the clinical plausibility of this value. As stated in the ERG report it was considered clinically implausible that the utility of crizotinib patients being treated beyond progression is higher than pemetrexed patients who are yet to progress. In the absence of any other evidence the ERG therefore considers the value used in the original company base-case of 0.74 to be the most plausible value for the utility of crizotinib patients being treated beyond progression. The ERG presents scenario analysis in Section 4 assuming this lower utility score.

3.5 Administration costs for crizotinib

The ERG base-case analysis included an additional costs related to the administration of crizotinib. This was based on the reasoning that while crizotinib is an oral therapy there would costs associated with delivering the treatment. This would include both dispensary costs as well as costs associated with monitoring compliance, adverse events and response to treatment beyond costs already included in the model with respect to the monitoring and management of patients. In line with the appraisal of crizotinib as a second-line treatment (TA296)[2] the ERG base-case included a monthly administration cost based on the cost of delivering oral chemotherapy.

The company response questions the appropriateness of including ongoing administration costs for an oral therapy such as crizotinib and reiterates arguments made in the CS that no such costs were included in TA347 where this was accepted by the Committee as appropriate. The response, however, further notes the expert testimony heard by the Committee suggests that there would be some administration costs involved with the administration of crizotinib. The company therefore opt to include an administration cost in their base-case analysis. The company, however, considers the value used in the ERG analysis to be inappropriate as the cost value used is for the administration of oral chemotherapy and not a target inhibitor such as crizotinib. The company further cite discussion with clinical experts at the ACD meeting stating that pharmacy dispensing costs would be incurred and therefore, in line with the recent appraisal of ceritinib, include a monthly cost of 14.40 to represent the administration costs associated with crizotinib. This value is significantly lower than the one used in the ERG base-case analysis of (£163.85) and consequently reduced the ICER by £3,425 per QALY.

The ERG acknowledges the apparent inconsistency between appraisals has created a degree of uncertainty with regards the appropriate costs to be included to represent the administration costs associated with oral cancer treatments such as crizotinib treatment Given that ceritinib is the most recent appraisal and the similarity between ceritinib and crizotinib, The ERG consider the revised costs included in company's model reasonable. However, given that a higher administration cost was assumed in the appraisal of crizotinib as a second-line therapy the ERG also considers it reasonable that the impact of alternative administration cost also be explored. The ERG therefore presents scenario analysis assuming the higher £163.85 administration cost in Section 4.

3.6 ALK testing costs

The base-case model presented in the CS included a cost associated with testing patients to identify patients who are ALK positive. The testing regime assumed that all potentially eligible patients receive an IHC test. Patients with equivocal score of 1 or 2 would then also receive a confirmation

FISH to confirm their ALK status. The company's base case assumed a cost of [redacted] for the IHC test and £120 for the FISH test. The cost associated with identifying a single ALK positive patient assuming these costs was [redacted]. The ERG noted in their report an alternative source of ALK testing from based on survey carried out by Cancer research UK which suggested that the average cost of ALK testing was £153. Based on this increased ALK testing cost the ERG estimated the cost of identifying a single ALK positive patient is £4500. At the first appraisal meeting the Committee heard expert testimony that suggested that the cost of ALK testing is likely to be between £50 and £100. Based on the expert testimony the company increased the cost of IHC testing to £75. The impact of this new assumption is increase the cost of identifying a single ALK positive patient to £2,379.89.

The ERG consider this assumption to be reasonable, given the testimony heard at the first appraisal meeting, but note that the expert testimony made reference to the direct costs of testing and, as the company acknowledge in their response, this does not include the laboratory costs associated with testing. The value used in the company's revised base-case of £75 may therefore still underestimate the actual cost of testing. Further, the ERG emphasise that the figure used in the ERG base-case of £153 was based on large scale survey of 26 testing centres carried out in 2014 and as such represents a recent and representative survey of the costs involved with ALK testing. The ERG therefore carries out additional analysis in Section 4 including the higher £153 testing based on the ERG original base-case analysis as a plausible scenario.

3.7 Proportional Hazards assumption and stratification of adjustment for baseline covariates

3.7.1 Proportional hazard assumption

The company's revised base-case assumes proportional hazards for both PFS and OS in line with the company's original base-case analysis. The company argue that relaxing the assumption of proportional hazards is not appropriate, arguing that all recommended checks were performed to test if the proportional hazards assumption held including inspection of the log-cumulative hazard plots; validation of the assumption with clinical expert opinion; and face validation of the resulting OS estimates with clinical experts and other published estimates. They therefore conclude that irrespective of the availability of patient level data it is reasonable to assume proportional hazards in the analysis of PFS and OS. In response to the ERG's reasoning that proportional hazards may not be valid because the two treatment regimens are administered differently, the company argue that there is no reason to assume that the different treatment regimens would impact on the proportional treatment effect. In support of this argument the company cites TA 190[3] which compared two pemetrexed regimens (one capped at 4 cycles, and one given until progression), and in which it was accepted by the Committee that the assumption of proportional hazards was appropriate.

The ERG wishes to highlight a number of points in relation to the assumption of proportional hazards assumption and implications in the analysis of survival data. The proportional hazard is an assumption of convenience made to improve the efficiency of survival estimation as it places a constraint on the structure of the relationship between the survival data in the treatment and comparator arm. It also allows for simpler interpretation of the relationship between the survival curves for the treatment and comparator and can therefore easier to interpret. Relaxation of this assumption therefore acts only to remove a constraint and allows greater flexibility in the fit of the selected parametric survival curves. It is for this reason that the DSU suggest that where individual patient data are available it is generally more appropriate to fit separate curves, as this is generally a more conservative position and avoids the potential for bias resulting from imposing the proportional hazards assumption. Given that the proportional hazards assumption can result in biased estimates of effect where it does not hold, the ERG considered that, based on the difference in the treatment in regimens and some indication of divergence in the curves in the log-cumulative hazard plots, it reasonable to assess the impact this assumption has on both estimates of PFS and OS as well the model ICER. The ERG's scenario showed that this assumption has significant bearing on the estimated ICER and it is important that this uncertainty is acknowledged. The ERG therefore considers the model where separate parametric curves are assumed to be at least as plausible as the model in which proportional hazards is assumed.

3.7.2 Selection of plausible survival curves where separate parametric curves are modelled

Recognising the Committee's preference for relaxing the proportional hazards assumption the company presents a series of analysis in which separate curves are fitted to the OS data. In total there are 36 combinations of survival curves possible, to select the most appropriate and plausible curves the company define a number of criteria on which to select the most plausible curves. These are summarised in Table 2 along with the justification for the criteria.

Table 2: Summary of curve selection criteria

	Criteria	Justification
1.	Mean OS for pemetrexed patients should not exceed 24 months	Given the committees view that crizotinib meets the end of life criteria mean OS for pemetrexed patients cannot exceed 24 months
2.	Mean OS gain should exceed 7.1 months	Data from PROFILE 1007 indicate that the survival benefit from crizotinib in a second setting is 7.1 months and therefore the minimum expected OS gain for crizotinib in the first-line setting is therefore 7.1 months.
3.	Mean OS should exceed median OS	This contradicts clinical opinion as it this implies no tail in the survival curve, which crizotinib's curve would be expected to have.
4.	Mean OS should be plausible given expectations on the survival of advanced ALK+ NSCLC patients	Clinical opinion

The ERG welcomes the approach by the company of using external sources of evidence to select from the curves, but has quite significant concerns regarding the validity of a number of the criteria set out by the company. These concerns are discussed in turn below.

Mean OS for pemetrexed patients should not exceed 24 months

The justification that the mean OS of pemetrexed should not exceed 24 months is based on the Committee's view that crizotinib meets the end of life criteria. This assumption is therefore not based on any actual evidence, but simply the opinion of the Committee. While the ERG acknowledges that Committee decisions are useful in determining how the future assumptions about input parameters may be view, Committee decisions are not a source of evidence in of themselves. The ERG therefore considers this assumption to be largely arbitrary and unjustified.

Mean OS gain should exceed 7.1 months

Based on the mean OS gain of 7.1 months predicted in the appraisal of crizotinib as a second-line treatment the company argue that the minimum OS one would expect in the first-line setting would be 7.1 months. In support company provide additional analysis of mature data that show the OS gain from crizotinib is better than predicted based on the data available when crizotinib was considered as second-line treatment. The company also further support this criterion by point to an increased PFS gain in the first-line setting when compared with the second-line.

The ERG considers that extrapolation of data from PROFILE 1007 to PROFILE 1014 is fraught with difficult for number reasons. These include the fact patients will receive therapy for different duration in a second-line setting than in a first-line setting; the fact that patients who receive second-lien treatment are different to those who receive first-line treatment; and, the fact the comparator in PROFILE 1007 was docetaxel and not pemetrexed. The impact of these factors is very difficult to assess and any extrapolation is subject significant uncertainty. However, evidence on the relative

magnitude of PFS gains across PROFILE 1007 and PROFILE 1014 provides some reassurance that realised OS gains will at least be as large as those observed in PROFILE 1007. The ERG therefore considers this criterion reasonable, but considers there to be a degree of risk in its application.

Mean OS should exceed median OS

The ERG considers this criterion reasonable given expectations about the shape of the survival curve.

Mean OS should be plausible given expectations on the survival of advanced ALK+ NSCLC patients

This criterion it to some extent very reasonable and in line with best practice regards the selection of the most appropriate curve. However, with respect to predicted mean OS for pemetrexed patients, it can be argued that all 6 curves predict a clinically implausible estimate of mean OS. For example, comparing this data with data reported in the CS on the survival of stage 3 and 4 NSCLC patients (Table 9) shows expected one year survival for stage 3 patients is only 35%. This compares with 68% assuming the most pessimistic Weibull curve. It is therefore clear that even after adjusting the data, the OS of chemotherapy patients in the economic model is not in line with current expectations about the OS of advanced and metastatic NSCLC patients. Selection of curves on this basis is therefore problematic. Further, the mean OS of crizotinib patients is not well known given the limited time crizotinib has been available and therefore to rule out some curves on the basis that patients could not possibly live so long is not appropriate.

Implications for interpretation for OS data

Given the weakness of a number of these criteria the ERG consider that a wider range curves are plausible. As such, based on analysis present in lower half of Table B1 of company's response (reproduced below; Table 3) the ERG considers that the most plausible range of ICERs for crizotinib is between £31,708 and £57,035 given all the other assumptions made in the company's revised model.

Table 3 ICERs when a minimum of 7.1 months mean & median OS gain with crizotinib is assumed

Separate curve modelling with independent covariate stratification (Committee's preferred model)				
Crizotinib curve	**Pemetrexed curve**	**Median OS gain**	**Mean OS gain**	**ICER (£ per QALY)**
Exponential	Gamma*	9.9	8.8	57,035*
Exponential	Exponential	9.9	13.0	47,921
Exponential	Weibull	9.9	14.1	46,004
Log−normal	Gamma*	9.9	22.9	36,126*
Log−normal	Exponential	9.9	27.2	32,529
Log−normal	Weibull	9.9	28.3	31,708
Log−normal	Log−normal*	9.9	14.4	46,656*
Log−normal	Log−logistic*	10.8	18.4	40,729*
Log−logistic	Gamma	7.9	15.5	44,817
Log−logistic	Exponential	7.9	19.8	39,181
Log−logistic	Weibull	7.9	20.9	37,939
Log−logistic	Log−logistic*	8.9	11.0	52,505*

3.7.3 Independent covariate stratification

In the company's critique of the relaxation of the proportional hazard assumption the company emphasizes that the analysis of PFS and OS in which separate parametric curves are fitted does not assume a common effect of covariates for both treatments. The company highlight that the use of independent covariate stratification model implies each covariate (such as age or gender) influences a patient's outcome to different proportions, depending on the treatment he or she receives. The company argue that there is no evidence to suggest that there should be a difference and considered this as evidence to justify their base-case assumption of proportional hazards in the analysis of PFS and OS.

The ERG note that it is not necessary to use independent covariate stratification when modelling separate parametric curves and indeed the points for clarification response included analysis in which this was the case. The relaxation of the proportion hazards assumption is therefore not connected to the assumption of independent covariate stratification. The company's claims regarding the use of independent covariate stratification therefore in no way supports the assumption of proportional hazards. The ERG's decision to use the survival modelling in which covariates are stratified was based on the lack of any evidence to the contrary and the desire to not make any assumption without evidence to substantiate them. Furthermore, given the similarity in parameter estimates from the two sets of analysis the ERG does not consider it likely that this would have a significant impact on the ICER. The ERG therefore does not present further analysis in which covariate effects are common across both treatment groups.

4 Additional analysis carried out by the ERG

In this section the ERG presents additional scenario analysis considering a variety of alternative input assumptions. A summary of the assumptions made in the ERG's re-analysis is presented in Table 4 along with details of the assumptions made in the company's original base-case, the Committee's preferred analysis and the company's revised base-case.

Table 4: Summary of assumptions in each model version

Parameter	Assumption in CS base-case	Committee's preferred analysis	Assumption in revised company model	Assumption in ERG re-analysis
Utility values for pre-progression pemetrexed patients (once off treatment)	Assumes constant utility score of 0.72 for pre-pre-progressed pemtrexed patients	Assumes a utility score of 0.81 for pemetrexed patients who have completed treatment, but not progressed.	Assumes a utility score of 0.75 for pemetrexed patients who have completed treatment, but not progressed.	Assumes a utility score of 0.81 for pemetrexed patients who have completed treatment, but not progressed.
Time on treatment with crizotinib	Assumes patients receive crizotinib beyond pre-progression for maximum of 4 cycles (mean 2.2)	Time on treatment is estimated from unadjusted parametric curve based on time on treatment in the PRORILE 1014 study.	Time on treatment is estimated from parametric curve adjusted using real world data.	Time on treatment is estimated from parametric curve adjusted using real world data.
(C) Crizotinib administration costs	No administration costs included	Administration costs of £163.85 per month included.	Administration costs of £14.40 per month included.	Administration costs of £163.85 per month included.
ALK testing costs	Cost of ALK testing based on file data. Cost of testing per ALK patient is [redacted].	Cost of ALK testing based on Cancer Research UK survey. Cost of testing per ALK patient is £4500.	Cost of ALK testing based on expert testimony. Cost of testing per ALK patient is £2379.89.	Cost of ALK testing based on Cancer Research UK survey. Cost of testing per ALK patient is £4500.
Post-progression utility score for crizotinib patients when still on treatment	Assumes a utility score of 0.74 based on improved symptom control and lower toxicity	Assumes a utility score of 0.74.	Assumes a utility score of 0.78 based on analysis of HRQoL data from PROFILE 1014.	Assumes a utility score of 0.74.
PFS and OS extrapolation	Assumes proportional hazard and common covariates for prognostic factors in each treatment group.	Separate curves are fitted to treatment and comparator and prognostic factors are stratified independently for each treatment group.	Assumes proportional hazard and common covariates for prognostic factors in each treatment group.	Separate curves are fitted to treatment and comparator and prognostic factors are stratified independently for each treatment group.

Table 5 presents the impact of each of the ERG's revised assumptions on the company's revised base-case while retaining the proportional hazards assumption. Table 4 also presents a revised ERG base-

case including all of these alternative assumptions. The ICER in the ERG base-case is £58,029 per QALY.

Table 5 Scenario Analysis (assuming proportional hazards)

Scenario	ICER	% change from base-case ICER
1. Pemetrexed off-treatment but pre-progression utility adjusted from 0.75 to 0.81	£50,168	2.0%
2. Crizotinib treatment beyond progression utility adjusted from 0.78 to 0.74	£50,150	2.0%
3. ALK testing cost adjusted from £2,380 to £4,500	£52,353	6.4%
4. Administration costs assumed to be £163.85 per month.	£52,611	6.9%
ERG base-case		
ERG base-case (Scenario's 1, 2, 3 and 4 combined)	£58,029	18.0%

Table 6 relaxes the assumption of proportional hazards in the analysis of PFS and OS and presents the results of all combinations of survival curves. The Table is split into four parts based on the mean OS gain for crizotinib patients. Assuming the mean OS gain exceeds 7.1 months, the estimated ICER assuming the ERG base-case assumptions is between £35,972 and £57,035 per QALY. The ICER assuming the company's preferred curve selection (highlighted in **bold text**) is £55,131 per QALY.

Table 6 Scenario Analysis (assuming separate parametric functions)

Crizotinib curve	Pemetrexed curve	Median OS Gain	Mean OS Gain	Company's revised base-case	ERG base-case	% change
Minimum 7.1 month mean OS gain						
Exponential	Gamma*	9.9	8.8	£57,035*	£66,079	15.9%
Exponential	**Exponential**	**9.9**	**13.0**	**£47,921**	**£55,131**	**15.0%**
Exponential	Weibull	9.9	14.1	£46,004	£52,841	14.9%
Log−normal	Gamma*	9.9	22.9	£36,126*	£41,172	14.0%
Log−normal	Exponential	9.9	27.2	£32,529	£36,938	13.6%
Log−normal	Weibull	9.9	28.3	£31,708	£35,972	13.4%
Log−normal	Log−normal*	9.9	14.4	£46,656*	£53,652	15.0%
Log−normal	Log−logistic*	10.8	18.4	£40,729*	£46,601	14.4%
Log−logistic	Gamma*	7.9	15.5	£44,817	£51,461	14.8%
Log−logistic	Exponential	7.9	19.8	£39,181	£44,770	14.3%
Log−logistic	Weibull	7.9	20.9	£37,939	£43,299	14.1%
Log−logistic	Log−logistic*	8.9	11.0	£52,505*	£60,641	15.5%
Minimum 3 month mean OS gain						
Weibull	Exponential	6.9	5.6	£67,292	£78,921	17.28%
Weibull	Weibull	6.9	6.6	£63,252	£73,960	16.93%
Log−logistic	Log−normal*	7.9	7	£63,404	£73,823	16.43%
Gompertz	Exponential	6.9	3	£79,952	£95,669	19.66%
Gompertz	Weibull	6.9	4	£73,839	£87,943	19.10%
No minimum mean OS gain						
Gamma[§]	Exponential	6.9	0.8	£98,384	£120,844	22.83%
Gamma[§]	Weibull	6.9	1.8	£88,551	£107,925	21.88%
Exponential	Log−normal*	9.8	0.3	£93,067	£110,495	18.73%
Exponential	Log−logistic*	10.8	4.3	£70,673	£82,650	16.95%
Weibull	Gamma*	6.9	1.3	£89,098	£106,113	19.10%
Chemotherapy mean OS exceeds crizotinib						
Gamma[§]	Gamma*	6.9	-3.5	£171,492	£222,921	29.99%
Gamma[§]	Log−normal*	6.9	-12	Crizotinib dominated	Crizotinib dominated	NA
Gamma[§]	Log−logistic*	7.9	-8	£692,220	£1,490,616	115.34%
Gamma[§]	Gompertz*	5.9	-27.2	Crizotinib dominated	Crizotinib dominated	NA
Exponential	Gompertz*	8.8	-14.9	Crizotinib dominated	Crizotinib dominated	NA
Weibull	Log−normal*	6.9	-7.2	£261,884	£350,609	33.88%
Weibull	Log−logistic *	7.9	-3.2	£132,538	£162,460	22.58%
Weibull	Gompertz*	5.9	-22.4	Crizotinib dominated	Crizotinib dominated	NA
Log−normal	Gompertz*	8.8	-0.8	£97,141	£115,490	18.89%

Log−logistic	Gompertz*	6.9	-8.2	£240,735	£313,934	30.41%
Gompertz	Gamma*	6.9	-1.3	£117,152	£144,043	22.95%
Gompertz	Log−normal*	6.9	-9.8	£2,335,313	Crizotinib dominated	NA
Gompertz	Log−logistic *	7.9	-5.8	£221,363	£293,377	32.53%
Gompertz	Gompertz*	5.9	-25	Crizotinib dominated	Crizotinib dominated	NA

** Asterisks indicate models in which pemetrexed's mean OS is greater than 24 months, which is at odds with the Committee' conclusion that the End of Life criteria are met.*

§ Symbol indicates implausible model due to mean OS < median OS.

5 Summary and Conclusions

The company's response to the ACD included a revised PAS and a revised economic model. The revised model makes a number of amendments and corrections intended to address the Committee's considerations and points raised in the ERG report. The revised company model also introduces new data to inform a number of input values. This new data is sourced from PROFILE 1007 and PROFILE 1014 and used to inform changes to the:

- Utility score for pre-progression pemetrexed patients once off treatment;
- Utility score for crizotinib patients treated beyond progression;
- Time on treatment data adjusted for 'real life' data.

The revised company model also makes new assumptions regarding administration costs of crizotinib and the costs of ALK testing. The company's base-case model does not, however, relax the assumption of proportional hazards made in the company's original base-case model. A series of scenario analyses, however, are presented in which separate parametric curves are fitted.

The ERG considers that a number of the changes made by the company are not well justified and are overly optimistic with respect to the costs and benefits of crizotinib. The ERG therefore carried out additional scenario analysis to assess the impact of these alternative assumptions on the ICER and a new ERG base-case is defined. If proportional hazards is assumed for PFS and OS this analysis estimates the ICER to be £58, 029 per QALY. The ERG, however, considers the model in which separate parametric curves are fitted for PFS and OS data to be at least as plausible as the model in which proportional hazards is assumed. Interpretation of this analysis is, however, more difficult due to difficulty in selecting the appropriate parametric curve. Assuming a minum mean OS gain of 7.1 months t and using ERG's preferred assumptions the estimated ICER is between £35,972 and £66,079 per QALY.

In addition to the above the ERG also note that since the company's original submission ceritinib has been recommended as second-line treatment for ALK positive NSCLC patients and that this is likely

to alter the treatment pathway for ALK positive NSCLC patients. The implications of this change are that the treatment pathway considered in the company's and ERG's base-case analysis no longer reflects how crizotinib is likely to be used in the England should it be recommend. These analyses therefore do not reflect the benefits and costs associated with the introduction of crizotinib. The company's' response to the ACD includes a scenario analysis to reflect this new treatment pathway. This analysis, however, only accounts for difference in costs and does not account for differences in OS. It therefore should not be interpreted as an accurate estimate of the ICER. A complete re-analysis of the OS data from PROFILE 1014 would be necessary to accurately model the impact of discontinuing treatment with crizotinib at progression.

6 References

1. NICE. Ceritinib for previously treated anaplastic lymphoma kinase-positive non small-cell lung cancer [ID729]. Committee Papers 2. 20th May 2016. Available at: https://www.nice.org.uk/guidance/GID-TAG478/documents/committee-papers-2 Accessed: 29th June 2016

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