NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer [ID1098]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Pfizer (company)
   - Roy Castle Lung Cancer Foundation
   - Association of Cancer Physicians, British Thoracic Oncology Group, Royal College of Physicians, Royal College of Radiologists, National Cancer Research Institute – joint submission
   - NHS England

   The Department of Heath submitted a "No Comment" response

   There were no comments received from patient or clinical experts

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

4. **Additional questions from NICE to clinical expert** – response from Dr Sanjay Popat, clinical expert nominated by nominated by British Thoracic Oncology Group, National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, and Royal College of Radiologists

5. **Appendix of new evidence –** submitted by Pfizer

6. **Evidence Review Group critique of company ACD comments** – prepared by Liverpool Reviews and Implementation Group

7. **Evidence Review Group addendum** – prepared by Liverpool Reviews and Implementation Group

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

Crizotinib for treating ROS1 positive advanced non small cell lung cancer

Single Technology Appraisal

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

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and 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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	BTOG-NCRI-ACP-RCP-RCR	We are disappointed that the NICE committee did not feel that the ICERs were robust enough to accept for an ACD recommending routine use. Whilst we do recognize that one option would be to have this indication within the Cancer Drugs Fund, given this fund's remit is for England, patients in Wales and Northern Ireland would be discriminated against and significantly disadvantaged by not being able to implement ROS1 testing and not being able to access crizotinib – a drug that the NICE committee agree is a "step change" for ROS1+ patients.	Thank you for your comment. The final appraisal determination (FAD) recommends crizotinib for use within the Cancer Drugs Fund (see section 1.1 of the FAD). The way NICE was established in legislation means that our guidance applies officially to England only (see sections 4.1 to 4.3 of the FAD). The evaluation of new medicines in Scotland and Wales may use a different process and different price discounts. For more details see https://www.nice.org.uk/about/who-we-are
2	Consultee	BTOG-NCRI-ACP-RCP-RCR	We are disappointed that the manufacturer chose not to give NICE the option of referring this indication directly to the Cancer Drugs Fund if uncertainties around the true ICER were identified	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
3	Consultee	BTOG-NCRI-ACP-RCP-RCR	If additional discussions between NICE and the manufacturer are not able to resolve the uncertainty around the ICER on drug cost grounds, we would prefer to see crizotinib funded in the Cancer Drugs fund than not at all available in the UK	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
4	Consultee	BTOG-NCRI-ACP-RCP-RCR	We have significant concerns around data collection aspects around progression-free survival if crizotinib is approved in the Cancer Drugs fund and would seek clarity from NICE on how data collection can be implemented and funded with adequate clarity to ensure that any future NICE re-review will not again be frustrated by ICER uncertainties, since it is unclear in this rare indication that any additional data captured on the small number of UK cases treated within the CDF will robustly answer uncertainties on post-progression survival identified, particularly in the second-line setting.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund. The data collection terms will be agreed by the company and NHS England.
5	Consultee	BTOG-NCRI-ACP-RCP-RCR	We ask NICE for clarity on how ROS1 testing will be reimbursed to laboratory departments.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund. The committee concluded that ROS1

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				status should be tested upfront in all non-squamous non-small-cell lung cancer (see section 3.2 of the FAD).
6	Consultee	NHS England	ROS1 positive NSCLC was discovered in 2011 and thus there is only a small amount of information as to its natural history, particularly in the real world setting, and there is a dearth of clinical outcome data for ROS1 patients treated with conventional cytotoxic chemotherapy.	Thank you, your comment has been noted. The committee discussed that the ROS1 oncogene is a recent discovery (see section 3.1 of FAD).
7	Consultee	NHS England	ROS1 pos NSCLC is almost always only seen in adenocarcinoma of the lung and never in patients with EGFR, KRAS or ALK mutations. ROS1 NSCLC and ALK pos NSCLC thus have oncogenic drivers that are mutually exclusive.	Thank you, your comment has been noted.
8	Consultee	NHS England	ROS1 NSCLC shares some demographic and clinical characteristics with ALK pos NSCLC: younger age (median 50 years), female sex (65%) and never smokers (68%). Brain metastases are also common in ROS1 NSCLC.	Thank you, your comment has been noted.
9	Consultee	NHS England	ROS1 NSCLC appears on preliminary evidence to be more sensitive to pemetrexed and possibly also to crizotinib than ALK pos NSCLC. Ceritinib is active in ROS1 NSCLC but probably only in crizotinib-naive patients unlike ALK pos patients where ceritinib is active in ALK pos crizotinib failures, Alectinib is active in ALK pos NSCLC but inactive in ROS1 NSCLC.	Thank you, your comment has been noted.
10	Consultee	NHS England	Some references state that ROS1 and ALK pos NSCLC have similar clinico-pathological features but there are important differences: the seemingly greater sensitivity to crizotinib in ROS1 NSCLC, the differing sensitivity to ceritinib and alectinib and of course the entirely different oncogenic drivers.	Thank you, your comment has been noted.
11	Consultee	NHS England	The most practical testing strategy for ROS1 would be screening of all adenocarcinoma patients at diagnosis. A two stage strategy of only testing the EGFR and ALK negative patients is in theory possible but would still require the testing of >85% of adenocarcinomas.	Thank you for your comment. The committee concluded that ROS1 status should be tested upfront in all non-squamous non-small-cell lung cancer (see section 3.2 of the FAD).
12	Consultee	NHS England	The cost of ROS1 testing must be included in the assessment of cost effectiveness of crizotinib as it is not currently in routine practice.	Thank you for your comment. The costs of ROS1 testing were included as part of the cost effectiveness assessment of crizotinib.
13	Consultee	NHS England	The key comparator for 1st line crizotinib is a platinum preparation plus pemetrexed followed by maintenance pemetrexed. The main comparators for crizotinib in the 2nd line setting are docetaxel and the combination of docetaxel and nintedanib, the latter being used much less frequently than the former in NSCLC as a whole. Whether this latter statement applies to	Thank you, your comment has been noted.

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			ROS1 NSCLC is unknown.	
14	Consultee	NHS England	NHS England notes that there is better evidence for the use of crizotinib beyond 1st line use but recognises the biological plausibility of at least equal benefit when used 1st line, such use coming at the expense of reduced toxicity when compared with standard combination chemotherapy.	Thank you, your comment has been noted.
15	Consultee	NHS England	The single arm Profile 1001 study is small in size and has a median duration of follow-up of 25 months. It is thus relatively immature when only 30% of patients had died at the last data cut off in November 2015. NHS England is disappointed that no further follow up appears to have been done in the past 2 years.	Thank you, your comment has been noted.
16	Consultee	NHS England	NHS England notes that there are only 7 previously untreated patients with ROS1 NSCLC treated with crizotinib in Profile 1001. This is a tiny number and imposes huge uncertainty in assessing the clinical and cost effectiveness of crizotinib in this setting.	Thank you, your comment has been noted.
17	Consultee	NHS England	The durations of treatment with 1st- and subsequent line crizotinib in ROS1 patients are highly likely to significantly exceed the durations of progression-free survival observed in Profile 1001 and thus this treatment period beyond disease progression must be modelled in the economic analysis of crizotinib.	Thank you, your comment has been noted. The costs of crizotinib after disease progression was included in the model.
18	Consultee	NHS England	NHS England notes that the correct cost for the HRG chemotherapy tariff for crizotinib administration has not been used by the company: a figure of £14-60 has been used whereas the 2017/18 oral chemotherapy tariff is £120 per month.	Thank you for your comment. The committee discussed the revised administration costs for crizotinib and agreed these were appropriate (see section 3.13 of the FAD).
19	Consultee	NHS England	NHS England notes the rather large contribution of the crizotinib post progression survival figures to the overall survival of both 1st and 2nd line crizotinib patients in the economic modelling, these figures significantly exceeding the total overall survival figures for the relevant comparator populations treated with just chemotherapy. NHS England finds these post progression survival figures after discontinuation of crizotinib as being implausible.	Thank you for your comment. The committee concluded that there was considerable uncertainty around the size of overall survival benefit with crizotinib but preferred the midpoint between the company's and ERG's scenario analyses (see sections 3.10 and 3.11of the FAD).
20	Consultee	NHS England	NHS England is surprised and sorry to observe that Pfizer do not wish crizotinib to be considered for entry into the CDF despite the NICE committee's clear indication that this was its wish. The huge uncertainty in the 1st line setting when there is so little data makes the CDF an excellent opportunity for national data collection for a large number of patients, thus providing help to NICE (and Pfizer) in a post-CDF re-appraisal of crizotinib and also giving a huge contribution to the world literature on crizotinib use and subsequent chemotherapy in ROS1 NSCLC.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
21	Consultee	NHS England	Crizotinib is clearly active in ROS1 NSCLC but follow up in the single arm	Thank you for your comment. The FAD

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			Profile 1001 study is relatively immature. Should NICE recommend this indication to the Cancer Drugs Fund then a large dataset could be collected on treatment duration, subsequent therapies and overall survival. Since there has not been any further follow up data since November 2015 used in this submission by the company, NHS England wonders whether there will be any further data collection and analysis from Profile 1001. If not, then any uncertainties that the NICE TA committee has as to mature outcomes of crizotinib in ROS1 NSCLC would have to be resolved by prolonged follow up in the CDF, potentially for up to 5 years.	recommends crizotinib for use within the Cancer Drugs Fund. The data collection terms will be agreed by the company and NHS England. The committee considered the longer data collection period as part of its discussion on the Cancer Drugs Fund (see section 3.18 of the FAD).
22	Consultee	Pfizer	Thank you for the opportunity to comment on the Appraisal Consultation Document for the above appraisal. Pfizer are disappointed with the draft recommendation made by the Committee, and believe that several assumptions which were made to reach this recommendation are flawed and lack clinical validity. It is Pfizer's opinion that the information contained within this response will provide sufficient evidence and clinical opinion for the Committee to reconsider their current preferred assumptions (in particular with regards to overall survival), and therefore allow the Committee to recommend crizotinib within its licensed indication for ROS1-positive non-small cell lung cancer (NSCLC), as both a clinically effective and cost-effective use of National Health Service (NHS) resources, especially considering the ultra-orphan nature of this disease and the considerable unmet need in ROS1-positive NSCLC patients. As part of Pfizer's response (and as agreed with the National Institute for Health and Care Excellence [NICE] secretariat), new evidence has been included from a re-analysis of the survival gain, taking into account the Committee's preferences for an adjustment to be made to the crizotinib survival rather than the comparator survival. The overall survival data for crizotinib in ROS1-positive NSCLC unequivocally demonstrates that patients treated with crizotinib in the first-line experienced at least a mean 13.1-month survival benefit and in subsequent-line, at least a mean 16.2-month survival benefit compared to current treatment options. The upper bound of the resulting incremental cost-effectiveness ratio (ICER) range was below £50,000 per quality-adjusted life year (QALY,) the threshold considering the Committee's conclusion that crizotinib meets the criteria to be an end-of-life therapy. Pfizer believes that, based on this conservative estimate of overall survival in ROS1-positive NSLCLC patients, crizotinib is cost-effective. Any further maturation of trial data would support that the assumptions made are indeed conservative. This is again emphasised in what has been observed in clinical practice for both first- and subsequent-	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund. Although the most plausible ICER was not clearly within the range normally considered a cost-effective use of NHS resources, crizotinib had plausible potential to represent cost effectiveness through its use in the Cancer Drugs Fund (see sections 3.14, 3.18 and 3.19).

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			line anaplastic lymphoma kinase (ALK)-positive NSCLC patients; survival gain is far greater than the minimum necessary to prove that crizotinib is cost-effective. The current Patient Access Scheme provides further certainty that crizotinib provides value for money to the NHS and aims to ensure that ROS1-positive patients receive timely access to targeted treatment. In addition, Pfizer do not believe the use of a proxy population in this submission sets a precedence for future appraisals, since it is unusual to find two patient populations with biological characteristics and clinical outcomes that are as similar as those in the ROS1-positive and ALK-positive NSCLC populations. Given the high quality of the ALK-positive NSCLC clinical trials, as well as NICE's recommendation to use first- and subsequent-line crizotinib for treatment of advanced ALK-positive NSCLC, there is a strong rationale to apply the data from ALK-positive NSCLC to inform this submission. Furthermore, this would be in line with EMA's recognition of the generalisability of data between ALK-positive NSCLC and ROS1-positive NSCLC. As we have seen from the results of the recent Marsden UK national audit, further efforts to obtain more data in the rare ROS1-postive NSCLC population, will not only be difficult due to lack of clinical equipoise but will add little to the existing evidence. The comparability between prospective and retrospective studies in ROS1-positive NSCLC (including the Marsden audit) clearly demonstrate the effect of crizotinib in ROS1-positive NSCLC to be consistent across trials. Pfizer has presented a compelling case within this response and strongly believes crizotinib is both a clinically- and cost-effective treatment option that should be made available for ROS1-positive NSCLC patients within England and Wales.	
23	Consultee	Pfizer	Pfizer consider the provisional recommendations to be based on clinically invalid assumptions which are not a suitable basis for guidance to the NHS. Whilst recognition from the Committee is welcomed that the innovative nature of crizotinib represents a step-change in the treatment of ROS1-positive NSCLC patients, it is disappointing that the cost-effectiveness of crizotinib has not been recognised. It has been noted from the appraisal consultation document (ACD) that the ICERs the Committee would consider as a starting point for its discussions were [redacted] per QALY (first-line) and [redacted] per QALY (subsequent-line). These ICERs are the mid-points between the Company's base case and the Evidence Review Group (ERG)'s exploratory analysis that assumed no survival benefit in progressed disease stages, and hence	Thank you for your comment. The committee discussed the clinical plausibility of survival assumptions in people with ROS1-positive non-small-cell lung cancer (see sections 3.10 and 3.11 of the FAD).

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			results in a modelled mean survival gain of only 7.6 months and 5.8 months for crizotinib compared to first-line pemetrexed plus platinum and subsequent-line docetaxel, respectively. Pfizer believes that these analyses, based on the mid-point between the Company's base case and the ERG's exploratory analysis, produce overestimations of the true ICERs, most notably because of the clinically invalid assumptions pertaining to the mean overall survival (OS) gains associated with crizotinib compared to first-line pemetrexed plus platinum and subsequent-line docetaxel. The modelled OS gains associated with the Committee's preferred upper range of ICERs for crizotinib in the first-line (7.6 months) and subsequent-line (5.8 months) are less than what is expected by clinical experts and less than the OS gain accepted by previous appraisals of crizotinib as first-line and subsequent-line therapies for ALK-positive NSCLC. This is in line with observations of ROS1-positive NSCLC patients treated in clinical practice, reported in the Marsden audit, where after median follow-up of 19.4 months, median OS had not been reached in first- and subsequent-line ROS1-positive NSCLC patients treated with crizotinib. In addition, Pfizer do not believe the use of a proxy population in this submission sets a precedence for future appraisals, since it is unusual to find two patient populations with biological characteristics and clinical outcomes that are as similar as those in the ROS1-positive and ALK-positive NSCLC populations. Because of the rarity of advanced ROS1-positive NSCLC and the absence of comparative efficacy data due lack of clinical equipoise to conduct further comparative studies, a pragmatic solution to modelling had to be used in this submission to inform decision making. In the response below, the ICERs that represent the Committee's preferred set of assumptions are presented first, as described in the ACD. New analyses are then presented and revised ICERs include an adjustment to the crizotinib OS curve, such that mean OS gain is reduced, but with some relative post-progression survival (PPS) gain attributed to crizotinib vs the comparator. The mean (and median) OS gains in these analyses have been validated by clinical experts to be in-line with the expected mean (and median) OS gains with crizotinib in ROS1-positive NSCLC in clinical practice. Clinical experts confirm that the expected mean OS gain of ROS1-positive patients treated with crizotinib would be approximately between 13.1–18.2 months compared to first-line pemetrexed plus platinum and 16.2–20.9	

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			months compared to subsequent-line docetaxel, i.e. at least the mean OS gain accepted by the Committee in the previous first-line (13.1 months) and second-line (16.2 months) appraisals of crizotinib in ALK-positive NSCLC. Indeed, the OS gains in these appraisals are already considered to be conservative with respect to crizotinib. Furthermore, based on threshold analyses, the absolute minimum mean OS gains that need to be realised for the ICER of crizotinib to be below £50,000 per QALY are 11.9 months in the first-line and 14.3 months in the subsequent-line, which is less than the mean OS gain expected in clinical practice for this population of patients. Pfizer are confident, based on these new analyses, that the most plausible ICERs for crizotinib are below the £50,000 per QALY threshold for end-of-life medicines and believe that the information presented in this response should allow the Committee to reconsider its provisional conclusions and recommend crizotinib for treatment of ROS1-positive NSCLC patients, enabling equitable access to crizotinib as a step-change therapy in this rare oncology disease area. The company presented additional data that are not reproduced here.	
24	Web comment	NHS Professional	ROS1 positive non-small cell lung cancer patients are a small but important population of lung cancer patients because they could benefit greatly from access to Crizotinib. I therefore feel strongly that they should be allowed access to Crizotinib as it has been demonstrated to be effective and tolerable.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
25	Web comment	NHS Professional	I was very sorry to read the initial NICE outcome. I understand the constrains of cost-effectiveness in view of the lack of direct evidence available due to low disease frequency, and rapidly evolving pharmacological and biological advances. I would like, however, to express my point of view from my own experience: I run a centralized "mutation-driven lung cancer clinic" at The Clatterbridge Cancer Centre, and have done so for over two years now. At CCC we see 1000 new lung cancer patients every year, and 9% have a cancer with a targetable mutation. I see, on average, one new patient a week with an EGFR mutation and one new patient a month with an ALK rearrangement and on average review 25 patients every week with mutation-driven lung cancers. These particular lung cancers (EGFR mutated, ALK positive. and, from the evidence available, ROS1 positive) behave very differently from wild type lung cancer, as can be seen in several publications reporting a much higher incidence of brain metastasis with no prognostic impact. These	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			tumours meet two criterira: (a) their growth and metastatic potential is dependent on ONE genetic anomaly and (b) inhibition of the abnormal protein expressed achieves almost universally disease control with high radiological response rates. The rare cases where I have not seen disease control in EGFR tumours have been when the initially reported anomaly before radical intervention has been lost years later on disease recurrence. I have always seen disease control in tumours with a targetable gene rearrangement. The question is not if there will be disease control, the question is when will the disease become resistant to it. Furthermore, these tumours have been excluded from first line immune therapy, and there is wide scepticism about the potential benefit of this novel therapeutic approach in this patient group: mutation burden (which correlates with smoking habits) is a good predictor of response to immune therapy, but mutation-driven lung cancers (more common in never smokers) are characterized by a low mutation burden. From the reported literature, ROS1 and ALK tumours are similar in that both arise through a gene translocation and present not only similar clinical evolution, but also excellent response to Crizotinib. Hence ROS1 tumours are mutation-driven lung cancers, and need to be treated as such. Beyond the necessary economic calculations that relate to survival, there are other economic arguments that need to be taken into account in the modern oncology context. Let me describe the patient population we are likely to deny diagnosis or treatment: never-smokers, with low co-morbidity, often with many productive years ahead, developing incapacitating brain metastasis. These patients will be denied a treatment that is likely to allow them to go back to work (as my patients do regardless of brain involvement) and will be offered instead more expensive radiotherapy, chemotherapy and/or immune therapy from which they will be unlikely to benefit as other patients with wild type tumours do. Those who live healthier lives will be punished because they happen to have a rare type of lung cancer, by not being offered an available treatment with low toxicity and high clinical effectiveness. Thank you for reading my comment. I hope it helps making the right decision for this small group of patients. Please do not hesitate to contact me if you think I can be of further help.	
26	Web comment	NHS Professional	I work at Guy's Hospital where we routinely screen for ROS1 rearrangements in non-squamous lung cancer at diagnosis (unlike many other UK centres). This means that we have more experience than most in treating this rare group. Our anecdotal experience is that these patients do	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			very well with crizotinib. We contributed our experience to a multicentre report presented last week at the British Thoracic Oncology Group meeting (Tokaca et al). 10 patients with ROS1-driven cancers received crizotinib with a response rate of 70%, and median PFS of 12.1 months despite many taking the targeted drug as 2nd or subsequent line. These are exceptional outcomes for advanced NSCLC. Patients receiving crizotinib have in some cases been able to access next-generation TKIs on progression, on a compassionate access basis from their manufacturers. So we are moving to a point where really outstanding quality and quantity of life is achievable in these patients, when given access to the appropriate targeted drugs. One of my ROS1 patients currently responding to his 2nd targeted drug has long ago returned to work as a teacher and currently leads a normal and economically productive life. I hope the NICE appraisal committee will take account of these comments. I truly believe we owe it to this very small group of patients to provide the very active and well tolerated treatment that is potentially available.	
27	Web comment	NHS Professional	It is very disappointing that NICE have not approved Crizotinib for the management of ROS-1 translocated lung cancer. ROS-1 translocations are very rare and therefore the clinical data for Crizotinib is going to be less comprehensive than that for other cancer treatments. In addition, because crizotinib has only recently been recognised as a treatment for ROS-1 translocated lung cancer, the patients involved in the clinical trials had received range of different lines and types of prior treatment. There is absolutely no doubt that Crizotinib is a highly, highly active drug in ROS-1 translocated lung cancer. The median PFS of 19 months is extraordinary and was unprecedented at the time of publication of PROFILE-1001. This patient cohort, who are frequently young and usually never-smokers, are in desperate need of an effective treatment. Whilst I agree that using Crizotinib data relating to ALK-translocated patients is not 'ideal', the need to do so reflects the rarity of the disease, and as a clinician I think it is a fair proxy. ROS-1 translocated lung care is rare, but utterly devastating for the often young patients who have it. There is a highly effective, licensed treatment with a remarkable clinical activity. There is no doubt about the benefit of this drug in the lung oncology community. I feel that the criticism of the clinical data has been unfair and has not taken into account the exceptional nature of this small group of patients.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			The costs to the country for this drug, given the small patient pool, is minimal. The benefits to each of those patient is, however, vast.	
28	Web comment	Patient	This description of the evidence is lacking a comprehensive view of the data available. Internationally there is a lot of both untreated and treated ROS1 cancer having a durable response to crizotinib. See 600+ referenced paper: http://www.nejm.org/doi/full/10.1056/NEJMoa1406766	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
29	Web comment	Patient	This section does not outline a TESTING PROGRAM for ROS1 this is direly needed. It agreed that testing for ROS1 status in all newly diagnosed non-squamous NSCLC would be the best strategy, in line with testing for other types of tumour expression in NSCLC. - Why is this testing not being done?	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
30	Web comment	Patient	As a current ROS1+ NSCLC patient, I am very disappointed that treatment will not be available for others like me. I was diagnosed two years ago at the age of 25, and I have had no other history of cancer and disease. This particular mutation effects younger people much more often. I have been living a normal and healthy life thanks to Crizotinib I was able to access from another source. (I am treated by a French doctor due to my diagnosis) I think it is a shambles that my doctor applied for this even with evidence of a strong response and that I tolerated the treatment very well. 1) ROS1 should be routinely tested as it is in any other major developed country. 2) Crizotinib should be available as a first line treatment as it saves lives and allows a good quality of life.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
31	Web comment	Patient	Crozitinib is indicated as first line treatment for ROS-1 patients in France and in many other countries. There is a strong body of evidence that this treatment is the best for lung cancer patients who carry the ROS-1 rearrangement. This also allow them to carry on with a normal standard of	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund (see section 1.1 of the FAD). The way NICE was established in legislation means

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			life comparing to traditional chemotherapy, and this is not to be neglected.	that our guidance applies officially to England only (see sections 4.1 to 4.3 of the FAD). The evaluation of new medicines in Scotland and Wales may use a different process and different price discounts. For more details see https://www.nice.org.uk/about/who-we-are
32	Web comment	Patient	I disagree with the NICE recommendation as set out in the consultation paper in relation to the use of crizotinib because: • The absolute requirement for further ROS 1 specific data, when further studies are considered unethical and patient population is low, unfairly disadvantages those with rare conditions such as ROS 1 positive cancer • A proxy population has been clearly identified and accepted by the European Medicines Agency and 12 UK clinical experts which should fulfil the data requirement • There is a clear societal benefit given that a) ROS 1 patients are, on average, much younger than other lung cancer sufferers with no targetable mutation and thus much more likely to have dependent children and b) the efficacy of the drug is undisputed; patient autonomy is preserved • Crizotinib has already been approved for use on the NHS for the proxy population • Making crizotinib available only via the Cancer Drug Fund reduces patient access in certain parts of the United Kingdom. Without this drug, sufferers of ROS 1 positive lung cancer will die an early death; this drug is keeping patients alive and functioning well across the world. I therefore call for routine testing throughout the UK for genetic mutations such as ROS 1, and for NICE to approve the use of crizotinib on the NHS for the ROS1 positive cancer patients thus identified. This will generate an extended, improved quality of life for patients and related societal benefits as described in more detail below.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
33	Web comment	Patient	A rarely occurring cancer	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			ROS1 positive lung cancer is a very rare cancer. This means that by definition, data will be hard to access due to difficulty in finding participants for studies. This is particularly the case in locations such as the UK where genetic testing has not, in recent years, been routine procedure. The UK is a very evidence based jurisdiction, as it is important that there is accountability for the use of public funds. Under normal circumstances, this evidence based approach is perfectly valid. However, there will always be exceptions to this and an extremely rare condition such as ROS1 would be one of those exceptions. Without a flexible approach, ROS 1 positive patients will be unfairly disadvantaged compared with other patient populations simply due to the rareness of their condition. Routine testing for targetable mutations would increase the potential data available, though it is likely to remain a rare finding; a recently published update to the IASLC/CAP/AMP molecular testing guidelines for NSCLC strongly recommended testing all NSCLC adenocarcinoma cases for ROS1.	Drugs Fund.
34	Web comment	Patient	The proxy population The European Medicines Agency and twelve UK clinical experts agreed that because of the rareness of this condition, and the similarities it has to another genetic mutation, ALK, that the ALK population could be used as a proxy population for ROS1. This appears to be a very pragmatic approach for a rare condition. It is true that as research continues some differences between ALK and ROS1 may be found; however, the PROFILE 1001 study generated such marked effects on its ROS1 participants (crizotinib was seen to be more effective for ROS 1 than ALK) that researchers concluded that a randomized controlled trial without access to crizotinib for the control population would actually be unethical. Therefore it does not seem likely that a further specific ROS1 study with comparator data will become available. It seems that this proxy population is now being rejected due to the much greater effect the drug has for ROS 1 than for ALK, which does not feel like an equitable result. Given the conclusion that further studies would be unethical, it seems extremely unfair to deny ROS1 patients the opportunity to access this life extending drug, which represents a step change in the treatment of such patients. Indeed, it has already been approved for use on the NHS for ALK positive patients. More generally, denial would mean that those with rare conditions have a much lesser chance of accessing the drug they need simply because they are few in number, even when the efficacy of the drug is “undisputed”. This does not, in my view, represent equitable treatment for this patient population -	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			access, when a known treatment is available, should not depend on patient numbers and the resultant availability of data when the patients are few in number and proxy data is available.	
35	Web comment	Patient	Societal benefit Crizotinib has a better safety profile than chemotherapy and is generally better tolerated. Because it is an oral treatment, patient autonomy is maintained, and medical resource usage reduced, generating a further benefit. The average age of diagnosis of ROS 1 patients also means that they are much more likely to have dependent children. I was diagnosed with ROS1 positive lung cancer in June 2017 and have been fortunate enough to be able to access crizotinib as a first line treatment privately. In my case, the drug has allowed me to remain a functioning parent to my two children. Without it, activities of daily living quickly become problematic. I am extremely grateful to have access to crizotinib.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
36	Web comment	Patient	Cancer Drug Fund Making crizotinib available only through the Cancer Drug Fund means that patients in Wales and Northern Ireland will not be able to access crizotinib at all, which would be inequitable. Further, ROS1 patients in these areas would not even be identified as there would then be no testing for the mutation. This will further reduce any potential future data gathering opportunities in what is already an extremely limited population.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund (see section 1.1 of the FAD). The way NICE was established in legislation means that our guidance applies officially to England only (see sections 4.1 to 4.3 of the FAD). The evaluation of new medicines in Scotland and Wales may use a different process and different price discounts. For more details see https://www.nice.org.uk/about/who-we-are
37	Web comment	NHS Professional	I am aware of the limitations of the data surrounding Ros-1 tumours. However these are rare tumours and it is unlikely that good quality randomised data will ever be available. I would agree with the NICE panel that these tumours behave in a similar fashion to the ALK positive group - they are adenocarcinomas and are predominantly in never smokers but additionally they appear to have a similar phenotype with multi-focal lung disease and a predilection for the CNS. I would therefore support the use of the ALK data in this group. The alternative of chemotherapy is problematic. It is toxic, with generally short term responses and a number of patients are not able to tolerate it at all leaving them with only the option of palliative care. This is particularly difficult to accept when there is a tablet available which is strikingly well tolerated with some evidence showing a	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			good chance of clinically significant benefit.	
38	Web comment	NHS Professional	Song et al (Cancer Med. 2016 Oct; 5(10): 2688-2693) reported a 6.7-month median PFS in 34 ROS-1 lung cancer patients treated with pemetrexed-based chemotherapy. Chen et al (J Thorac Oncol. 2016 Jul;11(7):1140-52) reported on 19 ROS-1 patients also treated with Pemetrexed-based chemotherapy and showed a 7.5 month median PFS. These studies compare with a 19.5 month median PFS in the 50 ROS-1 patients reported in the 2014 Shaw et al. NEJM paper. ROS-1 cancers are very likely to be analogous to EGFR and ALK translocated lung cancers in that more patients respond to targeted therapy than to chemotherapy, and those that respond do so more durably. The huge difference in PFS with crizotinib compared to chemotherapy reported in trials strongly suggests crizotinib is the more effective treatment. Disease control is associated with a reduction in cancer-related symptoms, and Crizotinib is well tolerated. Patients with ROS-1 lung cancer are likely to represent 1% or less of all lung cancer cases, and the cost of providing crizotinib will be relatively small compared to the overall drug budget for lung cancer patients. I would urge NICE to reconsider their decision not to approve Crizotinib in ROS-1 positive patients.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
39	Web comment	Patient	We are The ROS1ders, a group of 259 patients and caregivers dealing with ROS1-positive (ROS1+) non-small cell lung cancer (NSCLC) in 32 countries. We network and collaborate with clinicians, researchers, cancer advocacy organizations and industry as part of the Global ROS1 Initiative. Our global group represents more than four times the number of ROS1 patients found in any ROS1 clinical trial cohort to date. With this letter, we are contributing our collective experience to the appraisal consultation. Most of the patients in the ROS1ders have been treated with crizotinib. We believe crizotinib is an effective treatment for metastatic ROS1 non-small cell lung cancer (NSCLC), and gives us better quality of life than chemotherapy.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
40	Web comment	Patient	Crizotinib enables ROS1+ NSCLC patients to live normal lives instead of coping with a terminal disease. The majority of crizotinib-treated ROS1 patients are experiencing astonishing improvements in their state of health, which is unknown for chemotherapy. More than two-thirds of our members report a strong response to crizotinib and long progression-free periods with a very good quality of life. Many patients in our group started taking	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			crizotinib in 2011 or 2012, and several of them continue to take the drug and enjoy no evidence of disease. These patients are dealing with lung cancer as a chronic illness rather than a terminal disease. We may have a chronic illness that will one day claim our lives, but we are NOT at “end of life”.	
41	Web comment	Patient	Crizotinib gives ROS1+ NSCLC patients a superior quality of life compared to chemo Several of our members received one or more lines of chemotherapy prior to their treatment with crizotinib. Their quality of life was significantly worse while receiving chemo than while taking crizotinib. The QALY criteria for evaluating crizotinib does not capture the impact of crizotinib versus chemo on our daily lives. ROS1 patients are often younger than typical lung cancer patients; at the time of diagnosis, many of our members are employed and have children at home. When treated with crizotinib instead of chemo, most can continue living their usual lives with a minimum of side effects. When treated with chemo, many patients are too ill to participate in the aspects of life they most enjoyed, and most saw their cancer progress in less than a year. The results of several clinical trials worldwide have led to consensus among ROS1+ NSCLC patients and their doctors that crizotinib is significantly superior to all chemotherapy regimens in ROS1 patients in terms of response rate, progression-free time, toxicity, quality of life and survival time. Our experience would indicate an improvement in overall survival as well. The patient-relevant parameters are quite similar to ALK-positive NSCLC patients (for whom NICE covers crizotinib). Fortunately, the progression-free time for ROS1 patients is significantly longer than for ALK patients. Quality-adjusted Life Year (QALY) evaluation often does not capture all the relevant quality of life improvements experienced by patients on crizotinib. First, QALY analyses usually compare the state of health of NSCLC patients on crizotinib to that same patient’s state of health before taking crizotinib. A more honest evaluation would compare the health of a typical ROS1+ NSCLC patient on crizotinib (who survives for years with good quality of life) to the typical metastatic NSCLC patient on chemo (who usually dies within one year of diagnosis) or even on hospice. ROS1+ NSCLC patients on crizotinib are often able to continue working, caring for their families, and contributing to society, and are far less likely to be	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			hospitalized with treatment complications compared to chemotherapy recipients. This places less emotional and financial burden on spouses, caregivers, and consumes fewer healthcare system resources.	
42	Web comment	Patient	Conducting a Randomized Controlled Trial (RCT) for ROS1 is not ethical nor reasonable It is unethical to randomize patients to therapies known to be less effective. Several Phase 2 studies show crizotinib is effective in 70% to 80% of ROS1+ patients, whether those patients are untreated or heavily pretreated. Considerable scientific data shows chemotherapy is effective in about 20% of NSCLC patients in first line treatment, and effective in only 9% of NSCLC patients in second line treatment. An RCT would also be complicated by the fact that ROS1+ NSCLC occurs in a very small population of patients, which means not enough patients would be available for a Phase 3 trial. To demonstrate: • About 207,000 new NSCLC cases were predicted in the USA for 2017. • Two recent journal articles found only 60% of NSCLC patients are getting tested for known driving oncogenes. • ROS1 occurs in about 1% of tested NSCLC patients. • Typically 3% of cancer patients enroll in clinical trials. The EUCROSS trial had to test 200 patients to find one ROS1 patient willing and able to enter a trial. When all these factors are considered, about 37 new ROS1 patients were available to enrol in US ROS1 clinical trials during 2017â€”hardly enough to power a Phase 3 clinical trial. The UK has far fewer lung cancer patients than the USA. Therefore, creating a trial comparing crizotinib with chemotherapy in ROS1+ NSCLC patients would be an unnecessary waste of patients, time and money.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
43	Web comment	Patient	The scientific community strongly recommends testing NSCLC patients for ROS1 and treating them with crizotinib Based on a comprehensive evaluation of ROS1 studies and clinical trials, the International Association for the Study of Lung Cancer (IASLC), the	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			College of American Pathologists (CAP), and the Association for Molecular Pathology (AMP) strongly recommend testing for ROS1 in the 2018 update to their lung cancer molecular testing guideline: ROS1 testing must be performed on all lung advanced stage adenocarcinoma patients, irrespective of clinical characteristics. This recommendation is evidence based and supported by 9 studies. All included studies were assessed for quality and none were found to have methodologic flaws that would raise concerns about the study's findings Although relatively rare, accounting for <2% of none small cell lung carcinomas and 2% to 3% of lung adenocarcinomas, structural rearrangements involving the ROS1 gene generate an oncogenic fusion that can be treated successfully with targeted inhibitors. A single phase I clinical trial of 50 NSCLC patients demonstrated that the presence of a ROS1 rearrangement by FISH or RT-PCR predicts response to targeted inhibition using crizotinib, with a response rate of 72% and median progression-free survival of 19.2 months. Based on this trial, the FDA approved the expanded use of crizotinib in patients with ROS1-rearranged NSCLC in 2016. A European multi-institutional retrospective study of 32 patients with ROS1-rearranged NSCLC treated with crizotinib demonstrated an 80% response rate and 9.1-month progression-free survival. Overall survival for patients with ROS1-rearranged tumours irrespective of use of targeted therapy appears longer than that for patients with other molecular alterations undergoing targeted therapy. As with ALK, ROS1 activation is driven by structural variants, with multiple different partners fusing to the C-terminal portion of ROS1 containing the cytoplasmic tyrosine kinase and driving downstream signalling through MAPK, JAK/STAT, and PI3K pathways. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors (Journal of Molecular Diagnostics), http://jmd.amjpathol.org/article/S1525-1578(17)30590-1/fulltext Furthermore, the prospective European EUCROSS phase II trial evaluated crizotinib in ROS1+ lung adenocarcinoma and came to the conclusion: Crizotinib is a highly effective and safe treatment in the subset of ROS1 rearranged NSCLC patients as determined by FISH and DNA-sequencing.	

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			In total, 34 patients were enrolled in this trial. Of these, the patients whose ROS1+ was identified by sequencing showed a response rate of 83%. Even after a long study period the median progression-free survival has yet to be determined. EUCROSS: A European Phase II Trial of Crizotinib in Advanced Adenocarcinoma of the Lung Harboring ROS1 Rearrangements - Preliminary Results http://www.jto.org/article/S1556-0864(16)31669-0/fulltext (Journal of Thoracic Oncology)	
44	Web comment	Patient	Conclusion: Crizotinib is superior to existing therapies for ROS1+ NSCLC, and a wise investment for NICE For the first time ever, ROS1+ NSCLC patients have a truly effective therapy, with previously unattainable improvements in their quality of life and survival. There isn't a need to wait for an RCT comparing crizotinib to chemo when the improvement in outcomes is this dramatic. Allowing these patients to take crizotinib instead of other existing NSCLC therapies enables UK citizens to continue their lives instead of being end of lifepatients. NICE, please provide crizotinib as a treatment option for ROS1+ NSCLC patients.	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.
45	Web comment	Patient	I had been suffering from extreme vertigo for several weeks when I saw a consultant neurologist. She arranged for me to have a scan of the brain and I saw her afterwards. I was with my husband and son. The consultant asked how old my son was. I said five. She looked at me and hesitated as she muttered these words, looking at the scan of my brain on her computer, "You have cancer. You have many metastasized tumours in your brain." and looked at me as if it was a miracle that I was still alive. That was how I was diagnosed with stage 4 lung cancer in May 2012. I was told that I had non-small-cell adenocacinoma and the prognosis was bleak. 12 - 18 months perhaps. I was tested for Epidermal Growth Factor Receptor (EGFR) mutation as studies had shown that a large proportion of patients with EFGR mutation was relatively young female Asians (I am Japanese and was 43 at the time of diagnosis). My consultant had previously told me that the first line of treatment for EFGR was tablets that	Thank you for your comment. The FAD recommends crizotinib for use within the Cancer Drugs Fund.

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			are very effective and did not carry serious side effects, so I was very disappointed when the test came back negative. I had to have chemotherapy. I had 10 cycles of chemotherapy with various drugs. Platinum-based chemotherapy could be very effective at controlling a progression of cancer, however, the impact of the side effects on the patients' quality of life is devastating. By the time the third cycle completed, I was totally immobilised and bed-bound. I was unable to look after myself, let alone my young son. I needed a help of a social worker everyday just to have a wash and get dressed. After every cycle of chemotherapy, I became less able. By autumn, I was unable to do anything, not even turn over in bed. I would have to ask my husband to push me to turn over in bed. I thought I didn't want to live like that. I wanted to die. If anything had kept me alive, it was my son. I didn't want him to grow up without his mum. Fortunately my cancer stayed mostly problem-free over the summer of 2013, so I was allowed to stay "Chemo free" for a few months. In the mean time I learned from the US-based lung cancer group about other mutations, specifically Anaplastic Lymphoma Kinase (ALK) and c-ros Oncogene 1 (ROS1). I asked to be tested for these two new mutations – I was identified as ROS1 positive. It was all my consultant's effort that enabled me to obtain Crizotinib through my private medical insurance in November 2013 as it was, and still is, not available on the NHS. Crizotinib was already well known in the US as a second-generation treatment for ALK and ROS1, and many patients had been showing excellent response to the drug. In the UK, Crizotinib was approved by NICE for ALK patients in 2016 but not for ROS1. Without my medical insurance, I would not have had access to this amazing drug. Crizotinib is totally life changing. I no longer needed a social worker to look after me every day as I slowly regained mobility and brain functions while my cancer was controlled well. It brought back some normality to my and my family's life. Although there are some bad side effects with Crizotinib, they are cosmetic in comparison to those I experienced from chemo. The	

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			quality of life was good. I thought I wanted to live again. And I did live - for over 3 years on Crizotinib until I moved to another drug. Only 1% of stage 4 lung cancer patients are said to survive 5 years. I am living my 6th year as a survivor of stage 4 lung cancer and this would never have been possible without Crizotinib. Today, the 4th February, is the world cancer day. I heard several times on the TV and radio that the UK's lung cancer survival rate is one of the lowest in the developed world. Please give ROS1 patients a chance. We may be a small population amongst the larger lung cancer community but that shouldn't be a reason for denying us such a wonderful drug which could give us much longer prognosis of life with good quality.	

Pfizer Limited
Walton Oaks
Dorking Road
Tadworth
KT20 7NS
7th February 2018

Dear Prof Stevens and Prof O'Brien,

Re: Lung cancer (non-small-cell, untreated and previously treated, ROS1 positive) - crizotinib [ID1098] ACD

Thank you for the opportunity to comment on the Appraisal Consultation Document for the above appraisal. Pfizer are disappointed with the draft recommendation made by the Committee, and believe that several assumptions which were made to reach this recommendation are flawed and lack clinical validity. It is Pfizer's opinion that the information contained within this response will provide sufficient evidence and clinical opinion for the Committee to reconsider their current preferred assumptions (in particular with regards to overall survival), and therefore allow the Committee to recommend crizotinib within its licensed indication for ROS1-positive non-small cell lung cancer (NSCLC), as both a clinically effective and cost-effective use of National Health Service (NHS) resources, especially considering the ultra-orphan nature of this disease and the considerable unmet need in ROS1-positive NSCLC patients.

As part of Pfizer's response (and as agreed with the National Institute for Health and Care Excellence [NICE] secretariat), new evidence has been included from a re-analysis of the survival gain, taking into account the Committee's preferences for an adjustment to be made to the crizotinib survival rather than the comparator survival. The overall survival data for crizotinib in ROS1-positive NSCLC unequivocally demonstrates that patients treated with crizotinib in the first-line experienced at least a mean 13.1-month survival benefit and in subsequent-line, at least a mean 16.2-month survival benefit compared to current treatment options. The upper bound of the resulting incremental cost-effectiveness ratio (ICER) range was below £50,000 per quality-adjusted life year (QALY,) the threshold considering the Committee's conclusion that crizotinib meets the criteria to be an end-of-life therapy. Pfizer believes that, based on this conservative estimate of overall survival in ROS1-positive NSLCLC patients, crizotinib is cost-effective. Any further maturation of trial data would support that the assumptions made are indeed conservative. This is again emphasised in what has been observed in clinical practice for both first- and subsequent-line anaplastic lymphoma kinase (ALK)-positive NSCLC patients; survival gain is far greater than the minimum necessary to prove that crizotinib is cost-effective. The current Patient Access Scheme provides further certainty that crizotinib provides value for money to the NHS and aims to ensure that ROS1-positive patients receive timely access to targeted treatment.

In addition, Pfizer do not believe the use of a proxy population in this submission sets a precedence for future appraisals, since it is unusual to find two patient populations with biological characteristics and clinical outcomes that are as similar as those in the ROS1-positive and ALK-positive NSCLC populations. Given the high quality of the ALK-positive NSCLC clinical trials, as well as NICE's recommendation to use first- and subsequent-line crizotinib for treatment of advanced ALK-positive NSCLC, there is a strong rationale to apply the data from ALK-positive NSCLC to inform this submission. Furthermore, this would be in line with EMA's recognition of the generalisability of data between ALK-positive NSCLC and ROS1-

positive NSCLC. As we have seen from the results of the recent Marsden UK national audit, further efforts to obtain more data in the rare ROS1-postive NSCLC population, will not only be difficult due to lack of clinical equipoise but will add little to the existing evidence. The comparability between prospective and retrospective studies in ROS1-positive NSCLC (including the Marsden audit) clearly demonstrate the effect of crizotinib in ROS1-positive NSCLC to be consistent across trials.

Pfizer has presented a compelling case within this response and strongly believes crizotinib is both a clinically- and cost-effective treatment option that should be made available for ROS1-positive NSCLC patients within England and Wales.

Yours sincerely,

[redacted]
For and on behalf of Pfizer UK

Executive Summary

Pfizer consider the provisional recommendations to be based on clinically invalid assumptions which are not a suitable basis for guidance to the NHS. Whilst recognition from the Committee is welcomed that the innovative nature of crizotinib represents a step-change in the treatment of ROS1-positive NSCLC patients, it is disappointing that the cost-effectiveness of crizotinib has not been recognised.

It has been noted from the appraisal consultation document (ACD) that the ICERs the Committee would consider as a starting point for its discussions were [redacted] per QALY (first-line) and [redacted] per QALY (subsequent-line). These ICERs are the mid-points between the Company's base case and the Evidence Review Group (ERG)'s exploratory analysis that assumed no survival benefit in progressed disease stages, and hence results in a modelled mean survival gain of only 7.6 months and 5.8 months for crizotinib compared to first-line pemetrexed plus platinum and subsequent-line docetaxel, respectively.

Pfizer believes that these analyses, based on the mid-point between the Company's base case and the ERG's exploratory analysis, produce overestimations of the true ICERs, most notably because of the clinically invalid assumptions pertaining to the mean overall survival (OS) gains associated with crizotinib compared to first-line pemetrexed plus platinum and subsequent-line docetaxel. The modelled OS gains associated with the Committee's preferred upper range of ICERs for crizotinib in the first-line (7.6 months) and subsequent-line (5.8 months) are less than what is expected by clinical experts and less than the OS gain accepted by previous appraisals of crizotinib as first-line and subsequent-line therapies for ALK-positive NSCLC. This is in line with observations of ROS1-positive NSCLC patients treated in clinical practice, reported in the Marsden audit, where after median follow-up of 19.4 months, median OS had not been reached in first- and subsequent-line ROS1-positive NSCLC patients treated with crizotinib.

In addition, Pfizer do not believe the use of a proxy population in this submission sets a precedence for future appraisals, since it is unusual to find two patient populations with biological characteristics and clinical outcomes that are as similar as those in the ROS1-positive and ALK-positive NSCLC populations. Because of the rarity of advanced ROS1-positive NSCLC and the absence of comparative efficacy data due lack of clinical equipoise to conduct further comparative studies, a pragmatic solution to modelling had to be used in this submission to inform decision making.

In the response below, the ICERs that represent the Committee's preferred set of assumptions are presented first, as described in the ACD. New analyses are then presented and revised ICERs include an adjustment to the crizotinib OS curve, such that mean OS gain is reduced, but with some relative post-progression survival (PPS) gain attributed to crizotinib vs the comparator. The mean (and median) OS gains in these analyses have been validated by clinical experts to be in-line with the expected mean (and median) OS gains with crizotinib in ROS1-positive NSCLC in clinical practice.

Clinical experts confirm that the expected mean OS gain of ROS1-positive patients treated with crizotinib would be approximately between 13.1–18.2 months compared to first-line pemetrexed plus platinum and 16.2–20.9 months compared to subsequent-line docetaxel, i.e. at least the mean OS gain accepted by the Committee in the previous first-line (13.1 months) and second-line (16.2 months) appraisals of crizotinib in ALK-positive NSCLC. Indeed, the OS gains in these appraisals are already considered to be conservative with respect to crizotinib. Furthermore, based on threshold analyses, the absolute minimum mean OS gains that need to be realised for the ICER of crizotinib to be below

£50,000 per QALY are 11.9 months in the first-line and 14.3 months in the subsequent-line, which is less than the mean OS gain expected in clinical practice for this population of patients.

Pfizer are confident, based on these new analyses, that the most plausible ICERs for crizotinib are below the £50,000 per QALY threshold for end-of-life medicines and believe that the information presented in this response should allow the Committee to reconsider its provisional conclusions and recommend crizotinib for treatment of ROS1-positive NSCLC patients, enabling equitable access to crizotinib as a step-change therapy in this rare oncology disease area.

1. The Committee's most plausible ICERs

Given that the Committee agreed there would be some relative post-progression survival (PPS) advantage for crizotinib vs chemotherapy, Pfizer do not believe that the Committee should consider any scenario by the ERG that assumes equal PPS (first-line [redacted] per QALY with PAS; subsequent-line [redacted] per QALY with PAS).

The ACD notes that the Committee agreed, as a starting point for its discussion, that it would consider ICERs at the mid-point between the Company's base case and the ERG's exploratory analysis that assumed no survival benefit in progressed stages:

- Mid-point ICER for first-line patients: [redacted] per QALY (range [redacted] per QALY to [redacted] per QALY)
- Mid-point ICER for subsequent-line patients: [redacted] per QALY (range [redacted] per QALY to [redacted] per QALY)

The ACD also notes that these ICERs may be further affected if all of the Committee's preferred assumptions are taken into account. The Committee therefore considered that the most plausible ICERs for crizotinib in the Company's base case analysis were:

- First-line: around or just below £50,000 per QALY gained. However, the Committee agreed that this estimate came with far too much uncertainty to conclude on a figure below £50,000 without further evidence.
- Subsequent-line: above £50,000 per QALY gained.

Key assumptions which comprise the Committee's preferred alternatives are listed in the table below.

Table 1. Summary of the Committee's preferred key assumptions at ACD

Assumption preferred by the Committee for the most plausible ICERs	Considerations
(A) Use of a higher utility value (0.75) for post-treatment, pre-progression pemetrexed patients than used in Pfizer's base case (0.72)	The higher utility value is preferred by the Committee for consistency with the value accepted by the Committee in TA406. However, it should be noted that the higher utility value should only be applied when patients are off-treatment *[See Section 5]*
(B) Include disutility to account for any adverse reactions	The utility estimates the Company included in the economic model for the crizotinib, pemetrexed plus platinum and docetaxel are taken directly from patients on treatment in the PROFILE 1014 and PROFILE 1007 trials. Hence, the HRQoL reported is expected to already reflect the negative changes in utility incurred through the adverse event profiles of the specified treatments. The impact of including a disutility due to adverse events could be deemed 'double-counting'. This assumption was accepted in TA406 *[See Section 6]*
(C) Adjustment of the crizotinib OS curve so that PPS is similar to comparator PPS is the preferred approach, but with some relative PPS advantage for crizotinib	The ERG's second OS modelling scenario (equal PPS) is preferred by the Committee, but the Committee did not agree with the way the ERG implemented the analysis. The committee considered that adjusting the crizotinib OS curve was their preferred approach and concluded that that the OS gain for crizotinib was between the company's and ERG's estimates *[See Section 2]* New analyses *[see Section 2 and **Error! Reference source not found.**B]* included in this response now include the Committee's preferred method for adjusting crizotinib PPS
(D) Include docetaxel plus nintedanib as a comparator in the subsequent-line analysis	The Committee heard from a clinical expert that nintedanib plus docetaxel is more effective than docetaxel alone in this indication and therefore believed this may further increase the ICERs. However, the ERG agreed that the Company's use of a pooled chemotherapy (docetaxel or pemetrexed) comparator, which was based on the chemotherapy options included in the second study (PROFILE 1007), was a conservative approach due to the fact

	that pemetrexed is more efficacious than docetaxel. As such, any incremental difference attributed to docetaxel-nintedanib would be mitigated by the use of the pooled chemotherapy approach. Also, it is worth noting that the list price of nintedanib (£2,151.10) should be taken into account when considering this assumption in relation to cost-effectiveness *[See Section 3]*
(E) Increase cost of treating pulmonary embolism beyond that assumed in the Company's base case	The Committee noted that the values used in the Company's base case for pulmonary embolism were underestimated, which may further affect the ICERs. The ERG also stated that the cost of treating pulmonary embolism *may* have been under-estimated, however the impact of this on the size of the ICER per QALY gained was small and so the ERG did not amend the cost in the model
(F) Increase crizotinib administration costs	The ACD indicates that the Committee considered the Company to have underestimated the administration cost of crizotinib and that this might further affect the ICERs. However, no further information relating to this can be found in the ACD. Further, the ERG report does not comment on the administration cost estimate. This assumption (administration cost used in [ID1098]) was accepted in TA406 and ceritinib's recent NICE appraisals TA395 and TA500 [ID729 and ID1117] *[See Section 6]*

Abbreviations: ACD: appraisal consultation document; ERG: Evidence Review Group; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; NICE: National Institute for Health and Care Excellence; OS: overall survival; PPS: post-progression survival; QALY: quality-adjusted life year.

Table 2. Additional, preferred assumption as noted by the ERG in their report

Assumption preferred by the ERG for the most plausible subsequent-line ICERs	Considerations
(G) Sequential testing for second-line	While this assumption was not mentioned by the Committee in the ACD, the ERG considered that it would be more appropriate to use the cost of sequential testing in the subsequent-line setting

Abbreviations: ACD: appraisal consultation document; ERG: Evidence Review Group.

Table 3. Alternate assumption, based on near future amendments regarding testing for ROS1-positive NSCLC within NHS England

Assumption that removes the cost of testing for ROS1-positive NSCLC	Considerations
(H) Remove the cost of testing	Pfizer recognises that there is currently considerable activity in relation to the delivery of molecular diagnostics in the UK. This is exemplified by the investment of Genomics England in developing specialist genetic and molecular pathology laboratories through NHS England's re-procurement and designation to create a national genomics laboratory structure for England. With the move by NHS England to mainstream genomics medicine in rare diseases and cancer, testing for molecular subtypes of lung cancer, including potentially ROS1, may become part of routine healthcare commissioning in the near future. As such, scenarios presenting ICERs with no testing costs have also been explored (Appendix B)

Abbreviations: ICER: incremental cost-effectiveness ratio; NHS: National Health Service; NSCLC: non-small cell lung cancer.

Strong rationale is provided as to why assumptions [B], [D] & [F] should not further increase the ICERs. Following Pfizer's new analyses, which include the Committee's and ERG's remaining, preferred assumptions (changes to [A], [C], [E] & [G] above), the updated ICERs are:

- Base case first-line: £[redacted] per QALY
    - Base case first-line: £[redacted] per QALY (also including assumption [H] if ROS1 testing becomes routine in NHS England)

- Base case subsequent-line: £[redacted] per QALY
    - Base case subsequent-line: £[redacted] per QALY (also including assumption [H] if ROS1 testing becomes routine in NHS England)

When the Committee's and ERG's preferred assumptions (changes to [A], [C], [E] & [G] above) are included, both first- and subsequent-line treatment ICERs are below £50,000 per QALY gained.

These ICERs have incorporated an adjustment to the way PPS gain is modified with respect to assumption [C] in Table 1, specifically modifying the crizotinib OS curve rather than the comparator OS curve. This correction is described below in Section 2 and explained in more detail in Appendix B. Notably, because crizotinib OS gain is being modified in relation to comparator survival curves deemed plausible by clinical experts, analyses exploring the plausible OS gains in this response focus on the Company's base case.

2. Clinical Plausibility of the survival assumed in the Committee's most plausible ICERs

Pfizer do not agree with the assumptions which underpin the ERG's upper range of ICERs. informing the basis for the negative recommendation in the ACD (first-line [redacted] per QALY with PAS; subsequent-line [redacted] per QALY with PAS [see Error! Reference source not found.**]) These do not accurately reflect clinical reality, most notably for the assumptions that influence survival**.

First-line analysis

The ERG's ICER of £[redacted] per QALY represents a mean survival gain of 9.5 months with crizotinib (first-line), which is much less than that deemed plausible by clinical experts, what is reported in the clinical data, the OS gain accepted in the first-line appraisal TA406 (mean 13.1 months) and indeed, less than what was accepted in the subsequent-line appraisal for crizotinib in ALK-positive NSCLC (TA422), where the progression-free survival (PFS) benefit was more conservative (mean 16.2 months).

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 a mean of 13.1–18.2 months (median 8.9–12.8 months) (i.e. at least that accepted by NICE TA406 in first-line ALK-positive NSCLC) (see Company reanalyses in Appendix B). Using the Committee's preferred approach to model OS and including assumptions [A], [C], [E] & [G] from Tables 1 & 2, **all analyses that achieve at least a 13.1-month mean OS gain (crizotinib mean PFS=16.8 months; mean PPS=13.9 months) or meet the mid-point between the Company's and ERG's OS gain (18.2-month mean gain), produce an ICER of between £[redacted] per QALY when PAS is considered** (see Table B1 in **Error! Reference source not found.**). These ICERs include revised assumptions as set out in Table A1 in Appendix A.

Subsequent-line analysis

In the ERG's subsequent-line analysis, the ICER of £[redacted] per QALY represents a mean 5.8-month survival gain with crizotinib (subsequent-line), which is also lower than that deemed plausible by clinical experts, what is observed and reported in the data and the OS gain accepted in the second-line appraisal TA422 (mean gain of 16.2 months).

Clinical experts have agreed that the expected OS gain for crizotinib in subsequent-line, in the absence of crossover, would fall between a mean of 16.2–20.9 months (median 11.3–14.9 months) (i.e. at least that accepted by NICE TA422 in subsequent-line ALK-positive NSCLC) (see Company reanalyses in Appendix B). Further, given that the Committee for NICE TA422 preferred the use of an OS hazard ratio (HR) of 0.49 (the ERG's scenario of applying the PFS HR to OS), which resulted in an OS mean gain of 16.2 months, this was considered a conservative approach compared to use of the HR from the PROFILE 1007 trial (HR=0.38 (0.28, 0.52). Use of an arbitrary HR that further decreases OS is therefore not plausible and does not take into account the clinical data, or the effect that tumour shrinkage has during the post-progression stage. It is therefore most plausible that the true OS gain lies between the ERG's analysis using the PFS HR (remodelled with respect to assumption [C], [E] and [G] in Tables 1 & 2) and the HR from PROFILE 1007. Again, using the Committee's preferred approach to model OS, **all analyses that achieve at least a 16.2-month mean OS gain (crizotinib mean PFS=10.6 months; mean PPS=22.3 months) or meet the mid-point between the PROFILE 1007 HR and ERG's OS gain using the PFS HR (20.9-month mean gain), produce an ICER of between £[redacted] and £[redacted] per QALY when PAS is considered**). These ICERs include revised assumptions as set out in Table A1 in Appendix A.

For ease of consideration, Table 4 below presents the mean and median survival times associated with the extreme, modelled ICERs that were considered by the Committee at the ACD meeting. Note that the Committee's most plausible upper range of ICERs are underpinned by the ERG's adjustment to OS gain (equal PPS) (seen in rows 2 and 5).

Table 4. Mean and median first- and subsequent-line OS that pertains to the ICERs considered by the Committee at ACD

Scenario considered by the Committee	ICER (cost per QALY) with PAS	OS crizotinib	OS pemetrexed + platinum	OS gain with crizotinib (months)
(1) Company's base case (first-line)	[redacted]	Mean 46.4 months Median 32.5 months	Mean 17.7 months Median 12.8 months	28.7 mean gain 19.7 median gain
(2) ERG's (equal PPS) OS gain modelling (first-line)	[redacted]	Mean 46.4 months Median 32.5 months	Mean 36.9 months* Median 25.6 months*	9.5 mean gain* 6.9 median gain*
(3) Adaptation (modified crizotinib PPS) to ERG's OS gain modelling (first-line), **but with mid-point crizotinib OS gain applied**	[redacted]	Mean 35.9 months Median 25.6 months	Mean 17.7 months Median 12.8 months	18.2 mean gain 12.8 median gain
(4) Company's base case (subsequent-line)	[redacted]	Mean 33 months Median 23.7 months	Mean 16.7 months Median 11.8 months	16.3 mean gain 11.9 mean gain
(5) ERG's (equal PPS) OS gain modelling (subsequent -line)	[redacted]	Mean 39.5 months Median 27.6 months	Mean 33.7 months* Median 23.7 months*	5.8 mean gain* 3.9 mean gain*

Note: *These ICERs relate to the ACD-meeting.*
***** *Denotes assumptions relating to comparator OS estimates that are clinically implausible.*
Abbreviations: ACD: appraisal consultation document; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; OS: overall survival; PPS: post-progression survival; QALY: quality-adjusted life year.

First-line analysis

As noted above in Section 1, the ICER of [redacted] per QALY (first-line) is not based on the Committee's preferred approach to adjusting OS gain and does not take into account any OS advantage for crizotinib versus pemetrexed plus platinum therapy. When taking into account the Committee's preferred approach to modelling OS gain and also the conclusion that the OS gain for crizotinib was somewhere between the Company's and ERG's estimates, the ICER associated with a mid-point scenario is [redacted] per QALY with PAS. This analysis also takes into account assumptions [A] and [E] (Table 1). Importantly, this scenario models survival which is more clinically plausible than that generated by the ERG's scenario (see Appendix B for overview). This 'corrected' scenario is presented in row (3) in Table 4.

Pfizer believe that the survival gain modelling that best represents the clinical reality of using first-line crizotinib are those that demonstrate **at least** the survival benefit accepted in the first-line appraisal (TA406), supported by:

- Clinical validation of the economic model re-analysis since the publication of the ACD by experts experienced in treating ROS1-positive NSCLC patients with both crizotinib and pemetrexed plus platinum, confirming that it is appropriate to assume a mean OS gain of between **13.1 to 18.2 months of OS gain** with crizotinib.

- Data from a retrospective analysis of UK patients (N=26 from 7 UK centres) with ROS1-positive advanced NSCLC conducted by the Royal Marsden Hospital, which included 10 patients treated with crizotinib**. For all crizotinib-treated patients the median PFS observed was 12.1 months, and median OS was not reached by the time of median follow-up (19.4 months), with one-year and two-year OS rates of 81% and 66%, respectively**.

- During the subsequent-line NICE appraisal of crizotinib (TA422), NICE concluded that an estimate of mean OS gain of 16.2 months was plausible (crossover-adjusted HR of 0.49 [0.37, 0.64]).(1) The OS data from the pivotal trial for subsequent-line use of crizotinib was mature at this point, with the rank preserving structure failure time (RPSFT) crossover-adjusted HR demonstrating a much greater benefit to crizotinib (HR=0.38 (0.04, 0.99).(2) As the PFS gain with crizotinib in ALK-positive NSCLC is greater in first-line than in subsequent-line,(2, 3) it can reasonably be expected that crizotinib in the first-line would, at an absolute minimum, be expected to have an **OS gain somewhat greater than the 16.2-month mean accepted in the subsequent-line appraisal.(1)**

As noted at the start of this section, **even when the ERG's OS gain modelling is used, but amended such that the crizotinib survival curve is adjusted (as preferred by the Committee) to produce at least a 13.1-month mean survival gain, they are associated with ICERs of less than [redacted] per QALY with PAS, should only assumptions [A], [C], and [E] from Table 1 be modified to reflect the Committee's preferences**. In addition to the estimates of survival considered as clinically plausible by the Committee, three other issues influencing the model (assumptions [B], [D] and [F] in Table 1) warrant re-consideration by the Committee, with rationale for revision of assumption [D] presented in Section 3.

Subsequent-line analysis

As noted above in Section 1, the ICER of [redacted] per QALY (subsequent-line) is also not based on the Committee's preferred approach to adjusting OS gain and does not take into account any OS advantage for crizotinib versus docetaxel (pooled analysis). When the mid-point between the ERG's analysis using the PFS HR (remodelled with respect to assumption [C] in Table 1) and the HR from PROFILE 1007, the ICER associated with this scenario is [redacted] per QALY with PAS. This analysis also takes into account assumptions [E] and [G] (Tables 1 & 2). Notably, again this scenario models survival that is more clinically plausible than that generated by the ERG's scenario (see **Error! Reference source not found.** for overview). This 'corrected' scenario is presented in row (1) in Table 5.

Table 5. Mean and median subsequent-line OS that pertains to the ICER revised by Company following ACD

Scenario considered by the Committee	ICER (cost per QALY)	OS crizotinib	OS pemetrexed + platinum	OS gain with crizotinib

	with PAS			(months)
(1) Subsequent adaptation to (modified crizotinib PPS) ERG's OS gain modelling (subsequent-line), ***but with mid-point crizotinib OS gain applied (between PFS HR applied to OS and PROFILE 1007 HR)***	[redacted]	Mean 37.6 months Median 26.6 months	Mean 16.7 months Median 11.8 months	20.9 mean gain 14.8 median gain

Abbreviations: ACD: appraisal consultation document; ERG: Evidence Review Group; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year.

Pfizer believe that the survival gain modelling that best represents the clinical reality of using subsequent-line crizotinib are those that demonstrate **at least** the survival benefit accepted in the subsequent-line ALK-positive NSCLC appraisal (TA422), supported by:

- Clinical validation of the economic model re-analysis since the publication of the ACD by experts experienced in treating ROS1-positive NSCLC patients with both crizotinib and pemetrexed plus platinum, confirming that it is appropriate to assume a mean OS gain of between **16.2 to 20.9 months** with crizotinib.

- Data from the Marsden audit (N=26 from 7 UK centres), which included 10 ROS1-positive NSCLC patients who received crizotinib. **For all crizotinib-treated patients the median PFS observed was 12.1 months, and median OS was not reached by the time of median follow-up (19.4 months), with one-year and two-year OS rates of 81% and 66%, respectively.**

- As mentioned above, during the subsequent-line NICE appraisal of crizotinib in ALK-positive NSCLC (TA422), it was accepted that a mean OS gain of 16.2 months was appropriate (crossover-adjusted HR of 0.49 [0.37, 0.64]).(1) As use of the PFS HR was a conservative approach, it can be expected that crizotinib in the subsequent-line would be expected to have an **OS gain somewhat greater than the 16.2 months (mean OS gain) accepted in the second-line appraisal.(1)**

As noted earlier in this section, **even when the ERG's OS gain modelling is used, but adjusted such that the crizotinib survival curve is altered (as preferred by the Committee) to produce at least a 16.2-month survival gain, associated ICERs are less than £[redacted] per QALY with PAS, should only assumptions [C], [E], and [G] from Tables 1 & 2 be modified to reflect the Committee's and ERG's preferences**.

In addition to the estimates of survival considered as clinically plausible by the Committee, three other preferred assumptions at ACD that could potentially increase the ICER (assumptions [B], [D] and [F] in Table 1) warrant re-consideration by the Committee. Strong rationale is provided as to why they should not further increase the ICERs; most notably [B] & [D] have been accepted in previous technology appraisals (TA406 and ceritinib's recent NICE appraisals TA395 and TA500 [ID1117 and ID729]), and rationale for not including [D] is presented in Section 3.

Considerations to other assumptions or factors that contributed to the negative recommendation in the ACD are presented in the next sections.

3. Exclusion of docetaxel plus nintedanib as a comparator in previously treated disease (subsequent-line)

Pfizer do not believe the inclusion of docetaxel plus nintedanib as a comparator in subsequent-line patients would have further increased the ICER for crizotinib in subsequent-line ROS1-positive NSCLC. Clinical evidence from LUME-Lung1 in unselected NSCLC patients suggests docetaxel plus nintedanib to be associated with a median PFS gain of 0.7 months compared to docetaxel alone.(4) The analysis of subsequent-line patients presented in this submission applied pooled chemotherapy data from patients treated with pemetrexed or docetaxel monotherapy in PROFILE 1007. Subgroup analysis of PROFILE 1007 data shows the median PFS to be [redacted] months and [redacted] months in patients stratified by pemetrexed and docetaxel, respectively. Due to the lack of docetaxel plus nintedanib data from a ROS1-positive population or from an ALK-positive proxy population, Pfizer consider the use of pooled chemotherapy data from PROFILE 1007 to be a conservative approach with respect to crizotinib. Pfizer believes the overestimated docetaxel treatment effect offsets any difference in treatment efficacy between docetaxel alone and docetaxel plus nintedanib that would have impacted the ICER if docetaxel plus nintedanib had been included as a comparator.

As highlighted in the Committee discussions and acknowledged by the ERG, the subsequent-line analysis data from PROFILE 1007 were derived from a pooled chemotherapy analysis, where 99 patients (57%) received pemetrexed and 72 (41%) received docetaxel. The median PFS was 7.7 months for crizotinib and 3.0 months of pooled chemotherapy.(2) In subgroup analyses of patients stratified by chemotherapy treatment, there were significant improvements in PFS in patients treated with crizotinib compared to both pemetrexed (median PFS: [redacted] months; HR 0.59, 95% CI: 0.43, 0.80; p<0.001) and docetaxel (median PFS: [redacted] months; HR 0.30, 95% CI: 0.21, 0.43; p<0.001).(5) The median OS was [redacted] months (95% CI, [redacted]) with crizotinib, [redacted] months (HR [redacted] with pemetrexed, and [redacted] months (HR [redacted]) with docetaxel.(5)

In comparison, data from the LUME-Lung1 trial in unselected NSCLC demonstrated that docetaxel plus nintedanib was associated with a small increase in median PFS compared to docetaxel alone (median PFS: 3.4 versus 2.7 months; HR 0.79, 95% CI: 0.68, 0.92; p=0.0019).(6) In a predefined subpopulation of patients with adenocarcinoma tumour histology, the median PFS was 4.2 months for nintedanib plus docetaxel compared to 2.8 months for docetaxel alone (HR: 0.84, 95% CI: 0.71, 1.00; p=0.0485). Additionally in this subgroup analysis, the median OS was significantly longer with nintedanib plus docetaxel treatment compared to docetaxel alone (median OS: 12.6 versus 10.3 months; HR 0.83, 95% CI: 0.70, 0.99; p=0.0359).(6)

As presented in the submission, docetaxel plus nintedanib was not included in the submission as data was only available from the LUME-Lung1 trial in patients with unselected NSCLC or unselected adenocarcinoma. Data from these patients cannot be presumed to be generalisable to molecularly defined subgroups of patients, such as ROS1-positive advanced NSCLC patients.

Clinical expert opinion supports that, by virtue of the numerical difference in median PFS and numerical difference in median OS between the pemetrexed and docetaxel subgroups of PROFILE 1007, the use of the pooled chemotherapy data in the current submission is likely to provide an overestimate of the treatment effect of docetaxel and to be conservative with respect to crizotinib. The modelled approach is also considered to be at least similar to the outcomes that would be expected with the combination of docetaxel plus nintedanib in the treatment of patients with advanced NSCLC based on the available

evidence. The cost of nintedanib at list price (£2,151.10) should also be taken into account as the addition of nintedanib will increase the total cost of subsequent-line treatment.

4. Availability of data from ROS1-positive NSCLC and use of data from ALK-positive NSCLC patients as proxy

Pfizer do not believe the use of a proxy population in this submission sets a precedence for future appraisals, since it is unusual to find two patient populations with biological characteristics and clinical outcomes that are as similar as those in the ROS1-positive and ALK-positive NSCLC populations. Indeed, it is unusual for the generalisability of data between two oncogene mutations to be widely accepted by the clinical experts, as well as by the EMA, for clinical decision making and regulatory decision making. In the exceptional case for ROS1-positive and ALK-positive NSCLC, the overwhelming similarities in receptor structure, biological characteristics and clinical outcomes have been recognised by the clinical community. The unusual circumstances underlying the analyses provided in this submission should therefore be seen as an exception, rather than setting a precedence. As such, the use of ALK-positive NSCLC as a proxy population in this set of circumstances should be considered as a unique case.

Pfizer consider the use of comparative effectiveness data from ALK-positive NSCLC patients to be a conservative approach, supported by treatment efficacy data available from ROS1-positive NSCLC. Availability of comparative effectiveness data from ROS1-positive patients is limited by the rarity of the disease and by the lack of clinical equipoise for further comparative trials in ROS1-positive patients, rather than due to the timing of the ROS1 mutation discovery. Efficacy data from ROS1-positive patients treated by crizotinib or by chemotherapy reinforce the outcomes observed in ALK-positive NSCLC trials, further emphasising clinical expert opinion about the generalisability of data from ALK-positive NSCLC to ROS1-positive NSCLC.

Discovery and understanding of ROS1-positive NSCLC

ROS1 was identified as a key oncogenic driver in a number of cancers, including NSCLC in 2007.(7) The reason that there is limited information available on the biological and clinical characteristics of this patient group is because of the rarity of the disease and not due to the timing of the discovery of the mutation. Based on published studies, ROS1-positive advanced NSCLC is estimated to occur in less than 2% of NSCLC patients and to be found almost exclusively in non-squamous tumours.(8-10) This incidence is considerably lower than tumours harbouring ALK, epidermal growth factor receptor (EGFR) or Kirsten rat sarcoma virus (KRAS) mutations, which account for between 3.4%, 15.3% and 32.6% of NSCLC, respectively.(11) It is estimated that there are approximately 290 advanced ROS1-positive patients in England and Wales potentially eligible for crizotinib based on a ROS1-positive NSCLC incidence of 1.8% in adenocarcinoma patients.(10)

Information regarding the natural history of ROS1-positive NSCLC is described in published retrospective analyses.(8, 10, 12-17)

The clinical outcomes from PROFILE 1001 and other studies, as outlined below, provide evidence of the efficacy of crizotinib in ROS1-positive NSCLC patients. As such, clinical experts consider it unethical to conduct further comparative trials due to lack of clinical equipoise, and therefore there are no comparative data available from ROS1-positive NSCLC patients.

Availability of crizotinib to ROS1-positive patients would contribute to equitable access to targeted therapies, as is now standard for the treatment of NSCLCs driven by EGFR or ALK gene rearrangements. The clinical community strongly prefer targeted therapies over non-specific systemic therapies, and

ROS1-postive NSCLC is seen as representing another molecularly-defined subgroup of patients for whom an effective targeted therapy is available.

Clinical outcomes with crizotinib in ROS1-positive NSCLC

It is important to note that, as highlighted at the first committee meeting, there are many additional studies other than PROFILE 1001, a single-arm trial, that evaluate the efficacy and safety of crizotinib in patients with ROS1-positive advanced NSCLC, as detailed in Appendix D of the Company submission. Although these studies, published between 2015 and 2017, include small patient numbers, the clinical outcomes strongly reinforce the outcomes observed in PROFILE 1001 and the outcomes observed in ALK-positive NSCLC patients as observed from PROFILE 1014 and PROFILE 1007. The four prospective studies available in addition to the PROFILE 1001 trial are outlined in Table 6. From these studies, the objective response rate (ORR) ranges from 65%–71.7% and the median PFS ranges from 10–22.8 months. The median OS was not reached in three out of four of these studies, indicating the median OS to be at least as long as the study follow-up duration.

Real world data on the median PFS in ROS1-positive patients treated with crizotinib is also available from the UK clinical audit conducted by the Royal Marsden. Of the 26 ROS1-positive patients included in the audit, 14 received first-line pemetrexed plus platinum and 10 patients received first-line or subsequent-line crizotinib. The median PFS with crizotinib was 12.1 months in the first-line and subsequent-line settings. Median OS has not yet been reached, but survival rates are 81% and 66% at Year 1 and Year 2, respectively, for ROS1-positive advanced NSCLC patients treated by crizotinib in the first- and subsequent-line. Please see **Error! Reference source not found.** for a summary of the final data analysis results from the Royal Marsden national audit, as recently presented as a poster at the British Thoracic Oncology Group Conference in January 2018. Please note that preliminary data from the audit was presented in the company submissions and that the small number of changes from the final data analysis have been reflected in the summary above and in **Error! Reference source not found.**.

For comparison, the ORR of crizotinib-treated ALK-positive patients from PROFILE 1007 and PROFILE 1014 were 65.3% (95% CI: 57.7, 72.4) and 74.4% (95% CI: 67.2, 80.8), respectively, whilst the median PFS were 7.7 months (95% CI: 6.0, 8.8) and 10.9 months (95% CI: 8.3, 13.9), respectively. The probabilities of survival at 12 months were [redacted] and [redacted] for first-line and subsequent-line ALK-positive patients, respectively.

As discussed in the submission, these additional studies were not used for economic modelling due to the small trial sample size or because the trial population was predominantly Asian. However, these studies demonstrate the clinical outcomes in crizotinib-treated ROS1-positive NSCLC patients to be consistent across studies. Furthermore, they show the outcomes in ROS1-positive patients to be at least as good as in ALK-positive NSCLC patients when treated with crizotinib. As such, the use of data from ALK-positive NSCLC patients should be considered as conservative with respect to crizotinib.

Table 6. Clinical evidence of crizotinib in ROS1-positive NSCLC patients

Trial	Phase	No. of patients (majority population)	Treatment Lines	Duration of Follow-Up	Outcomes

PROFILE 1001 (NCT00585195)(18)	1	53 (Caucasian)	1L 13% (N=7) 2L 38% (N=20) 3L+ 49% (N=26)	Data cut-off, median duration of OS follow-up (reverse Kaplan-Meier method) was 25.4 months (95% CI: 22.5, 28.5).	ORR: 69.8% Median PFS: 19.3 months 12-month OS: 79%, Median OS: not reached
OxOnc (NCT01945021)(19)	2	127 (Asian)	1L 18.9% (N=24) 2L 41.7% (N=53) 3L 24.4% (N=31) 4L 15.0% (N=19)	76/127 patients (59.8%) were still in follow-up for survival at the time of data cut-off (30 July 2016) and thus the OS data is immature	ORR: 71.7% Median PFS: 15.9 months Median OS: 32.5 months 12-month OS 83.1%
EUCROSS (NCT02183870)(20)	2	34 (Caucasian) (n=30 response evaluable patients)	[redacted]	Study start date: May 2014 Estimated primary completion date: September 2017	[redacted]
AcSé (NCT02034981)(21)	2	37 (N=3 not eligible for assessment) (Caucasian)	1L 27% (N=10) 2L 27% (N=10) ≥3 lines 41% (N=15)	Patients enrolled from 5th August 2013 to 23rd February 2015	ORR: 71% Median PFS: 10 months Median OS not available
METROS (NCT02499614)(22, 23)	2	26 (Caucasian)	[redacted]	Study start date: December 2014 Data cut off April 30th 2017	ORR: 65% Median PFS: 22.8 months Median OS not reached

Abbreviations: ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

Comparative clinical outcomes in ROS1-positive NSCLC

Clinical outcomes from retrospective studies are available for patients with ROS1-positive advanced NSCLC who have been treated with chemotherapy, as detailed in Appendix D of the Company submission. Furthermore, PROFILE 1001 also captured data on the 46 patients with ROS1-positive NSCLC who received prior treatment for their advanced disease. The ORR was 21.7% for prior first-line chemotherapy (29.4% with pemetrexed), 16.7% for prior second-line chemotherapy (30.8% with pemetrexed), and 23.7% for any line therapy with pemetrexed.(18)

A within-patient TTP analysis was performed for patients who had received prior therapy. In this, TTP on crizotinib was compared with TTP on last prior therapy: the median TTP with crizotinib versus last prior therapy was 19.8 versus 8.1 months (HR 0.588; 95% CI 0.308, 1.125; p-value=0.1089).(18) Although this result was not statistically significant, there was a numerical decrease in the risk of progression with crizotinib compared with last prior therapy. These data are comparable to results observed in the Royal Marsden national audit (N=26), where a median PFS of 10.5 months was observed in the 14 patients who received first-line pemetrexed plus platinum.

The median PFS for ROS1-positive patients treated by chemotherapy, as observed in the prior therapy analysis in PROFILE 1001 and the Royal Marsden audit, are comparable with the clinical outcomes from ALK-positive NSCLC patients from PROFILE 1007 (subsequent-line) and PROFILE 1014 (first-line). The median PFS in PROFILE 1007 and PROFILE 1014 were 7.7 months (95% CI: 6.0, 8.8) and 10.9 months (95% CI: 8.3, 13.9), respectively.(2, 3) Further supported by similarities in receptor homology and

patients histological profile, as recognised by the European Medicines Agency (EMA) and clinical experts, Pfizer considers it reasonable to assume the survival outcomes in ROS1-positive and ALK-positive outcomes to be comparable.

As highlighted and discussed throughout the submission, because of the rarity of the disease and the absence of comparative efficacy data due lack of clinical equipoise to conduct further comparative studies, a pragmatic solution to modelling was used in the submission. As presented in the first committee meeting, the outcomes for ALK-positive advanced NSCLC are seen by the clinical community as an appropriate proxy for modelling of ROS1-positive advanced NSCLC and the use of a proxy population does not set a precedence for future appraisals as the level of similarity between ROS1-positive and ALK-positive NSCLC should be considered as a unique case.

5. Accuracy of the preferred assumption regarding pemetrexed plus platinum utility values

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

The Pfizer base case assumed the on-treatment utility value for pemetrexed was 0.72 for the duration of time pemetrexed plus platinum patients spent in the PFS health state. In TA406, the Committee felt a higher utility value (0.75) was appropriate for pemetrexed plus platinum patients during the period following treatment, but remain on the lower utility value (0.72) while they are still pre-progression to reflect few treatment-related toxicities (paragraph 4.14). The value used in the ERG's analysis to reflect this off-treatment rebound in utility was 0.75, however the ERG applied this to the whole PFS period, rather than applying it to the off-treatment, pre-progression period only as accepted by the Committee in TA406.

Based on the Committee's accepted preference (TA406) for a higher utility value (0.75) for pemetrexed plus platinum patients during the period following treatment, along with this Committee's decision to take this slightly higher utility value into account for consistency, Pfizer have applied a utility value of 0.75 for pemetrexed plus platinum patients in the post-treatment, pre-progression period. This modification has the effect of **reducing the ICER by £455 per QALY** in the Company's modified ERG OS gain (mid-point) analysis versus using a 0.75 utility for the entire PFS period for pemetrexed plus platinum patients, as was applied by the ERG. See Table A1 in **Error! Reference source not found.**.

6. Factual inaccuracies

Pfizer have included below a summary of factual inaccuracies contained within the ACD which should be addressed by the Appraisal Committee in their decision-making at the second Committee meeting:

- The ACD states (page 14) that: "The committee also noted that the Company had not included disutility to account for any adverse reactions, and agreed that this would add further uncertainty to the results". The utility estimates included in the Company submission already reflect the negative changes in utility incurred through the adverse event profiles of the specified treatments, as they are taken directly from patients on treatment in the PROFILE 1014 and PROFILE 1007 trials. The impact of including a disutility due to adverse events could be deemed 'double-counting'. **It would be appropriate to include the same assumption regarding disutilities that was accepted previously by NICE for crizotinib in ALK-positive NSCLC (TA406).**
- The ACD states (page 15) that: "The Company had also underestimated the administration cost of crizotinib…". The ERG report does not state that the cost of crizotinib administration was underestimated. The inclusion of a pharmacy dispensing cost is consistent with the approach taken within the first-line ALK submission for crizotinib (TA406) and ceritinib's recent NICE appraisals TA395 and TA500 [ID1117 and ID729] in which the Committee accepted the use of a monthly pharmacy dispensing cost as a suitable estimate for administration cost. **It would be appropriate to include the same administration cost for crizotinib in ROS1-positive NSCLC that was accepted previously by NICE for crizotinib in ALK-positive NSCLC and ceritinib.**
- The ACD states (page 6) that: "The ROS1 oncogene is found exclusively in non-squamous-cell lung cancer, mainly in tumours with adenocarcinoma histology". **The ROS1 oncogene is found *almost* exclusively in non-squamous-cell lung cancer, mainly in tumours with adenocarcinoma histology. There are rare cases of other underlying histologies, where in PROFILE 1001 96.2% of patients had adenocarcinoma and the remainder had squamous cell carcinoma or another histology.**

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Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Crizotinib for untreated, ROS1 – positive, advanced non squamous non small cell lung cancer. [ID 1098]

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. The is the first therapy to be reviewed in lung cancer in this small, segmented ROS-1 population. It would provide a targeted treatment option.

- We understand the complexity of undertaking this appraisal. We welcome the comments made in the covering note and the ongoing nature of this process, as the Appraisal Committee seeks further clarification from the manufacture, on a number of issues. We hope that this additional evidence and analysis will lead to a positive recommendation. These patients do not have time to wait.

Roy Castle Lung Cancer Foundation
January 2018

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer [ID1098]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 7 February 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	BTOG-NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We pleased that given the rarity of ROS1+ NSCLC, the NICE committee have agreed that ALK+ NSCLC is a reasonable clinical group that behave similarly to ROS1+ NSCLC. However, we are concerned that the committee are being inconsistent in accepting crizotinib indication for ALK+ NSCLC but not for ROS1+ NSCLC
2	We are disappointed that the NICE committee did not feel that the ICERs were robust enough to accept for an ACD recommending routine use. Whilst we do recognize that one option would be to have this indication within the Cancer Drugs Fund, given this fund's remit is for England, patients in Wales and Northern Ireland would be discriminated against and significantly disadvantaged by not being able to implement ROS1 testing and not being able to access crizotinib – a drug that the NICE committee agree is a "step change" for ROS1+ patients.
3	We are disappointed that the manufacturer chose not to give NICE the option of referring this indication directly to the Cancer Drugs Fund if uncertainties around the true ICER were identified
4	If additional discussions between NICE and the manufacturer are not able to resolve the uncertainty around the ICER on drug cost grounds, we would prefer to see crizotinib funded in the Cancer Drugs fund than not at all available in the UK
5	We have significant concerns around data collection aspects around progression-free survival if crizotinib is approved in the Cancer Drugs fund and would seek clarity from NICE on how data collection can be implemented and funded with adequate clarity to ensure that any future NICE re-review will not again be frustrated by ICER uncertainties, since it is unclear in this rare indication that

	any additional data captured on the small number of UK cases treated within the CDF will robustly answer uncertainties on post-progression survival identified, particularly in the second-line setting.
6	We ask NICE for clarity on how ROS1 testing will be reimbursed to laboratory departments.

Insert extra rows as needed

NHS England submission for the NICE Technology Appraisal of crizotinib in the treatment of ROS1 non small cell lung cancer (NSCLC): meeting post 1st ACD

1. ROS1 positive NSCLC was discovered in 2011 and thus there is only a small amount of information as to its natural history, particularly in the real world setting, and there is a dearth of clinical outcome data for ROS1 patients treated with conventional cytotoxic chemotherapy.
2. ROS1 pos NSCLC is almost always only seen in adenocarcinoma of the lung and never in patients with EGFR, KRAS or ALK mutations. ROS1 NSCLC and ALK pos NSCLC thus have oncogenic drivers that are mutually exclusive.
3. ROS1 NSCLC shares some demographic and clinical characteristics with ALK pos NSCLC: younger age (median 50 years), female sex (65%) and never smokers (68%). Brain metastases are also common in ROS1 NSCLC.
4. ROS1 NSCLC appears on preliminary evidence to be more sensitive to pemetrexed and possibly also to crizotinib than ALK pos NSCLC. Ceritinib is active in ROS1 NSCLC but probably only in crizotinib-naive patients unlike ALK pos patients where ceritinib is active in ALK pos crizotinib failures . Alectinib is active in ALK pos NSCLC but inactive in ROS1 NSCLC.
5. Some references state that ROS1 and ALK pos NSCLC have similar clinico-pathological features but there are important differences: the seemingly greater sensitivity to crizotinib in ROS1 NSCLC, the differing sensitivity to ceritinib and alectinib and of course the entirely different oncogenic drivers.
6. The most practical testing strategy for ROS1 would be screening of all adenocarcinoma patients at diagnosis. A two stage strategy of only testing the EGFR and ALK negative patients is in theory possible but would still require the testing of >85% of adenocarcinomas.
7. The cost of ROS1 testing must be included in the assessment of cost effectiveness of crizotinib as it is not currently in routine practice.
8. The key comparator for 1st line crizotinib is a platinum preparation plus pemetrexed followed by maintenance pemetrexed. The main comparators for crizotinib in the 2nd line setting are docetaxel and the combination of docetaxel and nintedanib, the latter being used much less frequently than the former in NSCLC as a whole. Whether this latter statement applies to ROS1 NSCLC is unknown.
9. NHS England notes that there is better evidence for the use of crizotinib beyond 1st line use but recognises the biological plausibility of at least equal benefit when used 1st line, such use coming at the expense of reduced toxicity when compared with standard combination chemotherapy.
10. The single arm Profile 1001 study is small in size and has a median duration of follow-up of 25 months. It is thus relatively immature when only 30% of patients had died at the last data cut off in November 2015. NHS England is disappointed that no further follow up appears to have been done in the past 2 years.

11. NHS England notes that there are only 7 previously untreated patients with ROS1 NSCLC treated with crizotinib in Profile 1001. This is a tiny number and imposes huge uncertainty in assessing the clinical and cost effectiveness of crizotinib in this setting.
12. The durations of treatment with 1st- and subsequent line crizotinib in ROS1 patients are highly likely to significantly exceed the durations of progression-free survival observed in Profile 1001 and thus this treatment period beyond disease progression must be modelled in the economic analysis of crizotinib.
13. NHS England notes that the correct cost for the HRG chemotherapy tariff for crizotinib administration has not been used by the company: a figure of £14-60 has been used whereas the 2017/18 oral chemotherapy tariff is £120 per month.
14. NHS England notes the rather large contribution of the crizotinib post progression survival figures to the overall survival of both 1st and 2nd line crizotinib patients in the economic modelling, these figures significantly exceeding the total overall survival figures for the relevant comparator populations treated with just chemotherapy. NHS England finds these post progression survival figures after discontinuation of crizotinib as being implausible.
15. NHS England is surprised and sorry to observe that Pfizer do not wish crizotinib to be considered for entry into the CDF despite the NICE committee's clear indication that this was its wish. The huge uncertainty in the 1st line setting when there is so little data makes the CDF an excellent opportunity for national data collection for a large number of patients, thus providing help to NICE (and Pfizer) in a post-CDF re-appraisal of crizotinib and also giving a huge contribution to the world literature on crizotinib use and subsequent chemotherapy in ROS1 NSCLC.
16. Crizotinib is clearly active in ROS1 NSCLC but follow up in the single arm Profile 1001 study is relatively immature. Should NICE recommend this indication to the Cancer Drugs Fund then a large dataset could be collected on treatment duration, subsequent therapies and overall survival. Since there has not been any further follow up data since November 2015 used in this submission by the company, NHS England wonders whether there will be any further data collection and analysis from Profile 1001. If not, then any uncertainties that the NICE TA committee has as to mature outcomes of crizotinib in ROS1 NSCLC would have to be resolved by prolonged follow up in the CDF, potentially for up to 5 years.

[redacted]

[redacted]

February 2018

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

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	ROS1 positive non-small cell lung cancer patients are a small but important population of lung cancer patients because they could benefit greatly from access to Crizotinib. I therefore feel strongly that they should be allowed access to Crizotinib as it has been demonstrated to be effective and tolerable.

Name	[redacted]
Role	NHS Professional
Other role	Medical Oncology Consultant
Organisation	[redacted]
Location	England
Conflict	[redacted]
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I was very sorry to read the initial NICE outcome. I understand the constrains of cost-effectiveness in view of the lack of direct evidence available due to low disease frequency, and rapidly evolving pharmacological and biological advances. I would like, however, to express my point of view from my own experience: I run a centralized "mutation-driven lung cancer clinic" at [redacted] and have done so for over two years now. At [redacted] we see 1000 new lung cancer patients every year, and 9% have a cancer with a targetable mutation. I see, on average, one new patient a week with an EGFR mutation and one new patient a month with an ALK rearrangement and on average review 25 patients every week with mutation-driven lung cancers. These particular lung cancers (EGFR mutated, ALK positive... and, from the evidence available, ROS1 positive) behave very differently from wild type lung cancer, as can be seen in several publications reporting a much higher incidence of brain metastasis with no prognostic impact. These tumours meet two criterira: (a) their growth and metastatic potential is dependent on ONE genetic anomaly and (b) inhibition of the abnormal protein expressed achieves almost universally disease control with high radiological response rates. The rare cases where I have not seen disease control in EGFR tumours have been when the initially reported anomaly before radical intervention has been lost years later on disease recurrence. I have always seen disease control in tumours with a targetable gene rearrangement. The question is not if there will be disease control, the question is when will the disease become resistant to it. Furthermore, these tumours have been excluded from first line immune therapy, and there is wide skepticism about the potential benefit of this novel therapeutic approach in this patient group: mutation burden (which correlates with smoking habits) is a good predictor of response to immune therapy, but mutation-driven lung cancers (more common in never smokers) are characterized by a low

	mutation burden. From the reported literature, ROS1 and ALK tumours are similar in that both arise through a gene translocation and present not only similar clinical evolution, but also excellent response to Crizotinib. Hence ROS1 tumours are mutation-driven lung cancers, and need to be treated as such. Beyond the necessary economic calculations that relate to survival, there are other economic arguments that need to be taken into account in the modern oncology context. Let me describe the patient population we are likely to deny diagnosis or treatment: never-smokers, with low co-morbidity, often with many productive years ahead, developing incapacitating brain metastasis. These patients will be denied a treatment that is likely to allow them to go back to work (as my patients do regardless of brain involvement) and will be offered instead more expensive radiotherapy, chemotherapy and/or immune therapy from which they will be unlikely to benefit as other patients with wild type tumours do. Those who live healthier lives will be punished because they happen to have a rare type of lung cancer, by not being offered an available treatment with low toxicity and high clinical effectiveness. Thank you for reading my comment. I hope it helps making the right decision for this small group of patients. Please do not hesitate to contact me if you think I can be of further help.

Name	[redacted]
Role	NHS Professional
Other role	Consultant in Medical Oncology; Professor of Experimental Cancer Medicine
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I work at [redacted] where we routinely screen for ROS1 rearrangements in non-squamous lung cancer at diagnosis (unlike many other UK centres). This means that we have more experience than most in treating this rare group. Our anecdotal experience is that these patients do very well with crizotinib. We contributed our experience to a multicentre report presented last week at the British Thoracic Oncology Group meeting (Tokaca et al). 10 patients with ROS1-driven cancers received crizotinib with a response rate of 70%, and median PFS of 12.1 months despite many taking the targeted drug as 2nd or subsequent line. These are exceptional outcomes for advanced NSCLC. Patients receiving crizotinib have in some cases been able to access next-generation TKIs on progression, on a compassionate access basis from their manufacturers. So we are moving to a point where really outstanding quality and quantity of life is achievable in these

	patients, when given access to the appropriate targeted drugs. One of my ROS1 patients currently responding to his 2nd targeted drug has long ago returned to work as a teacher and currently leads a normal and economically productive life. I hope the NICE appraisal committee will take account of these comments. I truly believe we owe it to this very small group of patients to provide the very active and well tolerated treatment that is potentially available.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Oncologist
Organisation	
Location	England
Conflict	[redacted]
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is very disappointing that NICE have not approved Crizotinib for the management of ROS-1 translocated lung cancer. ROS-1 translocations are very rare and therefore the clinical data for Crizotinib is going to be less comprehensive than that for other cancer treatments. In addition, because crizotinib has only recently been recognised as a treatment for ROS-1 translocated lung cancer, the patients involved in the clinical trials had received range of different lines and types of prior treatment. There is absolutely no doubt that Crizotinib is a highly, highly active drug in ROS-1 translocated lung cancer. The median PFS of 19 months is extraordinary and was unprecedented at the time of publication of PROFILE-1001. This patient cohort, who are frequently young and usually never-smokers, are in desperate need of an effective treatment. Whilst I agree that using Crizotinib data relating to ALK-translocated patients is not 'ideal', the need to do so reflects the rarity of the disease, and as a clinician I think it is a fair proxy. ROS-1 translocated lung care is rare, but utterly devastating for the often young patients who have it. There is a highly effective, licensed treatment with a remarkable clinical activity. There is no doubt about the benefit of this drug in the lung oncology community. I feel that the criticism of the clinical data has been unfair and has not taken into account the exceptional nature of this small group of patients. The costs to the country for this drug, given the small patient pool, is minimal. The benefits to each of those patient is, however, vast.

Name	[redacted]
Role	Patient
Other role	Student
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This description of the evidence is lacking a comprehensive view of the data available. Internationally there is a lot of both untreated and treated ROS1 cancer having a durable response to crizotinib. See 600+ referenced paper: http://www.nejm.org/doi/full/10.1056/NEJMoa1406766
Section 2 (The technology)	This section does not outline a TESTING PROGRAM for ROS1 this is direly needed. It agreed that testing for ROS1 status in all newly diagnosed non-squamous NSCLC would be the best strategy, in line with testing for other types of tumour expression in NSCLC. - Why is this testing not being done?
Section 3 (The manufacturer's submission)	As a current ROS1+ nsclc patient, I am very disappointed that treatment will not be available for others like me. I was diagnosed two years ago at the age of 25, and I have had no other history of cancer and disease. This particular mutation effects younger people much more often. I have been living a normal and healthy life thanks to Crizotinib I was able to access from another source. (I am treated by a French doctor due to my diagnosis) I think it is a shambles that my doctor applied for this even with evidence of a strong response and that I tolerated the treatment very well. 1) ROS1 should be routinely tested as it is in any other major developed country. 2) Crizotinib should be available as a first line treatment as it saves lives and allows a good quality of life.

Name	[redacted]
Role	
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Crozitinib is indicated as first line treatment for ROS-1 patients in France and in many other countries. There is a strong body of evidence that this treatment is the best for lung cancer patients who carry the ROS-1 rearrangement. This also allow them to carry on with a normal standard of life comparing to traditional chemotherapy, and this is not to be neglected.

Name	[redacted]
Role	
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I disagree with the NICE recommendation as set out in the consultation paper in relation to the use of crizotinib because: - The absolute requirement for further ROS 1 specific data, when further studies are considered unethical and patient population is low, unfairly disadvantages those with rare conditions such as ROS 1 positive cancer - A proxy population has been clearly identified and accepted by the European Medicines Agency and 12 UK clinical experts which should fulfil the data requirement - There is a clear societal benefit given that a) ROS 1 patients are, on average, much younger than other lung cancer sufferers with no targetable mutation and thus much more likely to have dependent children and b) the efficacy of the drug is undisputed; patient autonomy is preserved - Crizotinib has already been approved for use on the NHS for the proxy population - Making crizotinib available only via the Cancer Drug Fund reduces patient access in certain parts of the United Kingdom. Without this drug, sufferers of ROS 1 positive lung cancer will die an early death; this drug is keeping patients alive and functioning well across the world. I therefore call for routine testing throughout the UK for genetic mutations such as ROS 1, and for NICE to approve the use of crizotinib on the NHS for the ROS1 positive cancer patients thus identified. This will generate an extended, improved quality of life for patients and related societal benefits as described in more detail below.
Section 2 (The technology)	A rarely occurring cancer ROS1 positive lung cancer is a very rare cancer. This means that by definition, data will be hard to access due to difficulty in finding participants for studies. This is particularly the case in locations such as the UK where genetic testing has not, in recent years, been routine procedure. The UK is a very evidence based jurisdiction, as it is important that there is accountability for the use of public funds. Under normal circumstances, this evidence based approach is perfectly valid. However, there will always be exceptions to this and an extremely rare condition such as ROS1 would be one of those exceptions. Without a flexible approach, ROS 1 positive patients will be unfairly disadvantaged compared with other patient populations simply due to the rareness of their condition. Routine testing for targetable mutations would increase the potential data available, though it is likely to remain a rare finding; a recently published update to the IASLC/CAP/AMP molecular testing guidelines for NSCLC strongly recommended testing all NSCLC adenocarcinoma cases for ROS1.

Section 3 (The manufacturer's submission)	The proxy population The European Medicines Agency and twelve UK clinical experts agreed that because of the rareness of this condition, and the similarities it has to another genetic mutation, ALK, that the ALK population could be used as a proxy population for ROS1. This appears to be a very pragmatic approach for a rare condition. It is true that as research continues some differences between ALK and ROS1 may be found; however, the PROFILE 1001 study generated such marked effects on its ROS1 participants (crizotinib was seen to be more effective for ROS 1 than ALK) that researchers concluded that a randomized controlled trial without access to crizotinib for the control population would actually be unethical. Therefore it does not seem likely that a further specific ROS1 study with comparator data will become available. It seems that this proxy population is now being rejected due to the much greater effect the drug has for ROS 1 than for ALK, which does not feel like an equitable result. Given the conclusion that further studies would be unethical, it seems extremely unfair to deny ROS1 patients the opportunity to access this life extending drug, which represents a step change in the treatment of such patients. Indeed, it has already been approved for use on the NHS for ALK positive patients. More generally, denial would mean that those with rare conditions have a much lesser chance of accessing the drug they need simply because they are few in number, even when the efficacy of the drug is "undisputed". This does not, in my view, represent equitable treatment for this patient population - access, when a known treatment is available, should not depend on patient numbers and the resultant availability of data when the patients are few in number and proxy data is available.
Section 4 (Consideration of the evidence)	Societal benefit Crizotinib has a better safety profile than chemotherapy and is generally better tolerated. Because it is an oral treatment, patient autonomy is maintained, and medical resource usage reduced, generating a further benefit. The average age of diagnosis of ROS 1 patients also means that they are much more likely to have dependent children. I was diagnosed with ROS1 positive lung cancer in June 2017 and have been fortunate enough to be able to access crizotinib as a first line treatment privately. In my case, the drug has allowed me to remain a functioning parent to my two children. Without it, activities of daily living quickly become problematic. I am extremely grateful to have access to crizotinib.
Section 5 (Implementation)	Cancer Drug Fund Making crizotinib available only through the Cancer Drug Fund means that patients in Wales and Northern Ireland will not be able to access crizotinib at all, which would be inequitable. Further, ROS1 patients in these areas would not even be identified as there would then be no testing for the mutation. This will further reduce any potential future data gathering opportunities in what is already an extremely limited population.

Name	[redacted]
Role	Consultant in Medical Oncology
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am aware of the limitations of the data surrounding Ros-1 tumours. However these are rare tumours and it is unlikely that good quality randomised data will ever be available. I would agree with the NICE panel that these tumours behave in a similar fashion to the ALK positive group - they are adenocarcinomas and are predominantly in never smokers but additionally they appear to have a similar phenotype with multi-focal lung disease and a predilection for the CNS. I would therefore support the use of the ALK data in this group. The alternative of chemotherapy is problematic. It is toxic, with generally short term responses and a number of patients are not able to tolerate it at all leaving them with only the option of palliative care. This is particularly difficult to accept when there is a tablet available which is strikingly well tolerated with some evidence showing a good chance of clinically significant benefit.

Name	[redacted]
Role	Consultant Oncologist
Other role	
Organisation	
Location	Wales
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Song et al (Cancer Med. 2016 Oct; 5(10): 2688-2693) reported a 6.7-month median PFS in 34 ROS-1 lung cancer patients treated with pemetrexed-based chemotherapy. Chen et al (J Thorac Oncol. 2016 Jul;11(7):1140-52) reported on 19 ROS-1 patients also treated with Pemetrexed-based chemotherapy and showed a 7.5 month median PFS. These studies compare with a 19.5 month median PFS in the 50 ROS-1 patients reported in the 2014 Shaw et al. NEJM paper. ROS-1 cancers are very likely to be analogous to EGFR and ALK translocated lung cancers in that more patients respond to targeted therapy than to chemotherapy, and those that respond do so more durably. The huge difference in PFS with crizotinib compared to chemotherapy reported in trials strongly suggests crizotinib is the more effective treatment. Disease control is associated with a reduction in cancer-related symptoms, and Crizotinib is well tolerated. Patients with ROS-1 lung cancer are likely to represent 1% or less of all lung cancer cases, and the cost of providing crizotinib will be relatively small compared to the overall drug budget for lung cancer patients. I would urge NICE to reconsider their decision not to approve Crizotinib in ROS-1 positive patients.

Name	[redacted]
Role	Patient Group
Other role	[redacted]
Organisation	
Location	United States
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We are The ROS1ders, a group of 259 patients and caregivers dealing with ROS1-positive (ROS1+) non-small cell lung cancer (NSCLC) in 32 countries. We network and collaborate with clinicians, researchers, cancer advocacy organizations and industry as part of the Global ROS1 Initiative. Our global group represents more than four times the number of ROS1 patients found in any ROS1 clinical trial cohort to date. With this letter, we are contributing our collective experience to the appraisal consultation. Most of the patients in the ROS1ders have been treated with crizotinib. We believe crizotinib is an effective treatment for metastatic ROS1 non-small cell lung cancer (NSCLC), and gives us better quality of life than chemotherapy.
Section 2 (The technology)	Crizotinib enables ROS1+ NSCLC patients to live normal lives instead of coping with a terminal disease. The majority of crizotinib-treated ROS1 patients are experiencing astonishing improvements in their state of health, which is unknown for chemotherapy. More than two-thirds of our members report a strong response to crizotinib and long progression-free periods with a very good quality of life. Many patients in our group started taking crizotinib in 2011 or 2012, and several of them continue to take the drug and enjoy no evidence of disease. These patients are dealing with lung cancer as a chronic illness rather than a terminal disease. We may have a chronic illness that will one day claim our lives, but we are NOT at “end of life”.
Section 3 (The manufacturer’s submission)	Crizotinib gives ROS1+ NSCLC patients a superior quality of life compared to chemo Several of our members received one or more lines of chemotherapy prior to their treatment with crizotinib. Their quality of life was significantly worse while receiving chemo than while taking crizotinib. The QALY criteria for evaluating crizotinib does not capture the impact of crizotinib versus chemo on our daily lives. ROS1 patients are often younger than typical lung cancer patients; at the time of diagnosis, many of our members are employed and have children at home. When treated with crizotinib instead of chemo, most can continue living their usual lives with a minimum of side effects. When treated with chemo, many patients are too ill to participate in the aspects of life they most enjoyed, and most saw their cancer progress in less than a year. The results of several clinical trials worldwide have led to consensus among ROS1+ NSCLC patients and their doctors that crizotinib is significantly superior to all chemotherapy regimens in ROS1 patients in terms of response rate, progression-free time, toxicity, quality of life and survival time. Our experience would indicate an improvement in overall survival as well. The patient-relevant parameters are quite similar to ALK-positive NSCLC patients (for whom NICE covers crizotinib). Fortunately, the progression-free time for ROS1 patients is significantly longer than for ALK patients. Quality-adjusted Life Year (QALY) evaluation often does not capture

	all the relevant quality of life improvements experienced by patients on crizotinib. First, QALY analyses usually compare the state of health of NSCLC patients on crizotinib to that same patient's state of health before taking crizotinib. A more honest evaluation would compare the health of a typical ROS1+ NSCLC patient on crizotinib (who survives for years with good quality of life) to the typical metastatic NSCLC patient on chemo (who usually dies within one year of diagnosis) or even on hospice. ROS1+ NSCLC patients on crizotinib are often able to continue working, caring for their families, and contributing to society, and are far less likely to be hospitalized with treatment complications compared to chemotherapy recipients. This places less emotional and financial burden on spouses, caregivers, and consumes fewer healthcare system resources.
Section 4 (Consideration of the evidence)	Conducting a Randomized Controlled Trial (RCT) for ROS1 is not ethical nor reasonable It is unethical to randomize patients to therapies known to be less effective. Several Phase 2 studies show crizotinib is effective in 70% to 80% of ROS1+ patients, whether those patients are untreated or heavily pretreated. Considerable scientific data shows chemotherapy is effective in about 20% of NSCLC patients in first line treatment, and effective in only 9% of NSCLC patients in second line treatment. An RCT would also be complicated by the fact that ROS1+ NSCLC occurs in a very small population of patients, which means not enough patients would be available for a Phase 3 trial. To demonstrate: - About 207,000 new NSCLC cases were predicted in the USA for 2017. - Two recent journal articles found only 60% of NSCLC patients are getting tested for known driving oncogenes. - ROS1 occurs in about 1% of tested NSCLC patients. - Typically 3% of cancer patients enrol in clinical trials. The EUCROSS trial had to test 200 patients to find one ROS1 patient willing and able to enter a trial. When all these factors are considered, about 37 new ROS1 patients were available to enrol in US ROS1 clinical trials during 2017 hardly enough to power a Phase 3 clinical trial. The UK has far fewer lung cancer patients than the USA. Therefore, creating a trial comparing crizotinib with chemotherapy in ROS1+ NSCLC patients would be an unnecessary waste of patients, time and money.
Section 5 (Implementation)	The scientific community strongly recommends testing NSCLC patients for ROS1 and treating them with crizotinib Based on a comprehensive evaluation of ROS1 studies and clinical trials, the International Association for the Study of Lung Cancer (IASLC), the College of American Pathologists (CAP), and the Association for Molecular Pathology (AMP) strongly recommend testing for ROS1 in the 2018 update to their lung cancer molecular testing guideline: ROS1 testing must be performed on all lung advanced stage adenocarcinoma patients, irrespective of clinical characteristics. This recommendation is evidence based and supported by 9 studies. All included studies were assessed for quality and none were found to have methodologic flaws that would raise concerns about the study's

	findings Although relatively rare, accounting for <2% of none small cell lung carcinomas and 2% to 3% of lung adenocarcinomas, structural rearrangements involving the ROS1 gene generate an oncogenic fusion that can be treated successfully with targeted inhibitors. A single phase I clinical trial of 50 NSCLC patients demonstrated that the presence of a ROS1 rearrangement by FISH or RT-PCR predicts response to targeted inhibition using crizotinib, with a response rate of 72% and median progression-free survival of 19.2 months. Based on this trial, the FDA approved the expanded use of crizotinib in patients with ROS1-rearranged NSCLC in 2016. A European multi-institutional retrospective study of 32 patients with ROS1-rearranged NSCLC treated with crizotinib demonstrated an 80% response rate and 9.1-month progression-free survival. Overall survival for patients with ROS1-rearranged tumors irrespective of use of targeted therapy appears longer than that for patients with other molecular alterations undergoing targeted therapy. As with ALK, ROS1 activation is driven by structural variants, with multiple different partners fusing to the C-terminal portion of ROS1 containing the cytoplasmic tyrosine kinase and driving downstream signaling through MAPK, JAK/STAT, and PI3K pathways. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors (Journal of Molecular Diagnostics), http://jmd.amjpathol.org/article/S1525-1578(17)30590-1/fulltext Furthermore, the prospective European EUCROSS phase II trial evaluated crizotinib in ROS1+ lung adenocarcinoma and came to the conclusion: Crizotinib is a highly effective and safe treatment in the subset of ROS1 rearranged NSCLC patients as determined by FISH and DNA-sequencing. In total, 34 patients were enrolled in this trial. Of these, the patients whose ROS1+ was identified by sequencing showed a response rate of 83%. Even after a long study period the median progression-free survival has yet to be determined. EUCROSS: A European Phase II Trial of Crizotinib in Advanced Adenocarcinoma of the Lung Harboring ROS1 Rearrangements - Preliminary Results http://www.jto.org/article/S1556-0864(16)31669-0/fulltext (Journal of Thoracic Oncology)
Section 6 (Related NICE guidance)	Conclusion: Crizotinib is superior to existing therapies for ROS1+ NSCLC, and a wise investment for NICE For the first time ever, ROS1+ NSCLC patients have a truly effective therapy, with previously unattainable improvements in their quality of life and survival. There isn't a need to wait for an RCT comparing crizotinib to chemo when the improvement in outcomes is this dramatic. Allowing these patients to take crizotinib instead of other existing NSCLC therapies enables UK citizens to continue their lives instead of being end of life patients. NICE, please provide crizotinib as a treatment option for ROS1+ NSCLC patients. Sincerely, The ROS1ders

	[redacted] http://ros1cancer.com [redacted] [redacted] University of Colorado [redacted], MD, PhD [redacted] Division of Hematology-Medical Oncology, Department of Internal Medicine [redacted] [redacted] [redacted] Professor of Medicine, Harvard Medical School [redacted] MBBS, PhD, FRACP [redacted], Australia [redacted], MD, Professor [redacted], Cologne/Germany

Public comments received by email

I had been suffering from extreme vertigo for several weeks when I saw a consultant neurologist. She arranged for me to have a scan of the brain and I saw her afterwards. I was with my husband and son. The consultant asked how old my son was. I said five. She looked at me and hesitated as she muttered these words, looking at the scan of my brain on her computer, “You have cancer. You have many metastasized tumours in your brain.” and looked at me as if it was a miracle that I was still alive.

That was how I was diagnosed with stage 4 lung cancer in May 2012.

I was told that I had non-small-cell adenocacinoma and the prognosis was bleak. 12 - 18 months perhaps. I was tested for Epidermal Growth Factor Receptor (EGFR) mutation as studies had shown that a large proportion of patients with EFGR mutation was relatively young female Asians (I am [redacted] and was [redacted] at the time of diagnosis). My consultant had previously told me that the first line of treatment for EFGR was tablets that are very effective and did not carry serious side effects, so I was very disappointed when the test came back negative. I had to have chemotherapy.

I had 10 cycles of chemotherapy with various drugs.

Platinum-based chemotherapy could be very effective at controlling a progression of cancer, however, the impact of the side effects on the patients’ quality of life is devastating. By the time the third cycle completed, I was totally immobilised and bed-bound. I was unable to look after myself, let alone my young son. I needed a help of a social worker everyday just to have a wash and get dressed.

After every cycle of chemotherapy, I became less able. By autumn, I was unable to do anything, not even turn over in bed. I would have to ask my husband to push me to turn over in bed. I thought I didn’t want to live like that. I wanted to die. If anything had kept me alive, it was my son. I didn't want him to grow up without his mum.

Fortunately my cancer stayed mostly problem-free over the summer of 2013, so I was allowed to stay “Chemo free” for a few months. In the mean time I learned from the US-based lung cancer group about other mutations, specifically Anaplastic Lymphoma Kinase (ALK) and c-ros Oncogene 1 (ROS1). I asked to be tested for these two new mutations – I was identified as ROS1 positive.

It was all my consultant’s effort that enabled me to obtain Crizotinib through my private medical insurance in November 2013 as it was, and still is, not available on the NHS. Crizotinib was already well known in the US as a second-generation treatment for ALK and ROS1, and many patients had been showing excellent response to the drug. In the UK, Crizotinib was approved by NICE for ALK patients in 2016 but not for ROS1. Without my medical insurance, I would not have had access to this amazing drug.

Crizotinib is totally life changing. I no longer needed a social worker to look after me everyday as I slowly regained mobility and brain functions while my cancer was controlled well. It brought back some normality to my and my family’s life. Although there are some bad side effects with Crizotinib, they are cosmetic in comparison to those I experienced from chemo. The quality of life was good. I thought I wanted to live again. And I did live - for over 3 years on Crizotinib until I moved to another drug.

Only 1% of stage 4 lung cancer patients are said to survive 5 years. I am living my 6th year as a survivor of stage 4 lung cancer and this would never have been possible without Crizotinib.

Today, the 4th February, is the world cancer day. I heard several times on the TV and radio that the UK’s lung cancer survival rate is one of the lowest in the developed world. Please give ROS1 patients a chance. We may be a small population amongst the larger lung cancer community but that shouldn’t be a reason for denying us such a wonderful drug which could give us much longer prognosis of life with good quality.

[redacted]

The ROYAL MARSDEN
NHS Foundation Trust

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14/02/2018

Dear Abi,

Re: ID1098 crizotinib for treating ROS1-positive advanced non-small-cell lung cancer.

I have been asked to comment on the below questions. My answers are below and highlighted in yellow.

1. Although the trial evidence is very limited, in your clinical opinion how likely is it that people treated with crizotinib as a **first line treatment** will live at least 13 months longer than people treated with pemetrexed plus platinum-based therapy?

   The trial evidence is, indeed limited. However I think that a survival benefit of 13 months is reasonable and within the spectrum of that anticipated. In the absence of crizotinib, most ROS1 patients will receive platinum-pemetrexed (most not having maintenance pemetrexed) and then docetaxel +/- nintedanib. The clinical experience is that the survival with this strategy is dismal. Therefore the addition of first line crizotinib will significantly add to survival mainly since patients will be much fitter and better performance status when relapsed, and hence more fit for additional therapies, including clinical trials, in this small number of fit, young, patients usually with few co-morbidities. Moreover the ALK experience has demonstrated a median survival benefit for first-line crizotinib compared to chemotherapy in excess of 30 months (HR=0.346, 95% bootstrap CI: 0.081, 0.7180) using the RPSFT analysis approach for overall survival in the first-line PROFILE1014 trial (Mok et al. ESMO 2017 Annual Meeting).

   a. In your clinical opinion what is the average overall survival gain for people treated with crizotinib as a **first line treatment** compared with people treated with pemetrexed plus platinum-based therapy? Please report a range if possible.

      This is difficult to quantify as there is no direct quantifiable data. The above RPSFT approach to the PROFILE1014 trial for ALK patients has demonstrated a survival benefit in excess of 30 months. My clinical experience is for ROS1 patients receiving crizotinib to survive similarly to ALK patients, and an average 24 month survival

advantage is not unreasonable. I have no robust data on which to base a range on but clinical experience suggests that this could easily extend to 33+ months.

b. How clinically plausible is an overall survival gain of 18 months for crizotinib?

This is reasonable.

2. Although the trial evidence is very limited, in your clinical opinion how likely is it that people treated with crizotinib as a **subsequent line treatment** will live at least 16 months longer than people treated with docetaxel?

Current data across different types of oncogene-addicted NSCLC (eg EGFR mutant, or ALK positive) suggests that if the targeted therapy is given first or second line, the PFS is broadly similar. Of course in the second line setting, the comparator (chemotherapy) is less effective than in the first line setting. Thus, the survival benefit for ROS1 patients in the second line setting is likely to be similar to the first-line setting, if not better, due to the less effective docetaxel comparator. Hence, this level of survival benefit would be clinically plausible.

a. In your clinical opinion what is the average overall survival gain for people treated with crizotinib as a **subsequent line treatment** compared with people treated with docetaxel? Please report a range if possible.

As above, a survival benefit of 16 months is clinically reasonable. This is because patients will be fitter and less symptomatic when progressing on crizotinib and more suitable to additional therapies, including clinical trials. I have no robust data on which to base a range, but clinical experience suggests that this could extend to 24+ months.

b. How clinically plausible is an overall survival gain of 20 months for crizotinib?

This is reasonable.

c. Is sequential testing in the **subsequent line** setting likely to happen in clinical practice?

Sequential ROS1 testing is highly unlikely to be clinically effective and I strongly urge the committee to recommend ROS1 testing as part of the diagnostic suite of investigations alongside other biomarkers currently evaulated. It is far better to ROS1 test at time of diagnosis as this is the most efficient use of valuable, diagnostic tissue, often extremely small tissue material. Should a clinician need a ROS1 test at point of subsequent-line decision making our experience with other biomarkers in NSCLC to date (EGFR, ALK, PDL1) has taught us that this is a highly problematic approach, and indeed is contra current guidelines by specialist societies (eg ESMO guidelines, Novello et al. Ann Oncol 2016; ASCO/IASLC guidelines, Kalemkerian et al. J Clin Oncol 2018). This is because considerable time is taken to identify and retrieve the surplus diagnostic material from the pathology laboratory/archive which is often physically located in a separate institution from that where the oncologist is based/patient being treated. Moreover, there is a high risk of there being inadequate tumour material remaining for ROS1 IHC, FISH material since it will already have been used for PDL1, EGFR, and ALK testing, with excess tumour material wasted every time the diagnostic block is cut into for biomarker testing. If inadequate tumour material is identified, this will then result in a patient needing a re-biopsy which will take significant time and add additional cost, resource, and morbidity when unnecessary if testing undertaken at point of diagnosis. Additionally, patients

may not be well enough to wait additional time for a re-biopsy, tissue verification of diagnosis and ROS1 testing, or have tumour sites amenable to biopsy (eg CNS only relapse; central lung parenchymal relapse). Due to all of these issues, if ROS1 testing is only recommended in the subsequent-line setting there will be significant numbers of patients which will not receive this test and hence large numbers of ROS1 patients going unrecognized. Overall, the most cost efficient methodology is for routine testing at time of diagnosis, similar to current practice for EGFR, ALK, and PDL1.

Yours sincerely,

Dr Sanjay Popat FRCP PhD
Consultant Medical Oncologist

New Information Included within Pfizer's Response to the ACD for ID1098

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:

(A) New analyses: Summary of data behind the key assumptions.

Reference to ACD paragraph 3.12, 3.14

(B) New analyses: incorporating the Committee's preferences, with credible OS estimates.

Reference to ACD paragraph 3.11, 3.12, 3.14

(C) New data: Royal Marsden Audit, poster published at the British Thoracic Oncology Group Conference 2018.

Newly published data to support PROFILE data and model validation

(D) New analyses: Summary of changes to the model since ERG's version "14.11.2017"

Guide to which cells have been amended to reflect changes

Appendices

Appendix A. **New analyses: Summary of data behind the 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 **Error! Reference source not found.** and **Error! Reference source not found.** 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 (and shared with Pfizer along with the ERG report).

Table A1: Summary of the differing key assumptions between the ERG's base case (the Committee's higher range of plausible ICERs), the Company's base case, and the proposed revised base case

Assumption	**Pfizer Submission**	**ERG analysis**	**Revised: Pfizer ACD response**	**Comment on data in response to ACD** *(see Sections **Error! Reference source not found.** and **Error! Reference source not found.** for details)*
(A) Utility values for pre-progression pemetrexed patients once off treatment	0.72	0.75 (whole PFS period)	0.72 (PFS, on treatment) 0.75 (PFS, off treatment)	New 0.75 reflects the accurate application during the off-treatment PFS period only
(B) Increased cost of treating pulmonary embolism beyond that assumed in the Pfizer base case	£26.34	£26.34	£1,485.76	Reflects an increase in line with ERG's comments (£1,485.76), and for consistency with a previous appraisal of ceritinib (TA500) [ID1117]
(C) Application of sequential testing for second-line crizotinib	Up-front testing	Up-front testing	Sequential testing	Reflects comments from the ERG in their report (page 122) that it is more appropriate to use sequential testing for subsequent-line analyses

The deterministic ICERs with PAS, once the above three revised assumptions are included, are:

- [redacted] **per QALY** in the Company's first-line, base case model (modified crizotinib PPS) using adjusted OS gain (mid-point crizotinib OS gain applied).
- [redacted] **per QALY** in the Company's subsequent-line, base case model (modified crizotinib PPS) using adjusted OS gain (mid-point crizotinib OS gain applied between PFS HR applied to OS and PROFILE 1007 HR).

Appendix B. New analyses: incorporating the Committee's preferences, with credible OS estimates

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

1) Survival models with an OS gain of greater than 13.1 months (mean)

Section 2 sets out that the minimum expected OS gain for first-line patients treated with crizotinib is 13.1 months (mean), with scenarios not meeting this rule considered not clinically valid.

Pfizer explored the following scenarios to ascertain those that are clinically plausible:

- **ORIGINAL ERG scenario (PPS=PPS); PFS utility=0.75 (with and without testing costs)**
- **ADAPTED ERG scenario (PPS=PPS) with adjustment of crizotinib curve; PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase (with and without testing costs)**
- **THRESHOLD ANALYSIS: Adjustment of crizotinib OS curve to [redacted]/QALY); PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase (with and without testing costs)**
- **MINIMUM OS GAIN ANALYSIS [TA406]: Adjustment of crizotinib OS curve to 13.1-month mean OS gain; PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase (with and without testing costs)**

From these eight possible scenarios, Table B1 presents those which meet the threshold of a minimum of 13.1 months mean survival gain and OS mean gain attributed to pemetrexed plus platinum therapy that is considered clinically plausible. The remaining four clinically plausible analyses have ICERs that range from [redacted] per QALY, when PAS is considered.

Table B1. Modelled scenarios when OS gain with crizotinib is modified first-line

Scenario	HR	OS mean gain	Criz median OS	Criz mean OS	Criz median PFS	Criz mean PFS	Criz median PPS	Criz mean PPS	Pem median OS	Pem mean OS	Pem median PFS	Pem mean PFS	Pem median PPS	Pem mea PPS	ICER (£ per QALY) with PAS
ORIGINAL ERG scenario (PPS=PPS); PFS utility=0.75	-	9.5*	32.5	46.4	8.9	16.8	23.7	29.6	25.6	36.9†	6.9	7.3	18.7	29.6	[redacted]

ORIGINAL ERG scenario (PPS=PPS); PFS utility=0.75; no testing costs	-	9.5*	32.5	46.4	8.9	16.8	23.7	29.6	25.6	36.9†	6.9	7.3	18.7	29.6	[redacted]
ADAPTED ERG scenario (PPS=PPS) with adjustment of crizotinib curve; PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase	0.64	9.5*	18.7	27.2	8.9	16.8	9.9	10.4	12.8	17.7	6.9	7.3	5.9	10.4	[redacted]
ADAPTED ERG scenario (PPS=PPS) with adjustment of crizotinib curve; PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase; no testing costs	0.64	9.5*	18.7	27.2	8.9	16.8	9.9	10.4	12.8	17.7	6.9	7.3	5.9	10.4	[redacted]
THRESHOLD ANALYSIS: Adjustment of crizotinib OS curve to [redacted]/QALY); PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
THRESHOLD ANALYSIS: Adjustment of crizotinib OS curve to [redacted]/QALY); PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase; no testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MINIMUM OS GAIN ANALYSIS [TA406]: Adjustment of crizotinib OS curve to 13.1 month mean OS gain; PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase	0.56	13.1	21.7	30.8	8.9	16.8	12.8	13.9	12.8	17.7	6.9	7.3	5.9	10.4	[redacted]
MINIMUM OS GAIN ANALYSIS [TA406]: Adjustment of crizotinib OS	0.56	13.1	21.7	30.8	8.9	16.8	12.8	13.9	12.8	17.7	6.9	7.3	5.9	10.4	[redacted]

curve to 13.1 month mean OS gain; PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase; no testing costs														
Adjustment of crizotinib OS curve to mid-point OS gain (between Pfizer base case and ERG PPS=PPS analysis); PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase	0.48	18.2	25.6	35.9	8.9	16.8	16.8	19.0	12.8	17.7	6.9	7.3	5.9	10.4	[redacted]
Adjustment of crizotinib OS curve to mid-point OS gain (between Pfizer base case and ERG PPS=PPS analysis); PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase; no testing costs	0.48	18.2	25.6	35.9	8.9	16.8	16.8	19.0	12.8	17.7	6.9	7.3	5.9	10.4	[redacted]

** Asterisks indicate scenarios where crizotinib's mean OS gain is lower than 13.1 months (also shaded grey).*

† Daggers indicate pemetrexed plus platinum scenarios that are less likely to be plausible due to high mean OS.

Abbreviations: ERG: Evidence Review Group; OS: overall survival; PE: pulmonary embolism; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year.

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

From the above table (B1), there are four clinically plausible scenarios:

First-line crizotinib treatment

1. MINIMUM OS GAIN ANALYSIS [TA406]: Adjustment of crizotinib OS curve to 13.1 month mean OS gain; PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase (ICER with PAS of **£**[redacted] **per QALY**)
    a. *Without testing (ICER* with PAS *of* ***£***[redacted] ***per QALY****)*
2. Adjustment of crizotinib OS curve to mid-point OS gain (between Pfizer base case and ERG PPS=PPS analysis); PFS utility=0.72 on treatment, 0.75 off treatment; PE cost increase (ICER with PAS of **£**[redacted] **per QALY**)
    a. *Without testing (ICER* with PAS *of* ***£***[redacted] ***per QALY****)*

The range of mean OS gain (Table B1), which Pfizer believe are the most clinically plausible, produce ICERs that range from **£[redacted] to £[redacted] per QALY when PAS is considered.**

2) <u>Survival models with an OS gain of greater than 16.2 months (mean)</u>

Table B2 sets out that the minimum expected OS gain for subsequent-line is 16.2 months (mean), with scenarios not meeting this rule considered not clinically valid.

Pfizer explored the following scenarios to ascertain those that are clinically plausible:

- **ORIGINAL ERG scenario (PPS=PPS) (with upfront testing, sequential testing and without testing costs)**
- **ADAPTED ERG scenario (PPS=PPS) with adjustment of crizotinib curve; PE cost increase (with upfront testing, sequential testing and without testing costs)**
- **MINIMUM OS GAIN ANALYSIS [TA422]: Adjustment of crizotinib OS curve to 16.2-month mean OS gain; PE cost increase (with upfront testing, sequential testing and without testing costs)**
- **THRESHOLD ANALYSIS: Adjustment of crizotinib OS curve to [redacted]/QALY); PE cost increase (with upfront testing, sequential testing and without testing costs)**
- **ORIGINAL ERG scenario (PFS HR=OS HR) using unadjusted data (with upfront testing, sequential testing and without testing costs)**
- **ADAPTED ERG scenario (PFS HR=OS HR) with adjustment of crizotinib curve, PE cost increase (with upfront testing, sequential testing and without testing costs)**
- **Adjustment of crizotinib OS curve mid-point OS gain (between PROFILE 1007 HR=0.38 and ERG PFS HR=OS HR); PE cost increase (with upfront testing, sequential testing and without testing costs)**

From these 21 possible scenarios, Table B2 presents those which meet the threshold of a minimum of 16.2 months mean survival gain and an OS mean gain attributed to docetaxel (pooled chemotherapy) that is considered clinically plausible. The remaining nine clinically plausible analyses have ICERs that range from [redacted] per QALY when PAS is considered.

Table B2. Modelled scenarios when OS gain with crizotinib is modified subsequent-line

Scenario	HR	Mean OS gain	Criz median OS	Criz mean OS	Criz median PFS	Criz mean PFS	Criz median PPS	Criz mean PPS	Doc median OS	Doc mean OS	Doc median PFS	Doc mean PFS	Doc median PPS	Doc mean PPS	ICER (£ per QALY) with PAS
ORIGINAL ERG scenario (PPS=PPS)	-	5.8*	27.6	39.5	8.9	10.6	18.7	28.9	23.7	33.7†	3.9	4.9	19.7	28.8	[redacted]
ORIGINAL ERG scenario (PPS=PPS); sequential testing	-	5.8*	27.6	39.5	8.9	10.6	18.7	28.9	23.7	33.7†	3.9	4.9	19.7	28.8	[redacted]
ORIGINAL ERG scenario (PPS=PPS); no testing costs	-	5.8*	27.6	39.5	8.9	10.6	18.7	28.9	23.7	33.7†	3.9	4.9	19.7	28.8	[redacted]
ADAPTED ERG scenario (PPS=PPS) with adjustment of crizotinib curve; PE cost increase	0.73	5.7*	15.8	22.4	8.9	10.6	6.9	11.8	11.8	16.7	3.9	4.9	7.9	11.8	[redacted]
ADAPTED ERG scenario (PPS=PPS) with adjustment of crizotinib curve; PE cost increase; sequential testing	0.73	5.7*	15.8	22.4	8.9	10.6	6.9	11.8	11.8	16.7	3.9	4.9	7.9	11.8	[redacted]
ADAPTED ERG scenario (PPS=PPS) with adjustment of crizotinib curve; PE cost	0.73	5.7*	15.8	22.4	8.9	10.6	6.9	11.8	11.8	16.7	3.9	4.9	7.9	11.8	[redacted]

increase; no testing costs															
THRESHOLD ANALYSIS: Adjustment of crizotinib OS curve to [redacted]/QALY); PE cost increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
THRESHOLD ANALYSIS: Adjustment of crizotinib OS curve to [redacted]/QALY); PE cost increase; sequential testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
THRESHOLD ANALYSIS: Adjustment of crizotinib OS curve to [redacted]/QALY); PE cost increase; no testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MINIMUM OS GAIN ANALYSIS [TA422]: Adjustment of crizotinib OS curve to 16.2-month mean OS gain; PE cost increase	**0.49**	**16.2**	**22.7**	**32.9**	**8.9**	**10.6**	**13.8**	**22.3**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]
MINIMUM OS GAIN ANALYSIS [TA422]: Adjustment of crizotinib OS curve to 16.2-month mean OS gain; PE cost increase;	**0.49**	**16.2**	**22.7**	**32.9**	**8.9**	**10.6**	**13.8**	**22.3**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]

sequential testing															
MINIMUM OS GAIN ANALYSIS [TA422]: Adjustment of crizotinib OS curve to 16.2-month mean OS gain; PE cost increase; no testing costs	**0.49**	**16.2**	**22.7**	**32.9**	**8.9**	**10.6**	**13.8**	**22.3**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]
ORIGINAL ERG scenario (PFS HR=OS HR) using unadjusted data	**0.49**	**19.7**	**27.6**	**39.5**	**8.9**	**10.6**	**18.7**	**28.9**	**13.8**	**19.8†**	**3.9**	**4.9**	**9.9**	**14.9**	[redacted]
ORIGINAL ERG scenario (PFS HR=OS HR) using unadjusted data; sequential testing	**0.49**	**19.7**	**27.6**	**39.5**	**8.9**	**10.6**	**18.7**	**28.9**	**13.8**	**19.8†**	**3.9**	**4.9**	**9.9**	**14.9**	[redacted]
ORIGINAL ERG scenario (PFS HR=OS HR) using unadjusted data; no testing costs	**0.49**	**19.7**	**27.6**	**39.5**	**8.9**	**10.6**	**18.7**	**28.9**	**13.8**	**19.8†**	**3.9**	**4.9**	**9.9**	**14.9**	[redacted]
ADAPTED ERG scenario (PFS HR=OS HR) with adjustment of crizotinib curve, PE cost increase	**0.49**	**16.3**	**23.7**	**33.0**	**8.9**	**10.6**	**14.8**	**22.5**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]
ADAPTED ERG scenario (PFS HR=OS HR) with adjustment of crizotinib curve, PE cost increase; sequential testing	**0.49**	**16.3**	**23.7**	**33.0**	**8.9**	**10.6**	**14.8**	**22.5**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]
ADAPTED ERG scenario (PFS HR=OS HR) with adjustment of crizotinib curve, PE cost	**0.49**	**16.3**	**23.7**	**33.0**	**8.9**	**10.6**	**14.8**	**22.5**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]

increase; no testing costs														
Adjustment of crizotinib OS curve mid-point OS gain (between PROFILE 1007 HR=0.38 and ERG PFS HR=OS HR); PR cost increase	**0.43**	**20.9**	**26.6**	**37.6**	**8.9**	**10.6**	**17.7**	**27.0**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]
Adjustment of crizotinib OS curve mid-point OS gain (between PROFILE 1007 HR=0.38 and ERG PFS HR=OS HR); PE cost increase; sequential testing	**0.43**	**20.9**	**26.6**	**37.6**	**8.9**	**10.6**	**17.7**	**27.0**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]
Adjustment of crizotinib OS curve mid-point OS gain (between PROFILE 1007 HR=0.38 and ERG PFS HR=OS HR); PE cost increase; no testing costs	**0.43**	**20.9**	**26.6**	**37.6**	**8.9**	**10.6**	**17.7**	**27.0**	**11.8**	**16.7**	**3.9**	**4.9**	**7.9**	**11.8**	[redacted]

** Asterisks indicate scenarios where crizotinib's mean OS gain is lower than 16.2 months (also shaded grey).*

† Daggers indicate docetaxel scenarios that are less likely to be plausible due to high mean OS.

Abbreviations: ERG: Evidence Review Group; HR: hazard ratio; OS: overall survival; PE: pulmonary embolism; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year.

Note that the below ICERs include the "revised" input data for assumptions [B] & [C] in Table A1, Appendix A.

From the above table (B2), there are nine clinically plausible scenarios:

Subsequent-line crizotinib treatment

1. MINIMUM OS GAIN ANALYSIS [TA422]: Adjustment of crizotinib OS curve to 16.2-month mean OS gain; PE cost increase (ICER with PAS of **£**[redacted] **per QALY**)

2. MINIMUM OS GAIN ANALYSIS [TA422]: Adjustment of crizotinib OS curve to 16.2-month mean OS gain; PE cost increase; sequential testing (ICER with PAS of **£[redacted] per QALY**)
    a. Without testing (ICER with PAS of **£[redacted] per QALY**)
3. ADAPTED ERG scenario (PFS HR=OS HR) with adjustment of crizotinib curve, PE cost increase (ICER with PAS of **£[redacted] per QALY**)
4. ADAPTED ERG scenario (PFS HR=OS HR) with adjustment of crizotinib curve, PE cost increase; sequential testing (ICER with PAS of **£[redacted] per QALY**)
    a. Without testing (ICER with PAS of **£[redacted] per QALY**)
5. Adjustment of crizotinib OS curve mid-point OS gain (between PROFILE 1007 HR=0.38 and ERG PFS HR=OS HR); PR cost increase (ICER with PAS of **£[redacted] per QALY**)
6. Adjustment of crizotinib OS curve mid-point OS gain (between PROFILE 1007 HR=0.38 and ERG PFS HR=OS HR); PE cost increase; sequential testing (ICER with PAS of **£[redacted] per QALY**)
    a. Without testing (ICER with PAS of **£[redacted] per QALY**)

The range of mean OS gain (Table B2), which Pfizer believe are the most clinically plausible, produce ICERs that range from **£[redacted] to £[redacted] per QALY, when PAS is considered.**

Appendix C. New data: Royal Marsden Audit, poster published at the British Thoracic Oncology Group Conference 2018

Below are the results from the retrospective review of the clinical outcomes in ROS1-positive NSCLC patients in the UK. These provide an update to the data presented in the submission from the Royal Marsden audit.

Complete data were obtained for 26 ROS1-positive NSCLC patients from seven regional centres. Median age at diagnosis was 45.5 years (range 26–77). 46.2% of patients were never-smokers and 76.9% of patients were diagnosed at stage IV, with 96.2% classified as adenocarcinoma. The majority of patients (80.8%) had no previous experience of radical therapy.

Of the 26 patients in the review, 10 patients were treated with crizotinib. The objective response rate (ORR) was 70%, with a median PFS of 12.1 months and 1-year PFS in 56% of patients.

There were 14 patients who received pemetrexed in combination with platinum as first-line systemic therapy. These patients had an ORR of 78% and median PFS of 10.5 months.

Median OS for crizotinib was not reached by median follow-up time of 19.4 months in all ROS1-positive NSCLC patients; one-year and two-year OS rates were 81% and 66%, respectively.

Figure 1: Median PFS for ROS1-positive NSCLC patients treated with crizotinib from the Royal Marsden national audit

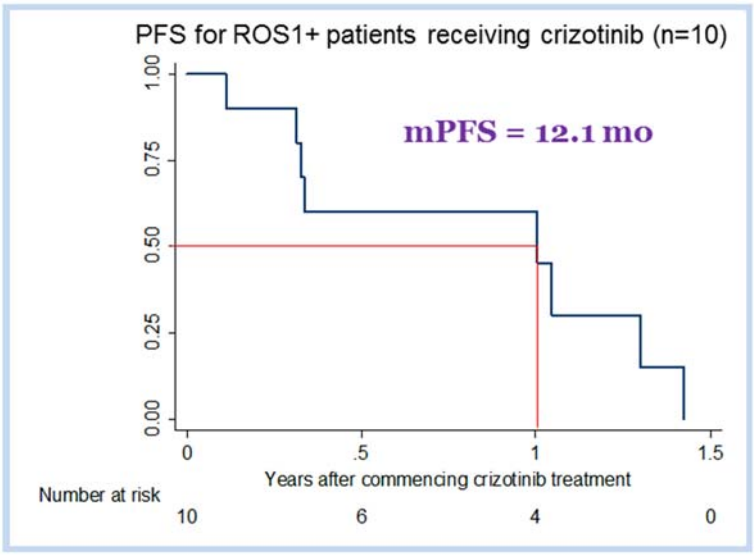
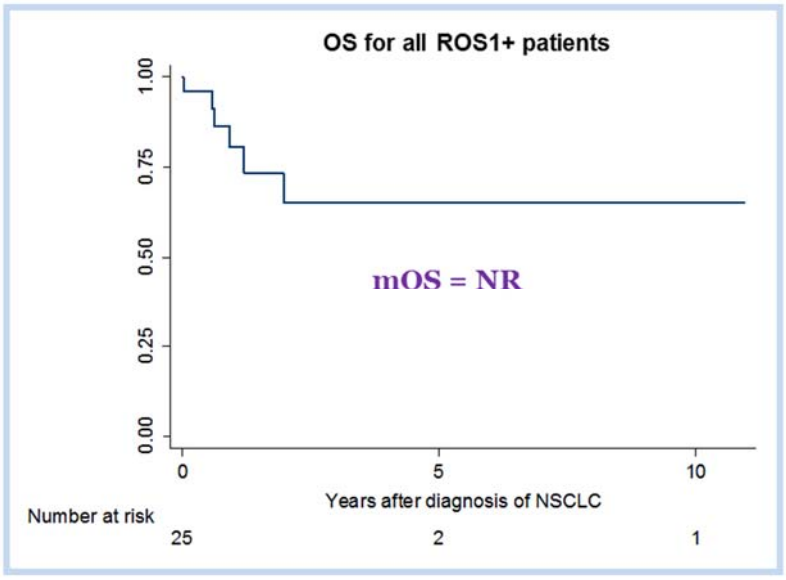


Figure 2: Median OS for ROS1-positive NSCLC patients treated with crizotinib from the Royal Marsden national audit


OS for all ROS1+ patients
1.00
0.75
0.50
0.25
0.00
mOS = NR
0
5
10
Years after diagnosis of NSCLC
Number at risk
25
2
1

Appendix D. New analyses: Summary of changes to the model since ERG's version "14.11.2017"

Sheet	Range	Change
Base case results	Row 97:99	Added mean PFS, OS and PPS to summary table
	C142:G142	Included Mod_9 to allow the user to select the company first-line OS for pemetrexed and apply a manual HR for crizotinib OS
	C143:G143	Included Mod_10 to allow the user to select the company second-line OS for docetaxel and apply a manual HR for crizotinib OS
	C147:G147	Included Mod_13 to allow the user to set the pre-progression pemetrexed utility equal to 0.72 when patients are on treatment and 0.75 when patients are off treatment
	C148:G148	Included Mod_14 to allow the user to increase the cost of pulmonary embolism to £1,485.76
AE costs	F61	Formula updated to increase the cost of pulmonary embolism, if Mod_14 = 1
1L ALK+ survival (TA406)	Column G	Updated the PFS curve formula to the Log-normal formula (see 'ALK+ 1L PFS' below)
	Column H	Updated the TTD curve formula to the Exponential formula (see 'ALK+ 1L TTD' below)
Crizotinib Calc (1st line)	Column I	Updated OS curve if MOD_9 is equal to 1
Pem + platinum Calc	Column I	Updated OS curve if MOD_9 is equal to 1
	Column AN	Updated formula to set pemetrexed utility equal to 0.72 on treatment and 0.75 off treatment, if Mod_13 = 1
Crizotinib Calc (Subs-line)	Column I	Updated OS curve if Mod_10 is equal to 1
Docetaxel calc	Column	Updated OS curve if Mod 10 is equal to 1
Lists	B97:C101	Updated crizotinib PFS curve parameters to 'Meanlog' and 'Sdlog' (see 'ALK+ 1L PFS' below)
	B109:C112	Updated crizotinib TTD curve parameter to 'Rate' (see 'ALK+ 1L TTD' below)
ALK+ 1L PFS	Row 22:45	Replaced the incorrect previously used crizotinib PFS curve (Gamma) with the correct curve (Log-normal), *as per amendment sent to NICE in 2017*
ALK+ 1L TTD	Row 22:41	Replaced the incorrect previously used crizotinib TTD curve (Gompertz) with the correct curve (Exponential), *as per amendment sent to NICE in 2017*
ERG first-line	R7	Manual hazard ratio that is applied to the pemetrexed Wilcoxon adjusted curve to estimate crizotinib OS
	Column R:S	Pemetrexed OS (Wilcoxon adjusted) and crizotinib OS (estimated using HR is cell R7)
	Y11:AC18	Added table pulling mean and median survival from PF sheets
	Q2:AA5	Added cells where 'Solver' is used to calculate HRs required to achieve an ICER of [redacted], an OS gain of 18.2 months and a PPS gain of 0, respectively
ERG subsequent-line	T7	Manual hazard ratio that is applied to the docetaxel TA422 OS curve to estimate crizotinib OS
	Column S:T	Docetaxel OS (TA422) and crizotinib OS (estimated using HR is cell T7)
	Z11:AD18	Added table pulling mean and median survival from PF sheets
	R1:AC5	Added cells where 'Solver' is used to calculate HRs required to achieve an ICER of [redacted], an OS gain of 11 months and a PPS gain of 0, respectively. Using upfront or sequential testing

Addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Crizotinib for treating ROS1-positive advanced non-small cell lung cancer [ID 1098]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 16/119/03

Completed 16 February 2018

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

CRIZOTINIB FOR TREATING ROS1-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER [ID1098]

ERG CRITIQUE OF COMPANY RESPONSE TO THE ACD

The Evidence Review Group (ERG) received the company's submitted response to the appraisal consultation document (ACD) on 8 February 2018. The company's response contained new analyses in four key areas: estimated survival gain; progression-free survival (PFS) utility values in the first line for treatment with pemetrexed+platinum; sequential testing for ROS1 in second line setting; and cost of treating pulmonary embolism. This addendum contains the ERG's critique of these four areas.

The ERG notes that the company reiterates in its response to the ACD that it considers the outcomes of a proxy population of patients with ALK+ advanced non-small cell lung cancer (NSCLC) appropriate to represent time-to-event outcomes for patients with ROS1+ advanced NSCLC. The company also presents an argument as to why treatment with nintedanib+docetaxel should not be considered a comparator in the subsequent-line setting.

1. Estimated survival gain

First-line setting

The company asserts that, based on clinical opinion, mean survival gain for first-line treatment with crizotinib would lie between 13.1 months and 18.2 months. The company's ensuing analysis is based on the assumption that any survival gain outside of this range is clinically implausible. The ERG considers that there is no certainty around this range of values and therefore that survival gain outside of 13.1 months to 18.2 months remains a possibility.

The company's lower bound value for total survival gain (13.1 months) is taken from the appraisal of crizotinib in the first-line setting for patients with ALK+ advanced NSCLC (TA406[1]). The company's lower bound value equates to 3.6 months (or 27.6%) of total survival gain being accrued after progression in the first-line setting. The ERG notes that the company's lower bound value for OS gain in TA406[1] was based on analysis of an earlier data cut from the PROFILE 1014 trial than the data cut that was presented in ID1098. The ERG considers it preferable to use analyses based on the most up-to-date data cut available and that the 13.1 month figure is superseded by analysis from ID1098.

The company calculates the upper bound value of survival gain (18.2 months) based on modelled PFS gain (9.5 months) plus survival gain beyond progression. The company determines the upper bound of survival gain beyond progression in the first-line setting as the

midpoint between the value of the lower estimate of the ERG's exploratory analysis of survival beyond progression in ID1098 (0 months) and the company's original base case value (19.2 months), i.e. 9.6 months or 47.6% of total survival gain. The ERG acknowledges that some post-progression survival gain might be plausible in this indication due to the level of tumour response observed; however, the ERG considers that the assumption that almost 50% of survival gain is accrued beyond progression is implausible without further biological justification.

The results of the company's revised overall survival (OS) scenarios and OS scenarios from ID1098 that have generated the lowest and highest estimates of mean OS gain in the first-line setting (when applied to the model in isolation) are summarised in Table 1.

Table 1 First line OS scenarios from lowest to highest mean OS gain

OS scenario	Mean OS gain (months)	Mean survival gain after progression (months)	% survival gain after progression (% total OS gain)	ICER per QALY gained
ERG lower estimate *Original report*	9.5	0.0*	0.8%	[redacted]
Company lower bound *ACD response*	13.1	3.6	27.6%	[redacted]
Company upper bound *ACD response*	18.2	9.6	47.6%	[redacted]
Company original base case *Original submission*	28.7	19.2	66.7%	[redacted]

ACD=appraisal consultation document; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year
* rounded
Source: Company model

Subsequent-line setting

The company puts forward a similar argument for survival gain in the subsequent-line setting as for the first-line setting. The company asserts that, based on clinical opinion, mean OS gain for treatment with crizotinib in the subsequent-line setting would lie between 16.2 months and 20.9 months.

The company's lower bound value for total survival gain (16.2 months) is taken from the appraisal of crizotinib in the subsequent-line setting for patients with ALK+ advanced NSCLC (TA422[2]). The lower bound value equates to 10.5 months (or 64.9%) of survival gain being accrued after progression in the subsequent-line setting. The lower bound value for OS gain taken from TA422[2] was based on an ERG scenario analysis (applying the PFS hazard ratio [HR] to OS) of data from the PROFILE 1007 trial. The ERG notes that the opinion of the AC for TA422[2] on the most plausible analysis of the OS data from PROFILE 1007 is not reported

in the final appraisal determination (FAD); however, the company states that this was the AC's preferred scenario in TA422.[2] The ERG acknowledges that there is potential for survival gain to be accrued beyond progression in this indication; however, clinical advice to the ERG is that a gain beyond progression of twice that accrued in PFS (10.5 months versus 5.7 months respectively) is implausible without justification.

The company determines the upper bound value of total survival gain (20.9 months) in the subsequent-line setting by applying an HR (0.43) to the crizotinib OS curve that is the midpoint between the crossover-adjusted OS HR (0.38) and the PFS HR (0.49) from the PROFILE 1007 trial. This approach results in a modelled survival gain beyond progression of 15.2 months, which equates to 72.8% of total survival gain. The company justifies assuming an OS treatment effect that is better than the PFS treatment effect by referring to the AC's acceptance of the use of the PFS HR in TA422.[2] The company states that the use of a PFS HR for OS is a conservative approach and appears to suggest that any method that would reduce OS to below that calculated by applying the PFS HR would be clinically implausible.

The ERG does not consider it to be clinically implausible for an OS treatment effect to be smaller than a PFS treatment effect for the same patient population. When the OS treatment effect is smaller than the PFS treatment effect, this means that patients treated with the intervention, once progressed, will benefit proportionately less from it than they did before progression. This only means that the treatment effect is smaller in PPS than in PFS, which translates to a treatment effect for OS that is also smaller than for PFS. It is still possible to accrue some survival advantage beyond progression when the OS treatment effect is smaller than the PFS treatment effect.

When the OS treatment effect equals the treatment effect in PFS, this means that patients treated with the intervention will continue to benefit from it after progression, and for the rest of their lives, by the same proportion as they did before progression (and whilst receiving treatment, if treated to progression). When the OS treatment effect is larger than the PFS treatment effect, this means that patients treated with the intervention, once progressed, will benefit proportionately more from it than they did before progression. This means that the treatment effect is larger in PPS than in PFS, which translates to a treatment effect for OS that is also larger than for PFS.

The results of the company's revised OS scenarios and OS scenarios from this appraisal that have generated the lowest and highest estimates of mean OS gain in the subsequent-line setting (when applied to the model in isolation) are summarised in Table 2.

Table 2 Subsequent line OS scenarios from lowest to highest mean OS gain

OS scenario	Mean OS gain (months)	Mean survival gain after progression (months)	% survival gain after progression (% total OS gain)	ICER per QALY gained
ERG lower estimate *Original report*	5.8	0.1	2.0%	[redacted]
Company lower bound *ACD response*	16.2	10.5	64.9%	[redacted]
Company original base case *Original submission*	16.3	10.7	65.2%	[redacted]
Company upper bound *ACD response*	20.9	15.2	72.3%	[redacted]

ACD=appraisal consultation document; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year
Source: Company model

2. Utility values (first line)

The company asserts that the AC in TA406[1] considered that a higher PFS utility value for treatment with pemetrexed+platinum (0.75) should only be applied when patients are off treatment and that the original base case PFS utility value (0.72) should be applied when patients are on treatment. The ERG notes that in the FAD for TA406[1] the distinction between utility values for on- and off treatment with pemetrexed+platinum is not made. The ERG also notes that according to the text of the FAD for TA406,[1] the AC concluded only that the PFS utility value "was closer to 0.75 than 0.81". However, the ERG acknowledges that the results of the company analysis using the 0.75 value, as reported in the committee papers for TA406,[1] did apply the higher value only after discontinuation of treatment with pemetrexed+platinum.

The ERG accepts that a PFS utility value of 0.72 should be applied during treatment and 0.75 after treatment with pemetrexed+platinum. However, the impact of this amendment on the company's original base case ICER per QALY gained is minimal (+£177).

The ERG notes that the AC in TA406[1] also concluded that there would be an impact on PPS utility for patients who continue to receive treatment with crizotinib after progression. It is reported in the FAD for TA406[1] that the AC considered this post-progression on-treatment utility value to lie between 0.74 and 0.78 (company base case uses the PFS utility of 0.81 for patients on treatment beyond progression). If a utility value of 0.74 is applied to patients receiving treatment with crizotinib beyond progression, the company's original base case ICER per QALY gained increases by £190. If a utility value of 0.78 is applied to patients receiving treatment with crizotinib beyond progression, the company's original base case ICER per QALY gained increases by £81.

The impact on the company's original base case of using different utility values on and off treatment for patients receiving crizotinib and receiving pemetrexed+platinum in the first line are summarised in Table 3.

Table 3 Utility value scenarios for first-line treatment

Utility value scenario	PFS on treatment		PFS off treatment		PPS on treatment		ICER per QALY gained
	Criz	Pem	Criz	Pem	Criz	Pem	
1. Company original base case	0.81	0.72	0.81	0.72	0.81	N/A	[redacted]
2. ERG scenario	0.81	0.75	0.81	0.75	0.81	N/A	[redacted]
3. Pemetrexed+platinum = 0.75 PFS off treatment	0.81	0.72	0.81	0.75	0.81	N/A	[redacted]
4. Crizotinib = 0.74 PPS on treatment	0.81	0.72	0.81	0.72	0.74	N/A	[redacted]
5. Crizotinib = 0.78 PPS on treatment	0.81	0.72	0.81	0.72	0.78	N/A	[redacted]
6. 3 & 4	0.81	0.72	0.81	0.75	0.74	N/A	[redacted]
7. 3 & 5	0.81	0.72	0.81	0.75	0.78	N/A	[redacted]

Criz=crizotinib; ICER=incremental cost effectiveness ratio; Pem=pemetrexed+platinum; PFS=progression free survival; PPS=post-progression survival; QALY=quality adjusted life year
Source: company model; TA406[1] FAD

3. ROS1 testing (subsequent line)

The company has included the assumption that sequential testing for ROS1 would be most likely in the subsequent-line setting. This assumption is in accordance with clinical advice to the ERG.

Assuming sequential ROS1 testing in the subsequent-line setting decreases the company's base case ICER to [redacted].

4. Cost of treating pulmonary embolism

The ERG noted in its original critique that the cost of treating pulmonary embolism had been underestimated in the company model, but concluded that the impact on the ICER per QALY gained was minimal. The company has included an increased cost of £1,485.76 for treating pulmonary embolism, which was reported in the committee papers for TA500[3] (Ceritinib for untreated ALK+ NSCLC) and taken from NHS Reference Costs 2015-2016.[4] The ERG agrees that the cost of treating pulmonary embolism is greater than the company included in its original model.

Increasing the cost of treating pulmonary embolism in isolation decreases the company's original base case ICER per QALY gained by £1 to [redacted] in the first-line setting and increases it by £55 to [redacted] in the subsequent-line setting.

5. Revised company base case

The company's revised base case ICER per QALY gained in the first-line setting including the amendments to OS, PFS utility value for pemetrexed+platinum, and increased cost of treating pulmonary embolism ranges from [redacted](18.2 months survival gain) to [redacted] (13.1 months survival gain).

The company's revised base case ICER per QALY gained in the subsequent-line setting including the amendments to OS, sequential testing in the subsequent-line setting and increased cost of treating pulmonary embolism ranges from [redacted] (20.9 months survival gain) to [redacted] (16.2 months survival gain).

The ERG considers any ICER estimates to be extremely uncertain due to the use of proxy data from the ALK+ advanced NSCLC population. Setting aside the issue of the use of proxy data, the ERG considers there to be more uncertainty in the ICER estimates than is represented in the company's revised range of base case ICERs given that the company's estimates of survival gain lack sufficient justification.

REFERENCES

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ADDENDUM 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Crizotinib for treating ROS1-positive advanced non-small cell lung cancer [ID 1098]

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

CRIZOTINIB FOR TREATING ROS1-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER [ID1098]: UPDATED ICERS FOLLOWING SECOND COMMITTEE MEETING

At the second Appraisal Committee (AC) meeting on 21 February 2018, the AC considered responses received during the consultation period following the first AC meeting. The AC concluded that four assumptions raised in the consultation responses and not previously included in combination in the company's or ERG's analyses should be considered when modelling treatment with crizotinib for patients with ROS1-positive advanced non-small cell lung cancer (NSCLC). These four assumptions are:

- Administration cost of crizotinib increased to £120 (based on estimate from NHS England response to consultation)
- Administration cost of crizotinib increased to £164 (NHS reference cost SB11Z for delivering exclusively oral chemotherapy, outpatient: £164 per cycle[1])
- Cost of treating pulmonary embolism increased to £1,485.76 (consistent with TA500[2])
- Higher progression-free survival (PFS) utility value in first-line setting for treatment with pemetrexed+platinum (0.75 vs 0.72) applied only when patients are off treatment

This addendum provides updated incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained for first- and subsequent-line treatment with crizotinib when applying these additional cost and utility assumptions alongside selected overall survival (OS) estimates. Included OS estimates are: company original base case, company revised OS estimates (from the company appraisal consultation document [ACD] response) and the ERG lower OS estimates (no survival gain accrued beyond progression. From the original ERG report).

Table 1 shows the resulting ICERs per QALY gained in the first-line setting. The ICERs range from [redacted] per QALY gained (company original base case OS with no additional assumptions) to [redacted] per QALY gained (ERG lower OS estimate with £164 administration cost for crizotinib, increased PE cost and amended PFS utility).

Table 2 shows the resulting ICERs per QALY gained in the subsequent-line setting. The ICERs range from [redacted] per QALY gained (company original base case OS with no additional assumptions) to [redacted] per QALY gained (ERG lower OS estimate with £164 administration cost for crizotinib and increased PE cost).

Table 1 First line OS scenarios from lowest to highest mean OS gain with assumptions from second Appraisal Committee meeting

OS scenario	Mean OS gain (months)	ICER per QALY gained						
			OS scenario + £120 admin cost	OS scenario + £164 admin cost	OS scenario + PE cost	OS scenario + PFS utility adjustment	OS scenario + £120 admin cost + PE cost + PFS utility adjustment	OS scenario + £164 admin cost + PE cost + PFS utility adjustment
ERG lower estimate *Original report*	9.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company lower bound *ACD response*	13.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company upper bound *ACD response*	18.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case *Original submission*	28.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACD=appraisal consultation document; ICER=incremental cost effectiveness ratio; OS=overall survival; PE=pulmonary embolism; PFS=progression-free survival; QALY=quality adjusted life year
Source: Company model

Table 2 Subsequent line OS scenarios from lowest to highest mean OS gain with assumptions from second Appraisal Committee meeting

OS scenario	Mean OS gain (months)	ICER per QALY gained					
		OS scenario + initial base case assumptions	OS scenario + £120 admin cost	OS scenario + £164 admin cost	OS scenario + PE cost	OS scenario + £120 admin cost + PE cost	OS scenario + £164 admin cost + PE cost
ERG lower estimate *Original report*	5.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company lower bound *ACD response*	16.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case *Original submission*	16.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company upper bound *ACD response*	20.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACD=appraisal consultation document; ICER=incremental cost effectiveness ratio; OS=overall survival; PE=pulmonary embolism; PFS=progression-free survival; QALY=quality adjusted life year
Source: Company model

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