HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Review

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296) [ID1010]

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

1. **CDF committee meeting slides** prepared by NICE project team

2. **Company submission** from Pfizer

3. **Patient group, professional group and NHS organisation submission** from:
   - **British Thoracic Oncology Group**
   - **British Thoracic Society**
   - **NCRI-ACP-RCP-RCR** (joint statement)
   - **The Roy Castle Lung Cancer Foundation**
   - **The Royal College of Pathologists**

4. **Expert personal perspectives** from:
   - **Clinical expert**, nominated by the Royal College of Pathologists
   - **Patient expert**, nominated by the National Lung Cancer Forum for Nurses
   - **Patient expert**, nominated by the Roy Castle Lung Cancer Foundation

5. **Evidence Review Group report** prepared by the Centre for Reviews and Dissemination, York

6. Evidence Review Group report – **factual accuracy check & ERG responses**

7. Evidence Review Group report – **Erratum**

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

Crizotinib for **previously** treated non-small cell lung cancer associated with anaplastic lymphoma kinase fusion gene

Cancer Drug Fund Reconsideration Meeting

29 September 2016

ERG: CHE and CRD Technology Assessment Group, University of York

NICE team for reconsideration: Sally Doss, Marcela Haasova, Helen Knight

Chair: Amanda Adler

Public observer slides

Recap

1st line

2nd line

3rd line

Crizotinib
Guidance published
28 Sep 2016
Recommended
TA406

Crizotinib
1st meeting 27 Feb 2013
2nd meeting 27 Jun 2013
Guidance published
25 Sept 2013
Not recommended
TA296

Crizotinib
TODAY
CDF reconsideration
[ID1010]

Ceritinib
after crizotinib
Guidance published
22 Jun 2016
Recommended
TA395

time

2013 Guidance

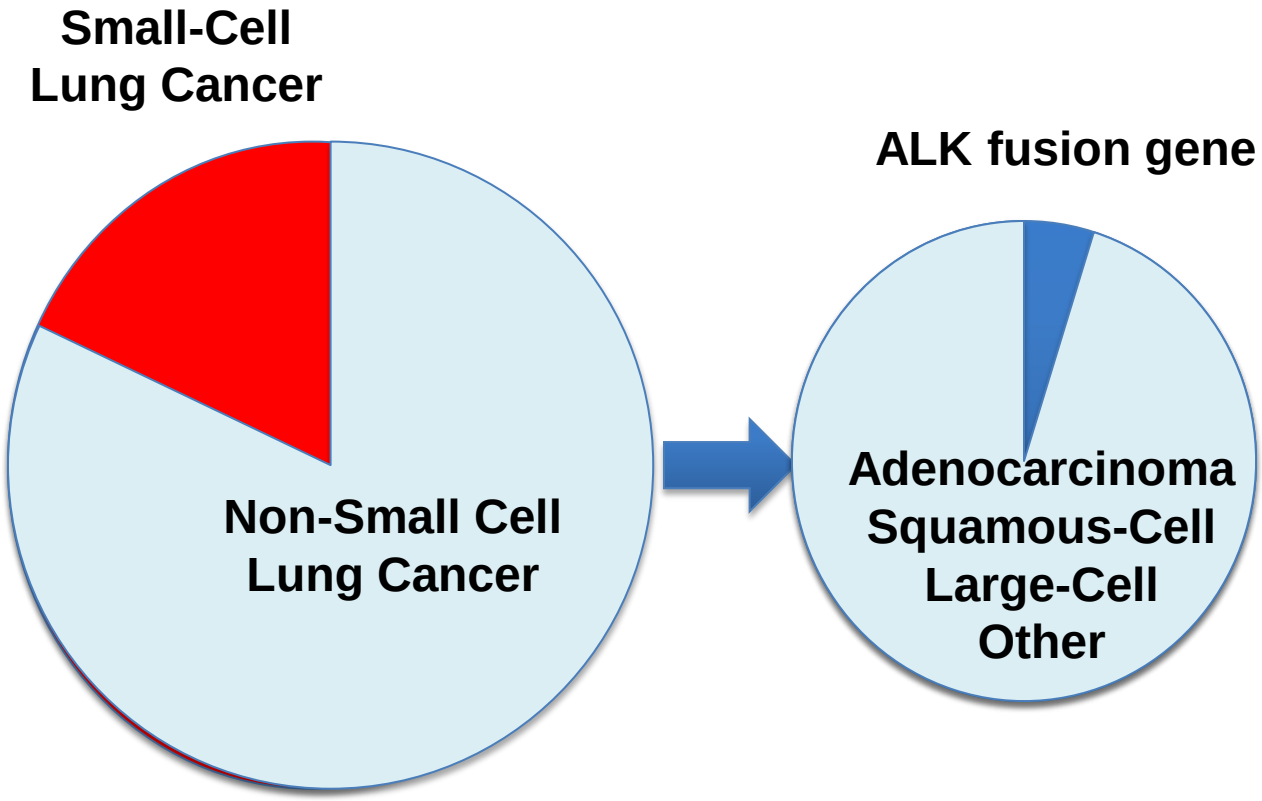
Crizotinib is not recommended within its marketing authorisation, that is, for **previously** treated anaplastic lymphoma kinase-positive advanced non-small cell lung cancer in adults

Crizotinib is currently funded through the Cancer Drugs Fund (CDF)

Question today

Is crizotinib an effective and cost effective use of NHS resources given new more mature data, new modelling assumptions and a new Patient Access Scheme (PAS)?

Anaplastic lymphoma kinase (ALK)
Crizotinib and ceritinib inhibit ALK



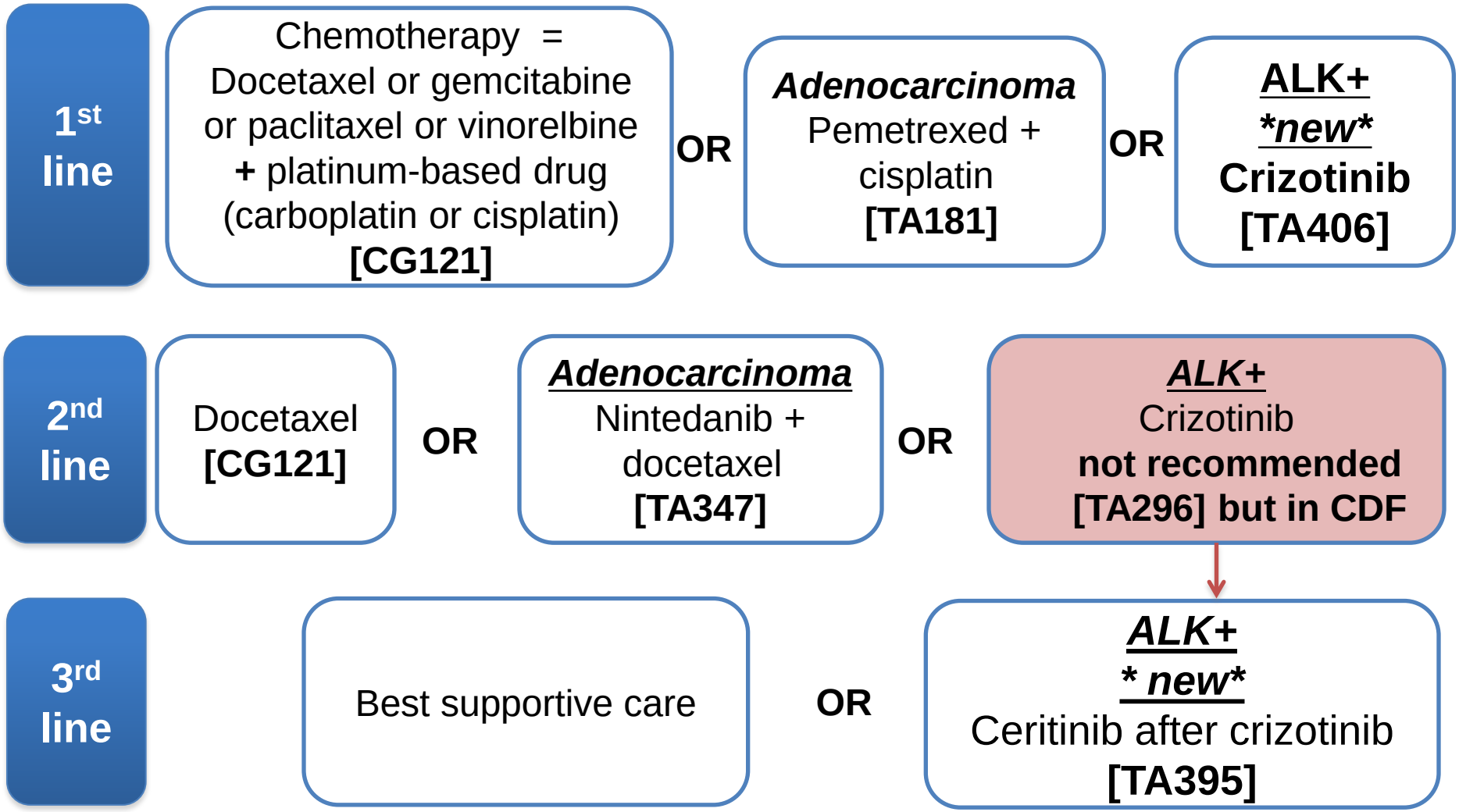
ALK fusion gene mutation – 'ALK-positive'

5% of stage III/IV Non-Small-Cell Lung Cancer

Crizotinib

Mechanism	Selective inhibitor of ALK receptor tyrosine kinase and variants	
Administration and dose	Oral 250 mg twice daily	
Costs	60 capsules (250 mg) List price: With PAS: Mean cost median treatment duration 11 cycles (list price):	 £4,689 XXXXX £51,579

Treatment pathway for non-small cell lung caner



Clinical Evidence

Comparison with docetaxel

1. PROFILE 1007 next slide
2. PROFILE 1005
   Single-arm multicentre trial with 901 participants.
   Data derived from ‘mature’ sub-group (n=261) with median follow-up time of 14.2 months
3. PROFILE 1001

Comparison with BSC

Mixed treatment comparison

Some trial populations included patients with ALK-negative NSCLC

Single open-label trial PROFILE 1007

Advanced or metastatic previously treated ALK-+ non-small-cell lung cancer n = 347

Crizotinib 250 mg BD oral

pemetrexed 500 mg/m^2 [58%] or docetaxel 75 mg/m^2 [42%]

1° endpoint: Progression Free Survival (PFS) defined by radiographic criteria RECIST

Stopping and cross-over	• Continued until radiographic disease progression • Patient randomised to crizotinib can continue despite disease progression • Cross over allowed at disease progression in either direction

PROFILE 1007 - primary outcome: progression free survival (PFS)

Company's clinical evidence: Original submission

Treatment	PFS (months)	Benefit (months)	Hazard ratio (95%CI)
Crizotinib	7.7	--	--
Chemotherapy	3.0	4.7	0.49 (0.37-0.64)
Docetaxel (post hoc)	2.6	5.1	0.30 (0.21-0.43)

Chemotherapy: Docetaxel and pemetrexed combined

PROFILE 1007– overall survival (OS)

Company's clinical evidence: Original submission

	Crizotinib (n=173)	Chemotherapy (n=174)
Unadjusted for cross-over median follow-up months (95% CI)	20.3 (18.1 to not reached)	22.8 (18.6 to not reached)
HR (95% CI) Unadjusted for cross-over	1.02 (0.68 to 1.54)	
HR (95% CI) Adjusted by IPTCW 2	0.79 (0.45 to 1.40)	
–64.4% crossed over from chemotherapy to crizotinib –XXXX crossed over to pemetrexed/docetaxel from crizotinib		

OS not presented for docetaxel subgroup (immature data)

IPTCW = inverse probability of treatment and censoring weighted

Committee conclusions FAD

Comparator	Pemetrexed not a comparator. Not in scope; patients likely to have been treated with pemetrexed 1st-line before being considered for crizotinib; not recommended by NICE 2nd-line. Docetaxel and best supportive care appropriate comparators
Duration	In UK, crizotinib would continue after progression, as in trials
PFS	Crizotinib delays progression relative to docetaxel/pemetrexed Relative to best supportive care 'area of substantial uncertainty'
Crossover	"IPTCW5 produced an overly optimistic overall survival benefit for crizotinib, for which there was no supporting evidence." IPTCW2 more reasonable
Utilities	Post progression utilities uncertain
Admin cost	Model assumed no cost, committee did not agree
ICER	Crizotinib compared with docetaxel >£100,000 per QALY gained Compared with best supportive care >£50,200 per QALY gained
Innovation	No
End of life	Yes

Issues, conclusions, what's new

Issue	Committee conclusion	What's new
Price crizotinib	Too high to be cost effective	PAS from 1st line crizotinib
Effect on OS	Uncertain immature data	More mature data
Cross over	Best method is IPCW	RPSFTM method
Utility during post-progression	Benefit expected when crizotinib stopped at progression, but no data to inform magnitude or duration	Same utility used for both modelled arms
Administration cost crizotinib	Did not accept 'no cost'. Used cost of chemotherapy (£126, HRG code SB11Z) in absence of crizotinib code	Include the chemotherapy administration cost
Cost of docetaxel	eMIT not BNF	eMIT
End of life	Met compared with docetaxel or BSC	Acknowledged
Treat beyond progression	Per time to treatment discontinuation in PROFILE 1007	Treat to progression only
Comparing to BSC	Indirect comparison not robust and therefore uncertain	No data presented

BNF, British National Formulary; IPCW, Inverse probability of censoring weighting; RPSFTM, rank preserving structural failure time model; eMIT, electronic market information tool.

More mature data; new analyses

	Crizotinib		Chemotherapy	
	TA296	2016	TA296	2016
Median follow-up (mo)	12.2	51.0	12.2	53.1
% died	28%	67%	27%	73%
Switched	XXX	23%	64%	87%

HR Overall Survival (95% CI)	TA296	Company 2016
ITT	1.02 (0.68,1.54)	0.86 (0.66,1.10)
IPTCW2 old base case	0.79 (0.45,1.40)	--
RPSFTM Log-rank new base case	0.83	**0.38 (0.04,0.99)***
RPSFTM Wilcoxon	--	0.40 (0.07,0.97)
RPSFTM Wald	--	0.35(0.04,0.85)

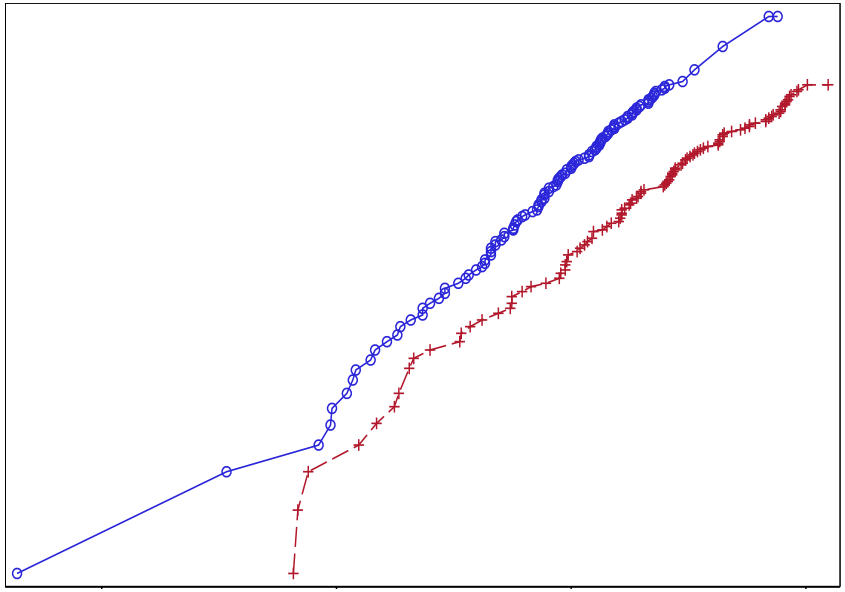
⊙ Has the company justified the choice of adjusting for cross over?

Difference from TA296 to 2016 increase life years gained from 0.46 to 2.11

* Lower value - 0.34 - used in modelling

New base case – company says depends on proportional hazards

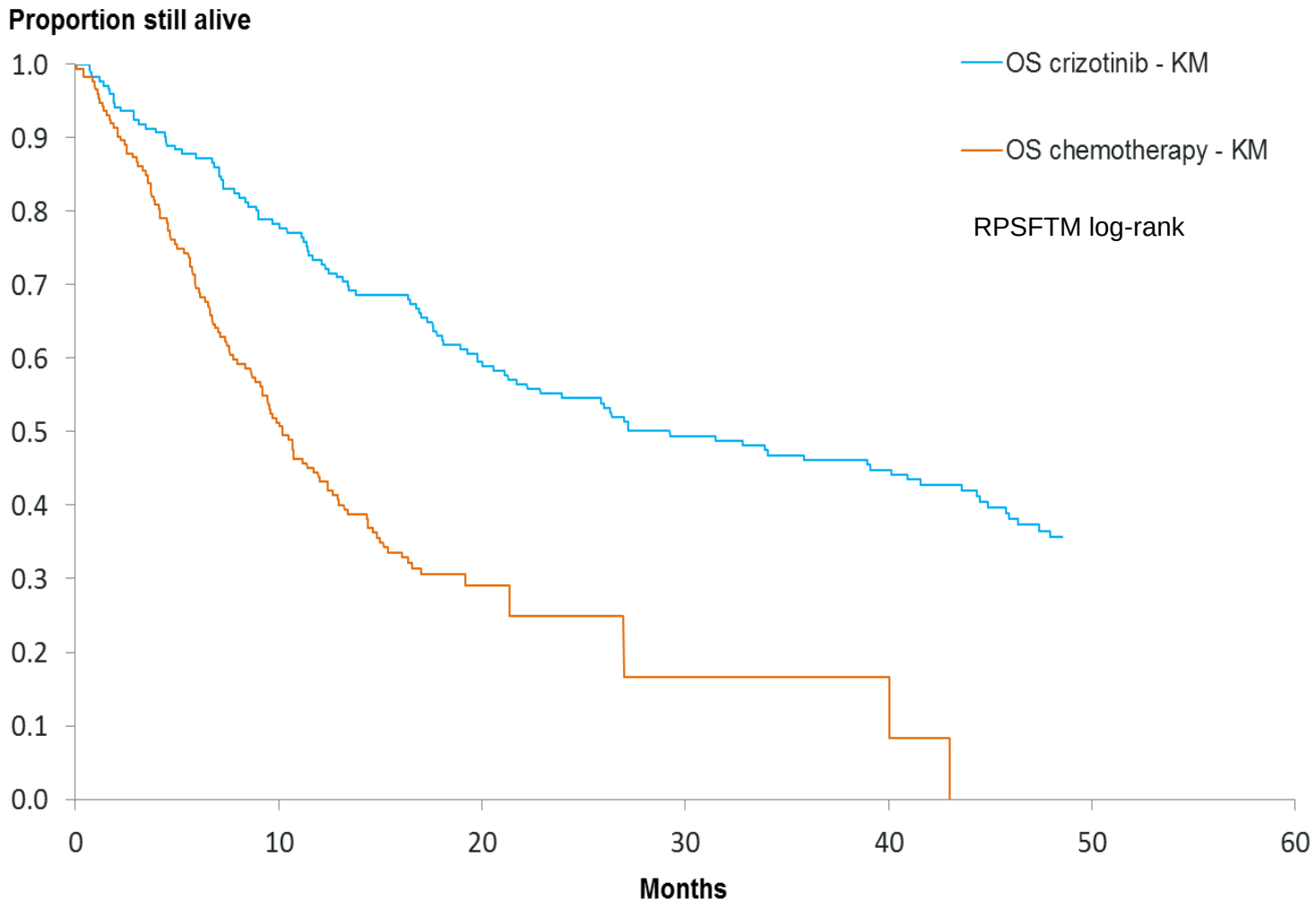
Log of negative log of estimated survivor functions for RPSFTM log-rank



ERG: "Theoretically, the methodology presented by the company is not a choice between a PH model and a non-PH model. Rather the choice is between fitting one parametric model to the whole dataset (with a covariate for treatment) or fitting a specific parametric model to each treatment arm separately."

⊙ Are proportional hazards required to interpret results of model?

Kaplan Meier Curve: new data crizotinib and chemotherapy



Question to company: Where are the numbers at risk ?

Company's Kaplan-Meier curves for crizotinib and chemotherapy extrapolated with exponential curve to 10 years

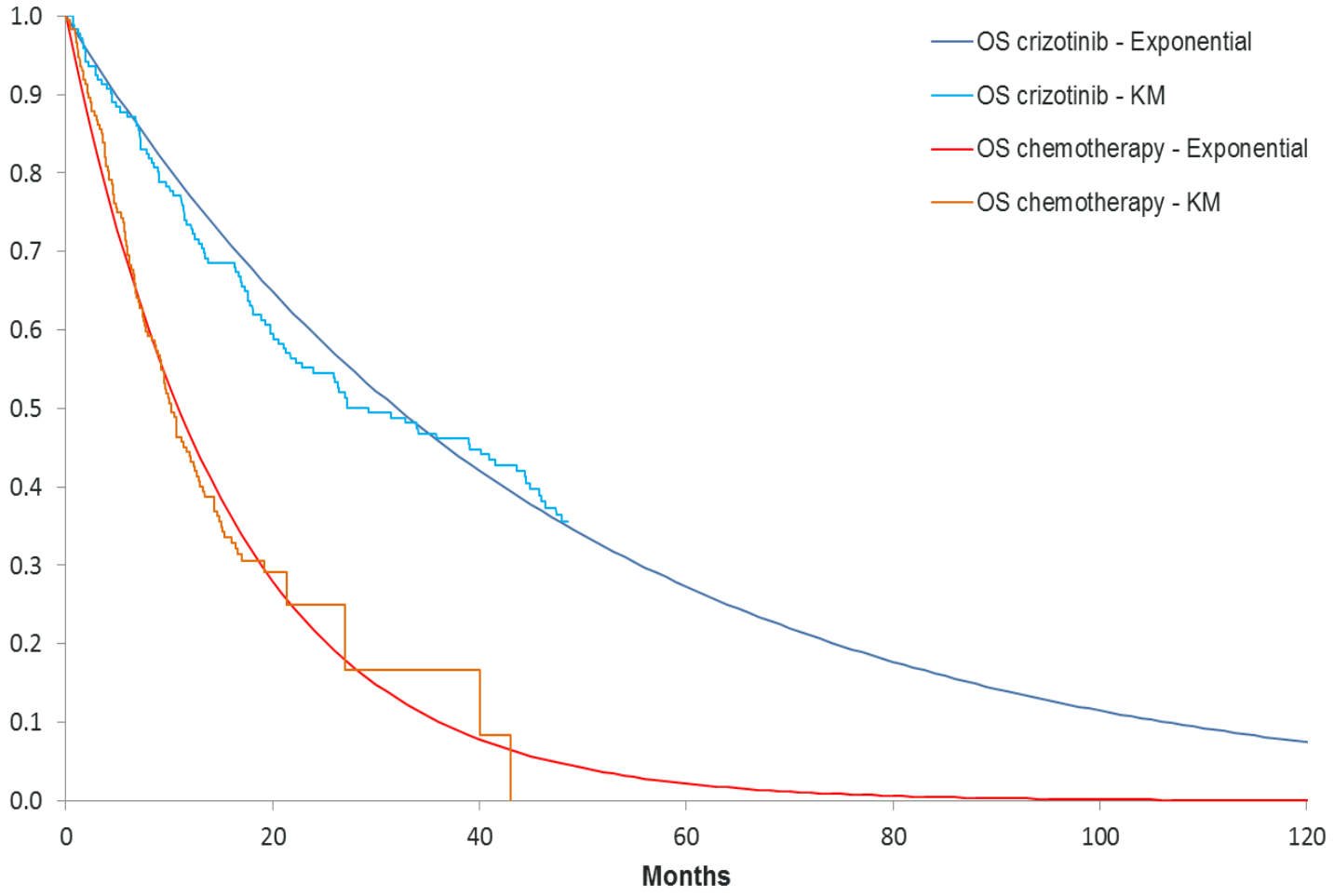


Fig 4 company submission

Data presented by company to 'validate' OS modelling

What company submitted

- UK audit data
- XXXXXXXXXXXXXXXXXXXX
- Previously treated ALK+ then treated with an ALK-inhibitor (XXXXXXX) similar median OS estimates (XXXXXXX) - as that derived from exponential curve for crizotinib RPSFTM log-rank method - median (32 months).
- XX ALK+ patients not subsequently treated with ALK-inhibitor (XXX vs XXX months based on exponential curve for pooled chemotherapy)

ERG comment

- "ERG considers that the UK audit provides useful supportive information as opposed to representing a formal validation approach"
- Company did not provide data on the patient characteristics or whether the groups were balanced or not

Crizotinib versus best supportive care

- Original submission mixed treatment comparison
- "…critiqued by the Committee as lacking robustness."
- "ICERs discussed in the FAD were higher for crizotinib versus docetaxel than for crizotinib versus BSC, implying that crizotinib was more cost-effective versus BSC than versus docetaxel."
- "Logic therefore dictates that if crizotinib is cost-effective versus docetaxel, it would also be cost-effective versus BSC"
- Company presents no new data for this comparison

Company's base case TA296 and now

	TA296, no PAS, updated costs		2016, no PAS, updated costs + OS		2016, with PAS, updated costs + OS	
	Crizo	**Chemo**	**Crizo**	**Chemo**	**Crizo**	**Chemo**
Drug cost	XXXXX	76	XXXXX	76	XXXXX	76
Other costs	12,781	9,236	14,735	7,939	14,735	7,939
Total costs	XXXXX	9,312	XXXXX	8,015	XXXXX	8,015
Δ total costs	XXXXX	NA	XXXXX	NA	XXXXX	NA
LYG	2.40	1.94	3.41	1.30	3.41	1.30
Δ LYG	0.46	NA	2.11	NA	2.11	NA
QALYs	XXXXX	1.24	XXXXX	0.84	XXXXX	0.84
Δ QALY	XXXXX	NA	XXXXX	NA	XXXXX	NA
ICER (£)	96,254	NA	XXXXX	NA	XXXXX	NA

Costs in £; LYG, life year gains; ICER, incremental costs effectiveness ratio.

Company's 2016 sensitivity and scenario analyses

Analysis	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Base case	XXXXX	XXXXX	XXXXX
Probabilistic results	XXXXX	XXXXX	XXXXX
Treatment beyond progression (additional cost only)	XXXXX	XXXXX	XXXXX
RPSFTM Wald test (HR=0.35)	XXXXX	XXXXX	XXXXX
RPSFTM Wilcoxon test (HR=0.40)	XXXXX	XXXXX	XXXXX
Independent curves for OS	XXXXX	XXXXX	XXXXX

ICER, incremental costs effectiveness ratio; QALY, quality-adjusted life-year.

ERG comments on new analyses

PAS	Appropriate
Company base case	‘more than just a simple update of the 2013 submission’
Treat to progression and not beyond	Company did not consider that not everybody gets 3rd line crizotinib ‘Not reasonable’ that company models fewer costs but all benefits
Crossover adjustment method: RPSFTM log-rank	Accepts rationale for RPSFTM (rather than original IPCW); Acknowledge 3 approaches log-rank, Wilcoxon and Cox model-based Wald tests. ‘Bit suspicious’ about choice of methods given ‘massive’ change in hazard ratio
Extrapolate OS with exponential	Reasonable on clinical and statistical grounds
‘Validation’	Not really validation
Pooling docetaxel and pemetrexed	Probably conservative
Administration cost	Conservative
Post progression utility	Conservative

ERG scenario analyses – 2 approaches

Used exponential distribution based on new mature data and 2 ways to estimate hazard ratio for overall survival

Scenario 1

- Same hazard ratio for OS reported in the original trial publication for progression free-survival:
  - '**HR1'= 0.49 (0.37-0.64)**
  - 'not affected by cross-over'
  - 'generally (although not universally) hazard ratios for OS are normally not greater than for PFS'
  - "Considered assuming the same HR for both PFS and OS a 'plausible alternative scenario'

Scenario 2

- Same crossover hazard ratio for OS reported for crizotinib in **previously untreated patients (i.e. 1st line – different appraisal)**, estimated through RPSFTM method with the Wilcoxon test:
  - '**HR2'= 0.60 (0.27-1.42)**

Summary slide: Company base case and scenarios & ERG scenarios

Analysis	Δ costs (£)	Δ QALYs	ICER (£ per QALY)
Company base case	XXXXX	XXXXX	XXXXX
Company: Treat beyond progression	XXXXX	XXXXX	XXXXX
Company: Independent OS curves	XXXXX	XXXXX	XXXXX
Company: HR=0.40	XXXXX	XXXXX	XXXXX
ERG: Original HR OS=0.49	XXXXX	XXXXX	XXXXX
ERG: HR 1st line OS =0.60	XXXXX	XXXXX	XXXXX
ERG: Original HR OS + treat beyond progression	XXXXX	XXXXX	XXXXX
ERG: HR 1st line OS + treat beyond progression	XXXXX	XXXXX	XXXXX

HR, hazard ratio; ICER, incremental costs effectiveness ratio; OS, overall survival; QALY, quality-adjusted life-year.

Submissions from consultees

- Royal College of Pathologists
- British Thoracic Society
- British Thoracic Oncology Group
- NCRI-ACP-RCP-RCR
- Roy Castle Lung Cancer Foundation

General comments

- “The Society (BTS) would encourage the NHS and the manufacturers to reach an agreement where it be supplied on a more cost effective basis.”
- “The concern for RCPath is who will fund the screening for the ALK translocation… and whether IHC should be approved as the method of screening rather than FISH testing (or other)”
- Roy Castle Lung Cancer Foundation: “Crizotinib in this indication under assessment, would make this targeted therapy available to patients, in whom positive ALK test results have become available, after first line platinum based chemotherapy.”

ALK, anaplastic lymphoma kinase; BTS, British Thoracic Society; IHC, ImmunoHistoChemistry; FISH, Fluorescence in situ hybridization; RCPath, Royal College of Pathologists .

Comments diminishing 2nd-line population

- "We (NCRI-ACP-RCP-RCR) note that NICE are going to approve crizotinib in the 1st line setting
- …and there is approval for the use of ceritinib for second line treatment for those patients who progress on ceritinib*.
- These changes will significantly reduce the use of crizotinib in the 2nd line setting but there is going to be a cohort of patients who predate the approval for use in the 1st line setting
- This cohort will be/have received chemotherapy as their 1st line treatment. It is important that 2nd line crizotinib remains accessible through CDF at least in the short term."

*Direct quote – potenial typo

Issues for discussion

- Is the new modelling of overall survival, including adjusting for cross-over, reasonable?
- Is it reasonable clinically to consider treatment to progression only? Is this modelled reasonably?
- Is it reasonable to combine docetaxel with pemetrexed in the evidence for chemotherapy?
- Are the company's assumptions reasonable regarding:
  - Utility during post-progression
  - Cost of administration (vs. crizotinib 1st line)
- Which modelling does the committee prefer: company vs. ERG?
- Is it reasonable to assume that if crizotinib is cost effectives vs. chemotherapy, then it is cost effective vs. best supportive care?
- Cost of diagnostic testing?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Submission template for the re-consideration of current CDF technologies under the new proposed CDF criteria

Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene

TA296 re-appraisal

7th July 2016

Version 2: amended on 24th Aug16 to include PAS details *[Commercial in confidence information removed]*

1 Introduction

1 All cancer drugs that were previously appraised by NICE and are currently funded through the current Cancer Drugs Fund (CDF) will be re-considered by NICE in line with Guide to the methods of technology appraisal (2013) and modifications to incorporate the proposed new CDF criteria outlined in the CDF consultation paper.

2 In order to allow for the transition of drugs currently in the CDF to take place before 31 March 2017, NICE needs to prepare for re-considering those drugs. This preparation is taking place in parallel with the consultation on the new CDF arrangements, without prejudging the outcome of that consultation. This content of this submission template is therefore provisional and may change if the proposed CDF arrangements are amended after the consultation. Companies will have the opportunity to change their evidence submissions to NICE if substantial changes are made to the proposals after the CDF consultation.

3 The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance.

4 The company evidence submission should focus on cost effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health (see Appendix 5.1) or as a commercial access arrangement with NHS England (for a definition of commercial access arrangement please see the CDF consultation paper).

5 A new patient access scheme, an amendment to an existing patient access scheme, or a commercial access arrangement, must have been formally agreed with the relevant organisation (that is, the Department of Health for a patient access scheme or NHS England for a commercial access arrangement by the time the Appraisal Committee meets for the first Committee meeting.

6 Some details of patient access schemes or commercial access arrangements, submitted through the rapid re-consideration process, can be treated by NICE as commercial in confidence if the company requests this.

7 The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance. If the published guidance refers to more than one plausible ICER, analyses relating to all plausible ICERs should be included in the submission.

8 Only in exceptional circumstances and with prior written agreement from NICE should new clinical evidence be included. New clinical evidence is acceptable only when it addresses uncertainties identified previously by the Appraisal Committee. Submission of new clinical evidence must not lead to structural changes in the company's cost-effectiveness model.

9 The submission should take account of the proposed changes to NICE's methods of technology appraisal set out in the CDF consultation paper, in particular those concerning the appraisal of life-extending products at the end of life.

2 Instructions for companies

If companies want the National Institute for Health and Care Excellence (NICE) to re-consider a NICE recommendation for a drug currently funded through the CDF, they should use this template.

The template contains the information NICE requires to assess the impact of a patient access scheme or commercial access agreement on the clinical and cost effectiveness of a technology, in the context of this re-consideration, and explains the way in the evidence should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

In addition to the CDF consultation paper, please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company submission of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal'. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme or commercial access agreement. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme or commercial access agreement incorporated, in accordance with the 'Guide to the methods of technology appraisal'.

3 Details of the patient access scheme/ commercial access agreement

3.1 Please give the name of the technology and the disease area to which the patient access scheme/ commercial access agreement applies.

[Commercial in confidence information removed]

The PAS will be applicable to the indication appraised in this submission: crizotinib (Xalkori®) for the treatment of adults with previously treated, anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

3.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

It has been established that the median life expectancy in second-line patients treated with docetaxel – the standard of care therapy prior to the introduction of crizotinib – is between 5.7 to 9.1 months.[1-5] The progression-free survival (PFS) achievable with second-line docetaxel is only 2.6 to 3.0 months.[3-6] There remains, therefore, a high unmet need for patients whose disease progresses after first-line treatment, if they have not yet had access to an ALK-inhibitor.

The patient access scheme aims to secure access for patients to the first-in class innovative targeted therapy, by improving the cost-effectiveness of crizotinib for use within its licensed indications. *[Commercial in confidence information removed]*

3.3 Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

[Commercial in confidence information removed]

3.4 Please provide specific details of the patient population to which the patient access scheme/ commercial access agreement applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

[Commercial in confidence information removed]

3.5 Please provide details of when the scheme/ commercial access agreement will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

[Commercial in confidence information removed]

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/ commercial access agreement criteria (specified in 3.5)?

[Commercial in confidence information removed]

3.7 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

[Commercial in confidence information removed]

Table 1. Price of crizotinib at list price and with PAS *[Commercial in confidence information removed]*

Formulation	Pack of 60× 200 mg (or 60x 250 mg) capsules. Pack lasts 30 days.	British National Formulary [7]
List price (ex VAT)	£4,689.00 for 1 pack	
Patient access scheme (ex VAT)	*[Commercial in confidence information removed]*	

3.8 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

[Commercial in confidence information removed]

3.9 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.

Figure 1. ***[Commercial in confidence information removed]***

[Commercial in confidence information removed]

3.10 Please provide details of the duration of the patient access scheme/ commercial access agreement.

[Commercial in confidence information removed]

3.11 Are there any equity or equalities issues relating to the patient access scheme/ commercial access agreement, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

[Commercial in confidence information removed]

3.12 If available, please list any patient access scheme/ commercial access agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

[Commercial in confidence information removed]

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

[Commercial in confidence information removed]

4 Cost effectiveness

4.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in table 1. Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

4.1.1 The Committee's previous conclusions (TAG296, 2013)

In the previous technology appraisal guidance for crizotinib for previously treated, ALK-positive, NSCLC (TAG296),[8] the most plausible probabilistic ICER, as judged by the Committee, was £96,000 per QALY versus docetaxel (paragraph 4.13, FAD). However, the Committee concluded that the final ICER versus docetaxel would be expected to exceed £100,000 per QALY due required revisions to the acquisition cost of docetaxel and the administration cost for crizotinib, which would respectively increase the ICER by £5,000 and £2,200 per QALY (paragraph 4.12, FAD).

The ICERs discussed in the FAD for crizotinib versus best supportive care (BSC) were consistently lower than the ICERs versus docetaxel. The Committee concluded that the ICER versus best supportive care (BSC) was subject to uncertainty, due to the mixed treatment comparison not being robust. It therefore believed the ICER would be higher than the base case of £50,200 per QALY (paragraph 4.14, FAD).

The Committee stated that crizotinib met the end-of-life criteria for both the comparisons versus docetaxel and best-supportive care (table of *'additional factors'*, FAD).

At the time of the original appraisal, the overall survival (OS) data from the pivotal trial (PROFILE 1007) were immature and subject to significant crossover. Accordingly, the Committee concluded key uncertainties around the estimates of

cost-effectiveness were those related to immaturity of the clinical data and the consequential variation in range of crossover adjusted results, all leading to uncertainty in the resulting estimate of OS gain.

The Committee concluded that selection of crossover adjustment model “IPTCW 2” was the most appropriate, yielding a 7.1 month OS gain with crizotinib versus docetaxel (hazard ratio of 0.79 [0.45,1.40]), noting it was a result between the two extremes and was broadly in agreement with clinical opinion at the time.

4.1.2 Committee’s preferred assumptions

Any issues in the first version of the model (original submission) that were accepted as resolved when the manufacturer resubmitted the second version (post-ACD, prior to FAD), are incorporated into the newly revised version of the model. Where the Committee has stated a clear preference for an alternate assumption in the FAD, this is now included in Table 2.

Table 2. Committee's preferred assumptions in the economic model

Assumption	Company model re-submitted as part of the original ACD response	Appraisal Committee's preferred assumption	Comments
Choice of crossover-adjusted hazard ratio	IPTCW2, interim OS data	IPTCW2, interim OS data	The newly mature crossover-adjusted survival data now supersede those from the interim analysis.
Post-progression utility	The utility benefit at the point of progression associated with crizotinib compared with docetaxel diminished over time.	The Committee accepted that some utility benefit might be expected from crizotinib discontinued at disease progression, though there are no data to suggest how great a benefit this might be or for how long it would persist.	To be conservative, post-progression utility is now the same in both treatment arms of the model.
Administration cost associated with crizotinib	No administration costs would be incurred because this oral treatment is taken at home. No administration costs had been included in other appraisals involving oral chemotherapies.	The Committee preferred to include an administration cost for crizotinib and opted to use the cost of chemotherapy (£126, HRG code SB11Z) in the absence of a specific HRG code for crizotinib administration.	We maintain that the use of a chemotherapy administration cost is inappropriate; however, for the sake of simplicity, this assumption has not been challenged in this instance. Updated costs for the HRG codes discussed by the Committee are available in the latest NHS Reference Costs.
Cost of docetaxel	MIMS was the source for docetaxel drug cost data.	The Committee agreed that eMIT costs were more appropriate.	eMIT cost of docetaxel is £17.77 for 140mg vial (accessed 25.06.2016)
Treatment beyond progression	Do not include the cost of treating beyond progression	Include the cost of treating beyond progression as per the treatment protocol of PROFILE 1007 as "at present there is no standard third-line therapy."	There is now a NICE recommended third-line therapy (ceritinib) with treatment beyond progression no longer likely in practice. Analyses in which crizotinib treatment is stopped at progression are likely to be most reflective of UK clinical practice moving forward.
Comparison versus best supportive care (BSC)	Indirect treatment comparison versus BSC	Indirect treatment comparison lacked robustness and as such produced uncertainty	The comparison has not been updated as there are no better data available.

4.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme/ commercial access agreement. You must also complete the rest of this template.

Not applicable.

4.3 Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

4.3.1 Treatment beyond progression

In the FAD, the Committee stated a preference to consider treatment beyond progression as there was no third-line therapy available to patients.

Although providing crizotinib treatment beyond progression would typically be administered to confer a benefit upon those receiving it, and that this likely benefit was acknowledged by the Committee, for the sake of simplicity in the analyses presented below, patients' utility immediately drops upon progression to the post-progression utility level and no benefit from continued treatment is assumed. This simplistic assumption produces a conservative ICER, as it assumes no quality of life benefit from treating beyond progression but does assume a cost.

No changes have been made to the input data used to estimate the degree of treatment beyond progression, or for the estimates of PFS; indeed, the Kaplan-Meier data for PFS and treatment duration were included in the originally submitted economic model. However, the original model assumed as its base case that crizotinib was given only until progression (so treatment duration equalled PFS and no treatment beyond progression was assumed). In this re-submission, Pfizer have amended the economic model so that the cost

of crizotinib is now a product of the treatment duration Kaplan-Meier curve, instead of the Kaplan-Meier PFS curve. The result is that treatment duration (and resulting cost) exceeds PFS, which is reflective of treatment beyond progression, and additional drug cost is accrued for this period.

The best fit parametric distribution was deemed in the original NICE submission as the Weibull curve, and this was applied to both PFS and treatment duration. Table 3 presents the median and mean treatment duration considered in the model when treatment is stopped at progression, and when treatment is allowed beyond progression.

Table 3. Treatment duration for crizotinib

	Median	Mean
Treatment until progression (equal to PFS)	7.9 months	10.1 months
Treatment allowed beyond progression	11.0 months	15.5 months

The Committee's preference in 2013 was that treatment beyond progression was should be reflected in the ICER as no third-line treatment option was available; however, NICE have recently recommended another ALK-inhibitor, ceritinib, for use post-crizotinib (TA395). In light of this new addition to the ALK-positive NSCLC treatment pathway, it is reasonable to assume that treatment with crizotinib would be unlikely to continue beyond progression. Indeed, UK clinical experts have indicated that treatment beyond progression with crizotinib would no longer be expected in practice due to this decision, with one expert stating treatment beyond progression may be a maximum of 1 month in some cases.

Analyses in which crizotinib treatment is stopped at progression are likely to be most reflective of UK clinical practice moving forward. Consequently, the ICERs including treatment beyond progression costs are included only to reflect a conservative upper-bound of crizotinib's true cost-effectiveness.

4.3.2 Differences in post-progression utility

The Committee considered differences in post-progression utility and accepted that some utility benefit might still be expected from crizotinib even after it discontinued at disease progression (owing to the reduction in tumour burden experienced pre-progression with crizotinib that is not experienced pre-

progression with docetaxel), though there were no data to suggest how great a benefit this might be or for how long it would persist.

To be conservative, the utility when patients' progress and stop treatment is now equal for both the crizotinib and chemotherapy treatment arms. This post-progression utility value is 0.61 for both, unchanged from the value in the original model.

4.3.3 Administration costs

The Committee's preference in 2013 was that an administration cost is applied to crizotinib. The Committee opted for the HRG code for the administration of oral chemotherapy in absence of an HRG code for oral targeted-inhibitors, which was £126 per cycle.

Pfizer posited in the 2013 appraisal that this cost is inappropriate for an ALK-inhibitor, as it is related to treatment with chemotherapy. Pfizer's position on this has not changed, and we still believe that is it not appropriate to apply the cost of oral chemotherapy administration to a treatment such as crizotinib.

Since the crizotinib appraisal in 2013, NICE has appraised a similar targeted oral inhibitor (nintedanib, also in NSCLC), in which no administration costs were assumed (TA347). In the recent appraisal of ceritinib (ID729; also a treatment for ALK-positive NSCLC), the Committee accepted that the use of a pharmacy dispensing cost (much lower than the administration cost for chemotherapy) was an appropriate proxy for any administration costs which might be associated with ceritinib.

Setting aside these inconsistencies, Pfizer acknowledge the Committee's preference from the 2013 appraisal to include the chemotherapy administration cost for crizotinib. For the sake of simplicity, it has therefore been included in the new base case, in line with Committee's original preference. The ICER is, as a result, necessarily conservative.

4.3.4 Updating costs to 2016

The following costs in the model have been updated to reflect 2016 values:

- Cost of administering oral chemotherapy (crizotinib) has been increased to £164 (code SB11Z) [9]

- Cost of administering docetaxel has been increased to £251 (code SB13Z) [9]
- Cost of IHC ALK-testing has been increased to £75 [10], and cost of FISH testing increased to £120 [11]
- Cost of generic docetaxel is £17.77 for 140mg [12]

4.3.5 New data for crizotinib's overall survival versus chemotherapy

Since publication of TAG296, the overall survival data for PROFILE 1007 have matured and the crossover adjustment analyses have been re-run on the mature dataset; the results are provided as new data within this submission. In the crizotinib arm, 67% (n=115) of patients have now died, (median follow-up 51.0 months [48.0, 53.8]), and 73% (n=72) in the chemotherapy arm have now died (median follow up 53.1 months [50.3, 55.1]).[13] This compares to only 28% at the interim analyses in 2013 (median follow up was 12.2 months), as described in the original submission. The now mature (yet unadjusted and therefore crossover-confounded) hazard ratio for OS for crizotinib versus pooled chemotherapy is 0.854 (CI 0.661, 1.104, p=0.11). Median unadjusted OS is 21.7 months (18.9, 30.5) in the crizotinib arm, and 21.9 (16.8, 26.0) in the pooled chemotherapy arm.[13] The OS was heavily confounded by crossover upon disease progression, with 87% (n=151) switching to crizotinib in the chemotherapy arm, and 23% (n=39) switching from the crizotinib arm to pemetrexed or docetaxel as the first follow-up anticancer therapy.

As the mature OS is a new dataset, crossover adjustment analyses had to be conducted again; a simple 'update' to the interim analyses would not have been appropriate. The feasibility and appropriateness of crossover adjustment models is dependent on the characteristics of the data set; the now mature data set is defined by new characteristics (e.g. 87% have crossed over from the chemotherapy arm, compared to previously 64%), so the available methods must be re-evaluated to ensure the most appropriate methods are considered.

The Rank-Preserving Structural Failure Time Model (RPSFTM) and the Inverse Probability of Treatment and Censoring Weighted (IPTCW) method were presented in the original submission and were assessed for feasibility again. The RPSFTM was conducted as a pre-specified analysis, with results

presented below. The feasibility of the ITPCW and the Inverse Probability of Treatment Weighting (IPCW) method were also assessed; however, given the larger variation in post-progression therapies in the mature OS analysis than at the interim OS analysis, these methods were no longer appropriate because, among other necessary assumptions (e.g. no unmeasured confounders), they assume that the survival experiences of the chemotherapy patients who do not switch treatment can be used to represent the survival experience of those who do.[14] Several publications illustrate how, in situations similar to ours, relatively small sample sizes and higher rates of crossover cause the IPCW method to produce significant bias.[15-17] Please see Section 5.3 for further explanation of the feasibility.

Three approaches for the RPSFTM were used to derive parameters to adjust for crossover, namely the log-rank, Wilcoxon and Cox model-based Wald tests. These adjusted for crossover from the chemotherapy arm to the crizotinib arm, and vice versa. The adjusted hazard ratios using the three tests are presented below for crizotinib versus pooled chemotherapy:

- 0.383 (95% bootstrap CI: 0.042, 0.991) from the stratified log-rank test
- 0.402 (95% bootstrap CI: 0.069, 0.971) from the stratified Wilcoxon test
- 0.352 (95% bootstrap CI: 0.037, 0.853), from the stratified Cox model based Wald test.

After adjusting for crossover with the RPSFTM using these three approaches, there was a statistically significant improvement in OS in the crizotinib arm compared to the chemotherapy arm, indicating that the primary OS analysis was impacted by high degree of crossover from chemotherapy to crizotinib. These ratios are within a narrow range (0.35 to 0.40), demonstrating a consistent improvement on the interim immature analyses. Indeed, they show that the hazard ratio in the Committee's originally preferred ICER was most likely an underestimate of crizotinib's true OS benefit.

In the FAD, the Committee selected a hazard ratio near to the centre of the range available to them at the time. Likewise, and in the absence of any methodological or clinical reason to select either of the extremes in preference to the other, the mid-range value is used in the updated modelled base case (RPSFTM log-rank, HR=0.38 [0.042, 0.991]). Validation of the absolute survival estimates pertaining to this hazard ratio can be found in Section 4.7.2.

The standard of care comparator appraised in the original submission was docetaxel. However, it is important to note that the mature crossover adjusted analyses presented above are for crizotinib versus the whole comparator arm of pooled chemotherapy from PROFILE 1007. In this pooled chemotherapy arm, 42% patients received docetaxel and 58% patients received pemetrexed. In the interim analyses used in the original submission, the crossover adjusted hazard ratio versus only docetaxel was presented as a subgroup analysis; however the PROFILE 1007 study was not pre-stratified to measure OS as a secondary endpoint for the docetaxel or pemetrexed only subgroups, but rather the pooled chemotherapy as a single group. Furthermore, n=72 in the docetaxel subgroup provides a smaller dataset for crossover adjustment modelling than the entire pooled arm (n=174). From the two chemotherapies, the mature trial data suggest that pemetrexed is a slightly more efficacious therapy than docetaxel:

- The 12 month survival probability for pemetrexed was *[Academic in confidence information removed]*%, but for docetaxel was *[Academic in confidence information removed]*% (not crossover adjusted).

- Crizotinib's ITT hazard ratios for survival (unadjusted for crossover) in the mature OS dataset are *[Academic in confidence information removed]* versus pemetrexed, and *[Academic in confidence information removed]* versus docetaxel.[13]

Given that the above indicate that those in the PROFILE 1007 trial performed better on pemetrexed than on docetaxel, crizotinib's crossover adjusted hazard ratio versus pooled chemotherapy is expected to be higher than what it would be versus docetaxel alone (i.e., pooled chemotherapy produces a better survival result than does the docetaxel subgroup on its own). However, as the pooled chemotherapy hazard ratio reflects the most robust data for comparator crossover adjusted OS, the pooled hazard ratio is used in the economic model. The positive effect that pemetrexed patients will have on this hazard ratio for OS likely leads to an over-estimation of crizotinib's true ICER versus docetaxel only. The results presented in this submission are thus a conservative representation of crizotinib's cost-effectiveness versus the standard of care docetaxel.

For the necessary extrapolations of the newly mature OS data, an evaluation of the proportional hazards assumptions is necessary to determine the most

plausible model. An assessment of the log hazard plots as per NICE DSU guidance [18] (Figure 2) does not show a departure from parallel lines. This indicates the hazard ratio remains proportional over time and as such, we have assumed a proportional hazards model in the new base case. For completeness, however, an alternative scenario analysis is presented in which independent curves are selected, which shows a minimal impact on the ICER.

Figure 2. Log of negative log of estimated survivor functions for the RPSFTM log-rank

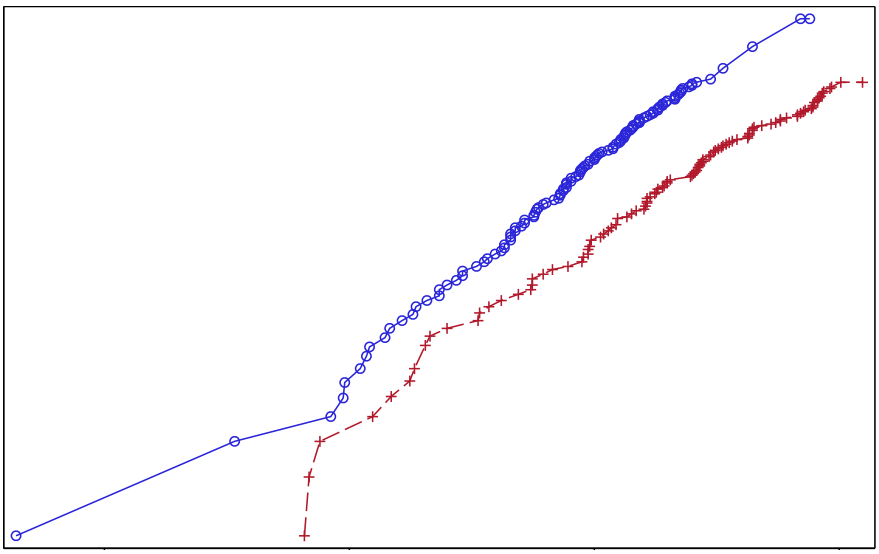


Figure 3 displays the Kaplan-Meier OS plots for crizotinib and chemotherapy adjusted using the RPSFTM log-rank. Plots for the other two crossover models can be found in Section 5.4.

Figure 3. Kaplan-Meier plots for crizotinib and chemotherapy spanning 5 years (60 months) for RPSFTM log-rank

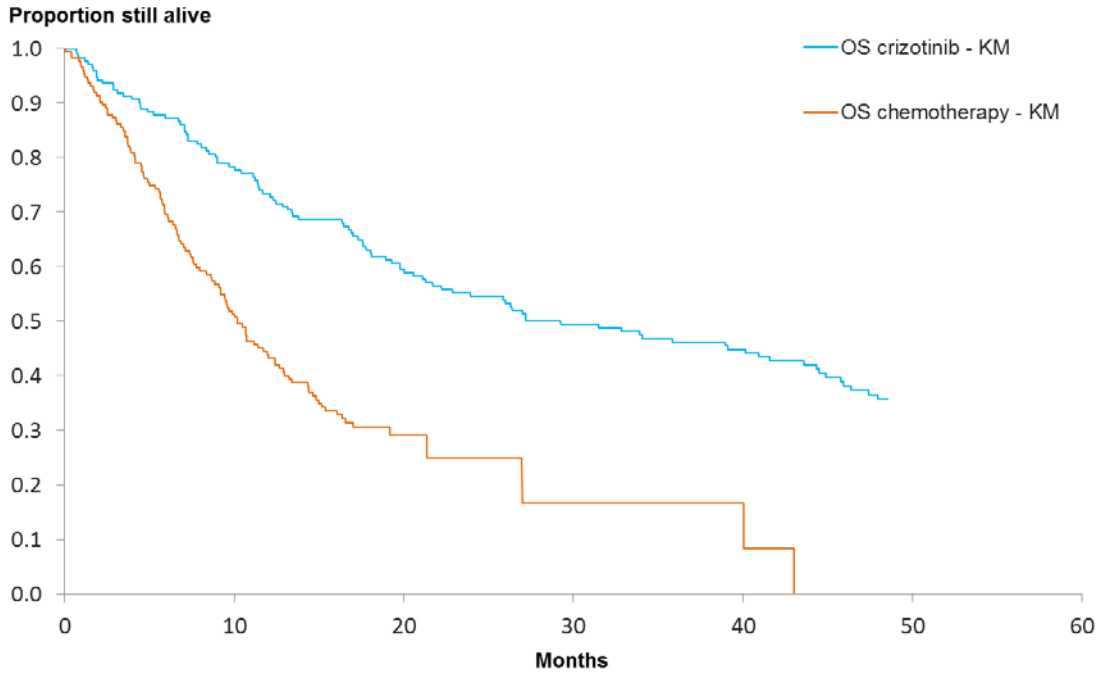


Table 4 displays the AIC and BIC criteria for the OS distributions for crizotinib and chemotherapy in a proportional hazards model using the RPSFTM log-rank test. The log-logistic has the lowest cumulative AIC and BIC, however the chemotherapy curve in this model has a mean OS that exceeds 24 months. Clinical opinion has indicated that it is implausible to expect the average life expectancy with chemotherapy to exceed two years and the 5 historical estimates of docetaxel OS presented in Section 4.7.2 show OS is consistency < 10 months.[1-5] Indeed, the Committee concluded that the End-of-Life criteria were met, reflective – in part – of this clinical opinion. It is therefore excluded as not having requisite face validity. The exponential has the lowest cumulative AIC and BIC that produces estimates of survival with face validity for both arms (see Section 4.7.2 for validation), and fit in Figure 4.

Table 4. AIC and BIC for OS curves in a proportional hazards model

Parametric model	AIC	BIC
Exponential	1924.47	1932.17
Generalised Gamma	1923.81	1939.20
Gompertz	1924.51	1936.06
Log-logistic	1921.66	1933.21
Log-normal	1926.73	1938.28
Weibull	1926.37	1937.92

Figure 4. Kaplan-Meiers with selected OS distributions for crizotinib and chemotherapy spanning 10 years (120 months)

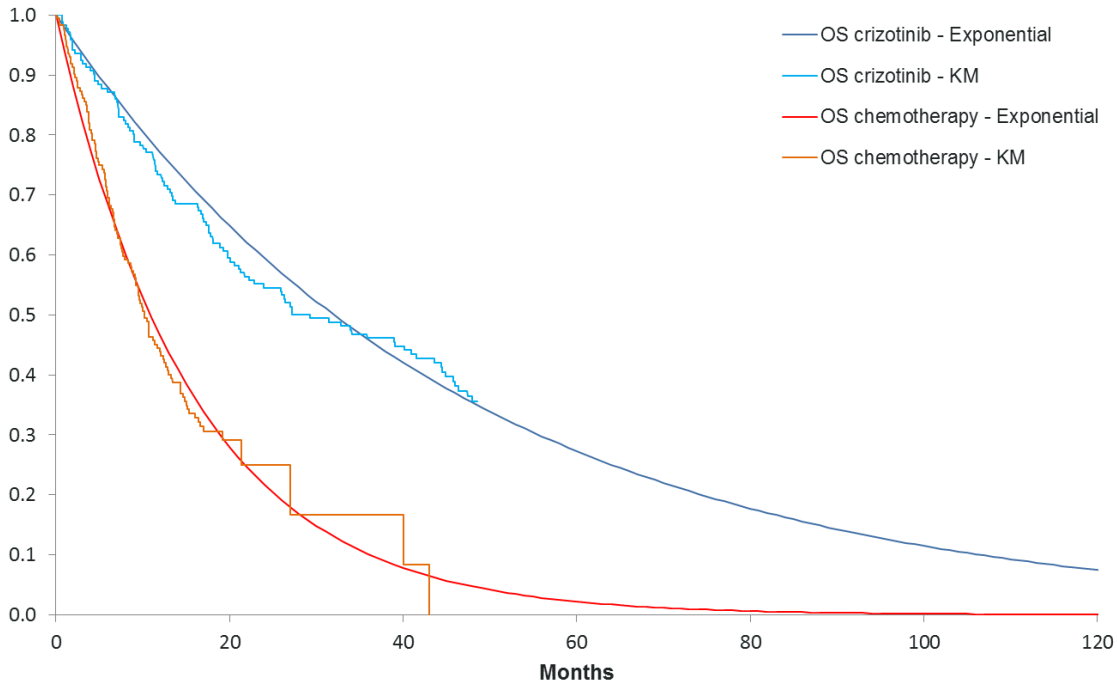


Table 5 compares the interim OS from the original appraisal to the newly mature OS. Estimated OS with crizotinib is vastly improved in the mature dataset than was estimated with the interim dataset, indicating the estimates of survival in the original NICE submission were an underestimate. Validation of these survival estimates is presented in Section 4.7.2. Table 15 in the Appendix contains estimates of survival gain for an independently fit model and how these compare to the proportional hazards model.

Table 5. Crossover adjusted hazard ratios and estimates of OS using proportional hazards model for OS

Model	**Hazard ratio**	**Median OS gain** (months)	**Mean OS gain** (months)
Interim OS analyses (2013) presented during TA296 vs. docetaxel			
Old Committee preference (IPTCW2)	**0.79** (0.45,1.40)	4.9	7.1
Mature OS analyses (2016) vs. pooled chemotherapy – proportional hazards			
RPSFTM Log-rank	**0.38** (0.04, 0.99)	21.1	29.6
RPSFTM Wilcoxon	**0.40** (0.07, 0.97)	*[Academic in confidence information removed]*	*[Academic in confidence information removed]*
RPSFTM Wald	**0.35** (0.04, 0.85)	*[Academic in confidence information*	*[Academic in confidence information*

		removed]	*removed]*

4.3.6 Crizotinib versus best supportive care (BSC)

A mixed treatment comparison for BSC was included in the original submission, but was critiqued by the Committee as lacking robustness because of key differences in the patient populations. The hazard ratio presented for crizotinib's OS versus best supportive care was 0.37 (0.12, 0.89). Pfizer note that in the FAD, the Committee did not specify a preference for a hazard ratio different than those which were submitted by the company. The hazard ratio presented for OS versus BSC was much lower than that for docetaxel; this is intuitive, because if docetaxel produced worse survival outcomes than BSC, it would likely not be used by clinicians. The ICERs discussed in the FAD were higher for crizotinib versus docetaxel than for crizotinib versus BSC, implying that crizotinib was more cost-effective versus BSC than versus docetaxel. Logic therefore dictates that if crizotinib is cost-effective versus docetaxel, it would also be cost-effective versus BSC.

The maturation of the OS data has produced a much improved crossover adjusted hazard ratio for crizotinib versus docetaxel, with crizotinib's absolute OS now far higher than was estimated in the interim analysis (Table 5). No new data for crizotinib's indirect efficacy versus BSC are presented, and as such the ICER versus BSC has not been revisited; however, it is assumed that crizotinib is transitively cost-effective versus BSC if crizotinib demonstrates it is cost-effective versus docetaxel. As such, and with no new data versus BSC available, only ICERs versus docetaxel are presented in this document.

4.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 2. Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'

Not applicable.

4.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable. The scheme is applied as a confidential discount to all original invoices.

Summary of results

New base-case analysis

4.6 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

A suggested format is shown below (table 4).

The new base case contains updates to the overall survival data and to the cost data (to reflect 2016 prices), alongside a revision to the Patient Access Scheme originally offered in TA296, which reflects the scheme recently approved as part of the NICE appraisal of crizotinib's first-line indication [ID865] . All other inputs are unchanged from the first appraisal and reflect the Committee's preferred set of assumptions, as set out previously. Tables 6 and 7 below present the resulting cost-effectiveness estimates from using the interim OS data used to inform the original appraisal versus using the mature OS data that has recently become available.

Table 6. Previous base-case (immature OS) cost-effectiveness results with the PAS price from the published technology appraisal (discounted at 3.5%, deterministic ICER)

	Crizotinib	Chemotherapy
Intervention cost (£)	*[Commercial in confidence information removed]*	76
Other costs (£)	12,781	9,236
Total costs (£)	*[Commercial in confidence information removed]*	9,312
Difference in total costs (£)	*[Commercial in confidence information removed]*	
LYG	2.40	1.94
LYG difference	0.46	
QALYs	*[Commercial in confidence information removed]*	1.24
QALY difference	*[Commercial in confidence information removed]*	
ICER (£)	96,254 per QALY	

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.
Treatment beyond progression (TBP) is not included in Table 6

Table 7. New base-case (mature OS) cost-effectiveness results with the revised PAS (discounted at 3.5%, deterministic ICER)

	Crizotinib	Chemotherapy
Intervention cost (£)	*[Commercial in confidence information removed]*	76
Other costs (£)	14,735 to 15,564	7,939
Total costs (£)	*[Commercial in confidence information removed]*	8,015
Difference in total costs (£)	*[Commercial in confidence information removed]*	
LYG	3.41	1.30
LYG difference	2.11	
QALYs	*[Commercial in confidence information removed]*	0.84
QALY difference	*[Commercial in confidence information removed]*	
ICER (£)	*[Commercial in confidence information removed]*	

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; TBP: treatment beyond progression

4.7 Please present in separate tables the incremental results as follows. 2

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 5.

[2] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

4.7.1 New base case results

Table 8 and Table 9, respectively, present the new base case incremental results with the immature crizotinib OS data from the original appraisal and the old PAS, versus crizotinib's newly matured OS data with the revised PAS (previously Tables 4a and 4b in this original template).

Table 8. Previous base-case (immature OS) incremental results with the old PAS price from the published technology appraisal, treatment till progression (discounted at 3.5%, deterministic ICER)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Chemotherapy	9,312	1.94	1.24				
Crizotinib	*[Commercial in confidence information removed]*	2.40	*[Commercial in confidence information removed]*	*[Commercial in confidence information removed]*	0.46	*[Commercial in confidence information removed]*	96,254

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.
Treatment beyond progression (TBP) is not included in Table 8

Table 9. New base-case (mature OS) incremental results with the revised PAS (discounted at 3.5%, deterministic ICER)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Chemotherapy	8,015	1.30	0.84				
Crizotinib	*[Commercial in confidence information removed]*	3.41	*[Commercial in confidence information removed]*	*[Commercial in confidence information removed]*	2.11	*[Commercial in confidence information removed]*	*[Commercial in confidence information removed]*

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.
Treatment beyond progression (TBP) is not included in Table 9

4.7.2 Validation of OS modelling

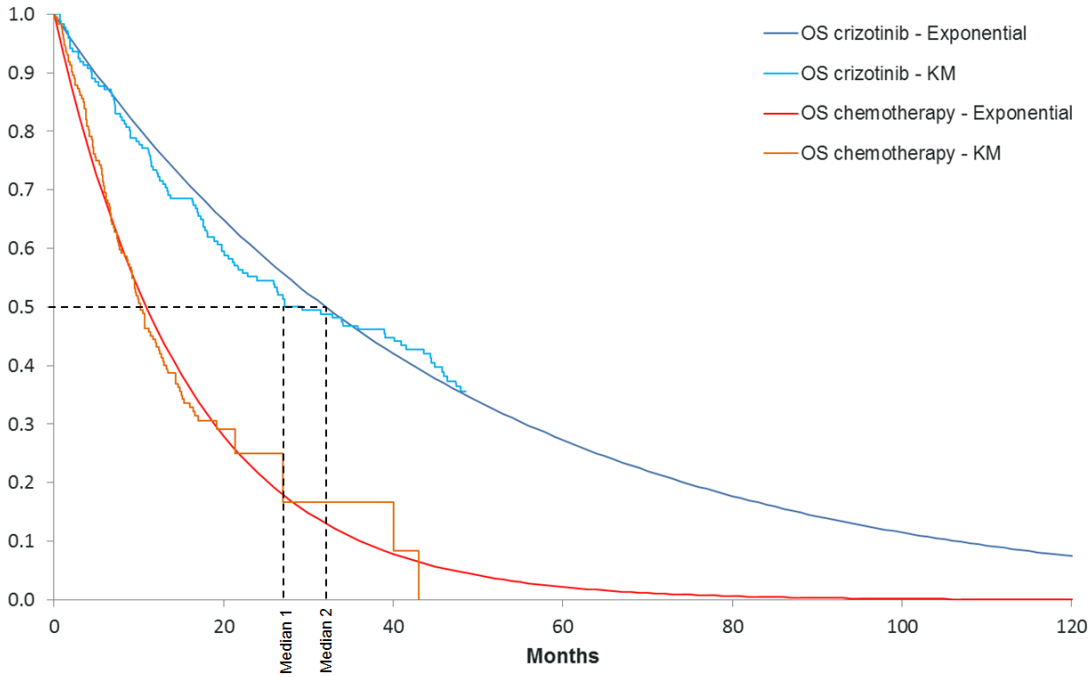
The base case ICER is now much lower than those discussed in the 2013 FAD, indicating an improvement in crizotinib's estimate cost-effectiveness. The key driver for this relates to the improved hazard ratio for crossover adjusted OS, moving from 0.79 for crizotinib versus docetaxel in the original appraisal to 0.38 for crizotinib versus pooled chemotherapy with the matured data. It is important to remember that the hazard ratio for crizotinib versus docetaxel alone is expected to be lower than that versus pooled chemotherapy, which means that the estimates of cost-effectiveness presented here are conservative, with ICERs versus docetaxel expected to be lower than those presented here.

Median overall survival

PROFILE 1007 is the most robust dataset available for estimating the long-term survival of second-line ALK-positive patients. The crossover adjusted crizotinib Kaplan-Meier is associated with a median OS of *[Academic in confidence information removed]* months, and the fit distribution with *[Academic in confidence information removed]* months. Longer term real-world survival data is sparse in ALK-positive patients, however recent UK audit data from *[Academic in confidence information removed]* shows a median survival of *[Academic in confidence information removed]* in previously treated ALK-positive patients who were then treated with an ALK-inhibitor *[Academic in confidence information removed]* [19]

The median OS for crizotinib is slightly higher with the modelled exponential curve (*[Academic in confidence information removed]* months) than with the Kaplan-Meier (*[Academic in confidence information removed]* months); however, it is important to note that it is the mean OS that directly impacts the ICER rather than the median. Figure 5 shows that visually the median of the exponential distribution is higher than the Kaplan-Meier because the first part of the distribution sits above the Kaplan-Meier. After around 55% of survival events, however, the distribution then sits below the Kaplan-Meier and as such has a more downward sloping gradient than the Kaplan-Meier, suggesting the exponential does not over-inflate mean OS (Section 5.7 contains further explanation).

Figure 5. Kaplan-Meier s with selected OS distributions for crizotinib and chemotherapy spanning 10 years (120 months), with median markings



The crossover adjusted chemotherapy distribution is associated with a median OS of *[Academic in confidence information removed]* months, similar to the Kaplan-Meier (as can be seen in Figure 4). The UK data discussed above also contain median OS for *[Academic in confidence information removed]* ALK-positive patients who were not treated with an ALK-inhibitor. Their median OS *[Academic in confidence information removed]* was *[Academic in confidence information removed]* 19] As such, *[Academic in confidence information removed]*

It should be noted that the modelled curve is a pool of pemetrexed (58%) and docetaxel (42%) patients, with it being expected the pemetrexed patients pull the pooled OS upwards, as explained earlier. Previous trial estimates of docetaxel median OS include:

- 5.7 months median [3]
- 7.9 months median [4]
- 9.1 months median [5]
- 7.0 months median [1]

- 8.0 months median [2]

Given the modelled median OS is between *[Academic in confidence information removed]* months higher than previously published estimates, this only serves to demonstrate that we are adopting a conservative approach in this submission and that the true ICER for crizotinib is likely to be much lower.

5-year survival rates

PROFILE 1007 is the most robust dataset of which we are aware for longer-term survival of second-line ALK-positive patients; 116 patients in the crizotinib arm were known to have died at the time of cut-off for the final survival analysis (median follow-up of 51 months). The selected curve for crizotinib in the model, the exponential, shows 33.2% of patients alive at 51 months in the crizotinib arm; this validates the chosen curve's accuracy versus the longer term trial data.

The median follow-up for the chemotherapy arm was 53.1 months. Considering first-line progression-free survival in ALK-positive patients with chemotherapy is 7 months,[20] this suggests the median follow-up of the chemotherapy arm was around 5 years (60 months) from diagnosis. The selected curve in the model for chemotherapy, the exponential, shows that 2.2% of patients are alive at 5 years from diagnosis. The patient population for this appraisal is stage IIIb and stage IV NSCLC. Cancer Research UK estimates the 5-year survival rate for stage III lung cancer at 6%, with stage IV being lower but too difficult to calculate due to the very small number of patients living past 2-years. The American Cancer Society report a similar 5-year survival rate for stage IIIb NSCLC of 5%, and report stage IV to be around 1%. Our modelled rate of 2.2% for the chemotherapy arm is in line with these estimates.

Sensitivity analyses with the relevant PAS/CAA

4.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

4.8.1 Deterministic sensitivity analyses

Table 10 presents the results from the sensitivity analyses that were conducted. The comparability of the deterministic and probabilistic ICERs (Table 9 and Table 12) suggests minimal differences between the two analyses. Due to the similarities, the sensitivity analyses below present only one set of ICERs (deterministic).

There is minimal variation from the base case ICER of *[Commercial in confidence information removed]* per QALY, apart from in the case of the treatment beyond progression analysis, which increased the ICER by *[Commercial in confidence information removed]* per QALY. In 2013, it was not possible for the use of ceritinib and its impact on treatment practices to be considered. However, in light of this new addition to the ALK-positive NSCLC treatment pathway following its NICE recommendation as a treatment to follow crizotinib, it is reasonable to assume that treatment with crizotinib would be unlikely to continue beyond progression; this has been confirmed by clinical experts. Analyses in which crizotinib treatment is stopped at progression are therefore likely to be most reflective of UK clinical practice moving forward.

Table 10. Results of deterministic scenario analyses with new discount

Input data or assumption	Sensitivity analyses	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Base case ICER		*[Commercial in confidence information removed]*		
Choice of crossover-adjusted hazard ratio	RPSFTM Wilcoxon test (HR=0.40)	*[Commercial in confidence information removed]*		
	RPSFTM Wald test (HR=0.35)	*[Commercial in confidence information removed]*		
Parametric model for OS	Independent curve selection*	*[Commercial in confidence information removed]*		
Treatment beyond progression (TBP)	TBP included (additional cost only)	*[Commercial in confidence information removed]*		

**Independent curves selected are those with lowest cumulative AIC and BIC, log-normal (crizotinib) and log-logistic (chemotherapy)*

Figure 6 displays one-way deterministic sensitivity analysis results. It can be seen that the parameters that alter the ICER the most do so by only a small amount, with variations all staying within £1,200 per QALY of the base case.

Figure 6. 'Tornado' diagram illustrating sensitivity of ICER to one-way to parameters

[Commercial in confidence information removed]

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

4.9.1 New base case probabilistic results

Table 11 and Table 12 present the incremental costs and QALYs and the resulting ICERs for the new base case with the previously approved PAS in TA296 and the new commercial access agreement, respectively. These probabilistic ICERs are the average (mean) of 10,000 probabilistic simulations in the model.

There is consistency across the deterministic and probabilistic ICERs, with the new base case probabilistic ICER (*[Commercial in confidence information removed]* per QALY) being very close to the deterministic (*[Commercial in confidence information removed]* per QALY) when treated till progression.

Table 11. Previous base-case (immature OS) results with the old PAS price from the published technology appraisal, treatment till progression (discounted at 3.5%, probabilistic ICER)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Chemotherapy	*[Commercial in confidence information removed]*	0.41	*[Commercial in confidence information removed]*	102,581
Crizotinib				

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio. Treatment beyond progression (TBP) is not included in Table 11

Table 12. New base-case (mature OS) results using the revised PAS, treatment till progression (discounted at 3.5%, probabilistic ICER)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Chemotherapy	*[Commercial in confidence information removed]*	2.27	*[Commercial in confidence information removed]*	*[Commercial in confidence information removed]*
Crizotinib				

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

It should be noted that for investigational purposes, we also calculated a probabilistic ICER for the analysis in Table 10 that looks at the choice of OS parametric model (proportional hazards versus independent model). The independent probabilistic ICER was very similar to the independent deterministic ICER model *[Commercial in confidence information removed]*

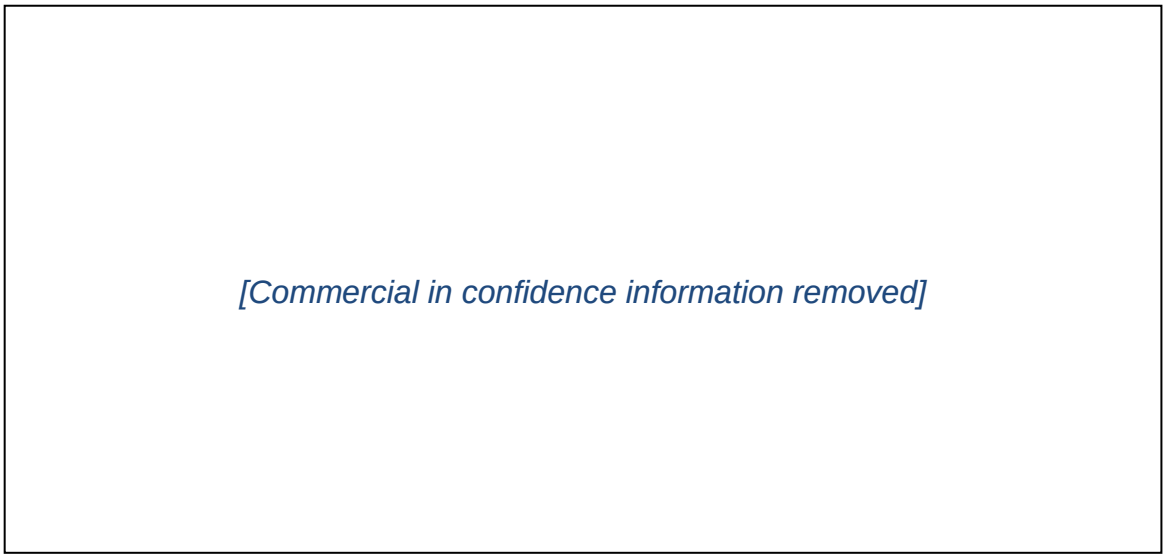
per QALY vs. *[Commercial in confidence information removed]* per QALY), which are both similar to the proportional hazards ICER *[Commercial in confidence information removed]* per QALY).

4.9.2 Scatter plots and cost-effectiveness acceptability curves

Figures 6 and 7 demonstrate that when crizotinib is offered till progression, it is cost-effective at the £50,000 per QALY threshold in *[Commercial in confidence information removed]* of the 10,000 probabilistic simulations that were modelled.

Figure 7. Scatter plot of probabilistic ICER simulations

Figure 8. Probabilistic cost-effectiveness acceptability curve at a willingness-to-pay threshold of £50,000 per QALY (blue = criz; purple = chemo)



4.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

5 Appendices

5.1 Information about patient access schemes

5.1.1 The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2014 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2014 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

5.1.2 Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2014 PPRS.

5.1.3 Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

5.2 Additional documents

5.2.1 If available, please include copies of patient access scheme agreement forms/ commercial access agreement, patient

registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

[Commercial in confidence information removed]

Details of outcome-based schemes

5.2.2 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.3 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.4 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable.

For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the

additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

5.3 Appendix A: Crossover adjustment methods

Three variations of the RPSFTM were conducted, with statistically significant hazard ratios for survival ranging from 0.35 to 0.40 (see Section 4.3.1).[13]

At the time of the interim OS results presented in the previous appraisal in 2013, in addition to the RPSFTM, the Inverse Probability of Treatment and Censoring Weighted (IPTCW) method was implemented. The IPTCW method is a double inverse weighting method constructed from the concurrent application of Inverse Probability of Treatment Weighting (IPTW) to balance the treatment-specific baseline covariates (that is, adjusts for time-dependent confounders that are affected by previous treatment) and inverse probability of censoring weighting (IPCW) overcomes dependent censoring due to time-varying factors for which no adjustment is made.[21] The IPTCW is the product of IPTW and IPCW. These methods were again considered for use with the final dataset. However, given the larger variety of post-progression anticancer therapies at the time of the final OS analysis than at the interim OS analysis, the IPTW to adjust for post-progression therapy was no longer considered appropriate. Similarly, the strict IPCW-related method, which only attempted to adjust for the crossover from chemotherapy to crizotinib, was, as described below, also not considered appropriate for the final analysis of OS adjusted for crossover.

Among other necessary assumptions for the IPCW (e.g., no unmeasured confounders assumption; that data must be available on all baseline and time-dependent prognostic factors for mortality that independently predict switching; and lack of deterministic predictors for censoring and outcome), the method assumes that the survival experiences of the chemotherapy patients who do not switch treatment can be used to represent the survival experience of those who do.

At the time of the interim OS analysis, a total of 112 (64%) patients randomized to chemotherapy received crizotinib as their first follow-up systemic anticancer therapy. However, at the time of the final OS analysis, the figure increased to 151 (87%) patients randomized to chemotherapy who received crizotinib as their first follow-up systemic anticancer therapy, leaving only 23 (13%) patients randomized to chemotherapy did not crossover. Of these 23 patients who did not crossover, *[Academic in confidence information removed]* patients died, including *[Academic in confidence information*

removed] patients who were not allowed to crossover as they died prior to documented disease progression. Thus, the survival experience of only *[Academic in confidence information removed]* patients who did not crossover could be used to reflect the survival experience of 151 patients who did crossover.

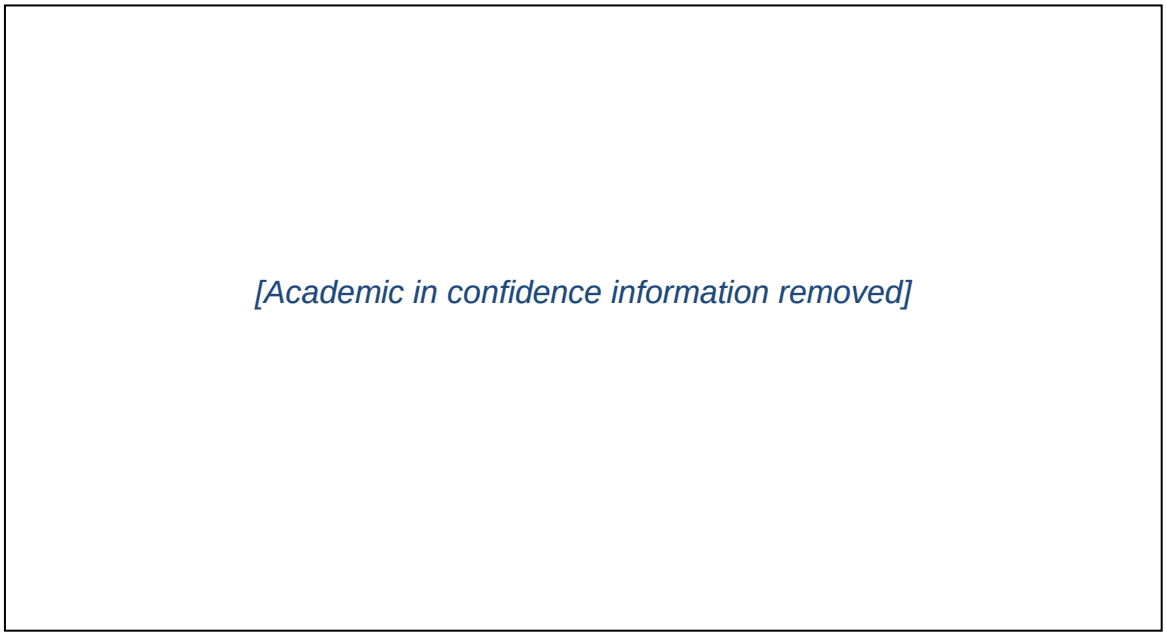
Several publications have shown that in scenarios similar to those described above, i.e., relatively small sample size and high crossover rate, the IPCW method produced significant bias.[15-17] This is due to the fact that the survival outcome from the small proportion of control group patients who do not switch is used to represent the survival outcome of the entire control group. As such, the survival times of a few patients who do not switch have a very large impact on IPCW estimation. Given that only 23 patients randomised to chemotherapy did not crossover, and of these, only *[Academic in confidence information removed]* patients had an opportunity to crossover, it was deemed inappropriate to implement an IPCW model for the final OS analysis.

5.4 Appendix B: Crossover adjusted Kaplan-Meier OS

Figure 9 and Figure 10 present the Kaplan-Meier plots for OS crossover adjusted using the RPSFTM Wilcoxon and Wald tests, respectively.

Figure 9. Kaplan-Meier plots for OS adjusted for crossover with the RPSFTM Wilcoxon test (spanning 5 years)

Figure 10. Kaplan-Meier plot for OS adjusted for crossover with the RPSFTM Wald test (spanning 5 years)



5.5 Appendix C: AIC and BIC in an independently fit parametric model

In the proportional hazard models for OS, the only covariate included is treatment. The shape parameters of both crizotinib and chemotherapy curves are the same, with the scale of the curve differing (driven by treatment effect). Likewise, treatment is the only covariate in the alternative 'independent' parametric modelling. However, this independent parametric modelling sees the data first divided in two groups (by treatment), then all parameters (shape and scale) are estimated for each treatment. As such, there are sets of AIC and BIC per treatment when fitting independent curves. Table 13 and Table 14 display the AIC and BIC for the RPSFTM log-rank crossover adjusted OS data, for crizotinib and chemotherapy respectively.

Table 13. AIC and BIC for crizotinib in an independent model

Parametric model	AIC	BIC
Exponential	1036.36	1039.51
Generalised Gamma	1035.54	1045.00
Gompertz	1035.78	1042.08
Log-logistic	1034.63	1040.93
Log-normal	1033.85	1040.16
Weibull	1037.55	1043.85

Table 14. AIC and BIC for chemotherapy in an independent model

Parametric model	AIC	BIC
Exponential	888.11	891.27
Generalised Gamma	888.05	897.53
Gompertz	890.08	896.40
Log-logistic	885.00	891.32
Log-normal	891.54	897.86
Weibull	888.27	894.59

5.6 Appendix D: Estimates of overall survival using RPSFTM log-rank test

Table 15 displays four sets of crossover adjusted survival data, using the RPSFTM log-rank test (as this hazard ratio is in the middle of the range, HR=0.38; CIs 0.04, 0.99):

1) **Base case:** A proportional hazards survival model, choosing the curves with the lowest cumulative AIC and BIC, that have life expectancy of <24 months as no trials have shown survival data for docetaxel in second-line line NSCLC to be over 2 years. This is an extreme allowance considering the five trials listed in the main body of this document show survival is less than 10 months.[1-5] It is such compelling evidence that led the Committee to award End Of Life criteria in TA296.

2) A proportional hazards survival model, choosing the curves with the *second* lowest cumulative AIC and BIC, that has comparator OS <24 months.

3) A non-proportional independently fit survival model, choosing separate curves with the lowest cumulative AIC and BIC, that has comparator OS <24 months.

4) A non-proportional independently fit survival model, choosing separate curves with the *second* lowest cumulative AIC and BIC, that has comparator OS <24 months.

Across the base case and three scenarios, the range of median OS gain is narrow, from *[Academic in confidence information removed]* months. The mean OS gain range is wider, from *[Academic in confidence information removed]* months. Pfizer's base case is model (1), which is the most conservative of these mean gains. All models consistently demonstrate there is a substantial survival benefit for patients using crizotinib versus using pooled chemotherapy. This benefit is expected to be even greater if measured versus docetaxel alone (as described in 4.3.1). Using the alternative RPSFT models causes minimal change to median or mean OS gain, typically around 1 or 2 months.

Table 15. RPSFTM log-rank crossover adjusted estimates of OS for crizotinib versus pooled chemotherapy

Model	Median OS			Mean OS		
	Criz	Chemo	Gain	Criz	Chemo	Gain
(1) Proportional hazards, choosing lowest cumulative AIC and BIC	*[Academic in confidence information removed]*		21.1	*[Academic in confidence information removed]*		29.6
(2) Proportional hazards, choosing second lowest AIC and BIC			20.0			35.0
(3) Independently modelled curves, choosing lowest cumulative AIC and BIC			19.0			34.5
(4) Independently modelled curves, choosing second lowest AIC and BIC			18.7			38.4

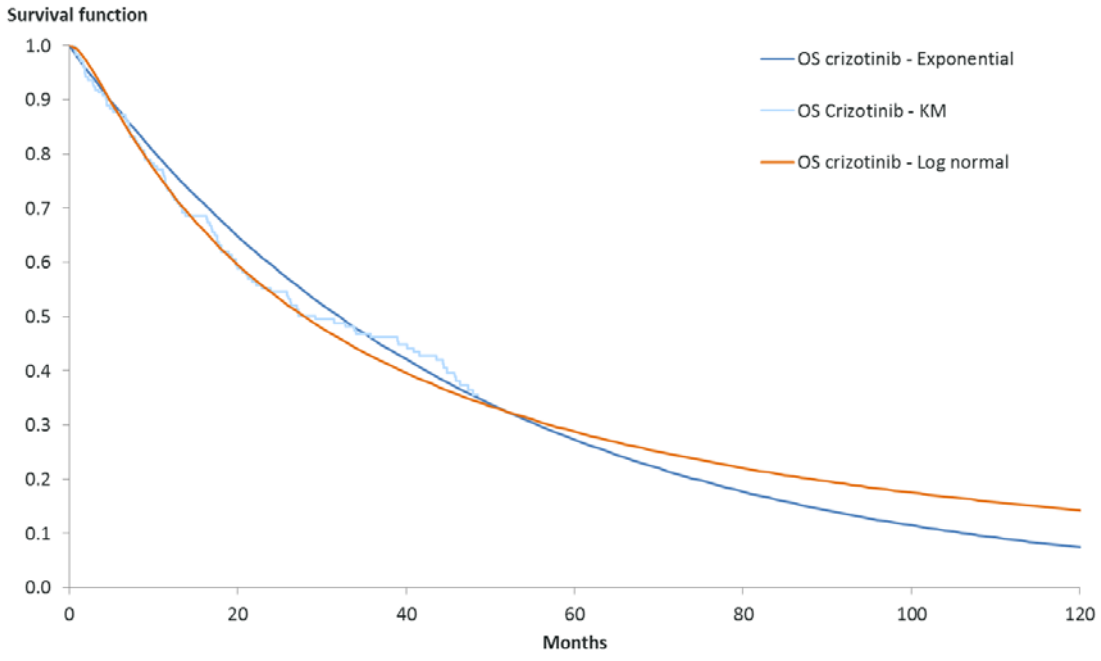
Abbreviations: *Criz = crizotinib; Chem = chemotherapy; OS = overall survival*

Note: *Exponential curve selected in basecase scenario 1 (log-logistic did not meet EOL); Gompertz curve selected in scenario 2; Log-normal (crizotinib) and log-logistic (chemotherapy) curves selected in scenario 3; Log-logistic (crizotinib) and exponential (chemotherapy) curves selected in scenario 4.*

5.7 Appendix E: The role of median OS in selecting curves

Figure 11 displays two possible distributions for crizotinib's OS in the proportional hazards model; the blue is the exponential that was seen in Figure 5, and the orange is the log-normal. The log-normal is more "in-line" with the Kaplan-Meier and indeed shares the same median; however, it has a bigger tail than the exponential as the exponential is more downward sloping. So although the log-normal has a closer median to the Kaplan-Meier data (and is 3.8 months lower that the exponential), it actually has a greater mean OS than the exponential (6.0 months higher). Hence, the log-normal produces more mean QALYs for crizotinib. The exponential, although a higher median, thus provides a more conservative estimate of crizotinib's OS benefit (and resultant QALYs) due to the mean determining the ICER rather than the median. As such, it is reasonable to consider that the exponential is the most suitable curve, even though its median does not exactly match that of the Kaplan-Meier.

Figure 11. Kaplan-Meier plots with two alternative OS distributions for crizotinib spanning 10 years (120 months), with median markings



6 References

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☎ **Direct Line** [redacted]
[redacted]

NICE
1st Floor
10 Spring Gardens
London
SW1A 2BU

16 August 2016

Dear Sirs

Lung cancer (non-small-cell, anaplastic lymphoma kinase fusion gene, previously treated) – crizotinib (review of TA296) [1010]

Thank you for the opportunity to comment on the ACD.

We note that NICE are going to approve crizotinib in the first line setting and there is approval for the use of ceritinib for second line treatment for those patients who progress on ceritinib. These changes will significantly reduce the use of crizotinib in the second line setting but there will be a cohort of patients who predate the approval for use in the first line setting. This cohort will be receiving or have received chemotherapy as their first line treatment and I think it is very important that second line crizotinib remains accessible through CDF at least in the short term. If the drug is taken off the CDF they will have created a population for whom equality of access becomes a major issue.

Yours faithfully
For and on behalf of BTOG

[redacted]

[redacted]

British Thoracic Oncology Group - Company Number 9816385
The Registrar of Companies for England and Wales
Registered Charity number 1166012
Registered address: Adam Longley Accountants Limited, The Old Barn, 1815 Melton Road,
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Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

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CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

This is an important technology that had been rejected on the basis of cost but the Society would encourage the NHS and the manufacturers to reach an agreement where it be supplied on a more cost effective basis.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology

appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

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CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], RCP registrar, submitting on behalf of:

Name of your organisation: NCRI-ACP-RCP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

We note that NICE are going to approve crizotinib in the first line setting and there is approval for the use of ceritinib for second line treatment for those patients who progress on ceritinib.

These changes will significantly reduce the use of crizotinib in the second line setting but there is going to be a cohort of patients who predate the approval for use in the first line setting.

This cohort will be/have received chemotherapy as their first line treatment it is important that second line crizotinib remains accessible through CDF at least in the short term.

If the drug is taken off the CDF NICE will have created a population for whom equality of access becomes a major issue.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

<u>Submission from Roy Castle Lung Cancer Foundation</u>, for consideration by NICE, in their CDF Rapid Reconsideration of Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 10%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of non small cell lung cancer (nsclc).

General Points – Advanced non small cell lung cancer

1. For patients with advanced or metastatic nsclc, cure is not a treatment option. In this scenario, improving quality of life and even small extensions in duration of life are of considerable significance to the individual and their family.

2. As overall outcomes for this patient population remain poor, the availability of new therapy choices are of key importance.

3. The importance of 'end of life' therapies. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life, as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with advanced or metastatic non small cell lung cancer are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief.

This Product

1. Oral Preparation
   Oral therapy is of obvious importance to patients, in spending less time at hospital and in not requiring intravenous cannulation for treatment.

2. Good side effect profile
   In the anecdotal patient experience reported to us, Crizotinib is well tolerated – in particular, when compared with current standard cytotoxic therapy for nsclc. Common side effects include visual disturbances, nausea, vomiting, diarrhoea, constipation. Serious side effects reported include hepatotoxicity, pneumonitis and heart problems.

3. Outcome data
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available.

4. Very targeted population.
   It is reported that ALK rearrangements are found in 2% to 7% of nsclc patients. This therapy therefore represents a targeted treatment option, for a clearly defined small segment of non small cell lung cancer.

   Crizotinib, for ALK positive disease, has been available in England in second line, after platinum-based chemotherapy, via the Cancer Drugs Fund, over several years. It has recently received a positive FAD for first line ALK positive disease. For ALK positive patients, with Crizotinib resistant nsclc, two therapies are currently available - Ceritinib (recent positive NICE appraisal) and Alectinib (currently undergoing NICE appraisal).

   We would therefore anticipate that, in the near future, with a positive NICE recommendation for first line ALK positive disease, Crizotinib will be available for this patient group in this indication. In the second line setting (after platinum based chemotherapy), we would assume that ALK testing has been delayed, results misplaced, rebiopsy etc… , and that this would be the availability for this 'missed' group of patients,

   Our observations come from a combination of one-to-one discussion with lung cancer patients, published research, on line patient contact and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer are in a particularly devastating situation. Even with the currently recommended options, the outlook for the majority is relatively poor.

ALK gene rearrangement is found in a very small number of lung cancer patients. Crizotinib in this indication under assessment, would make this targeted therapy available to patients, in whom positive ALK test results have become available, after first line platinum based chemotherapy.

[redacted], **RCLCF. (August 2016).**

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

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To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: ROYAL COLLEGE OF PATHOLOGISTS
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

I AM A PATHOLOGIST WITH SPECIALIST INTEREST IN LUNG CANCER AND THE MECHANISMS FOR TESTING FOR THE RELEVANT MOLECULAR ABNORMALITY

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

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In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

International guidelines including the testing for ALK translocations have been published in 2013

Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M.
J Thorac Oncol. 2013 Jul;8(7):823-59.

These are relevant to the testing for the ALK translocation

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

N/A for RCPath

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The concern for RCPath is who will fund the screening for the ALK translocation in relation to all advanced NSCC, and whether IHC should be approved as the method of screening rather than FISH testing (or other)

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by The Royal College of Pathologists and consequently I will not be submitting a personal statement.

Name: .....[redacted].....

Signed: .....[redacted].....

Date: .....29/8/16.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Patient/carer expert statement

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: National Lung Cancer Forum for Nurses
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☐X No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes X☐ No

- a carer of a patient with the condition?

☐ Yes X☐ No

- a patient organisation employee or volunteer?

☐ Yes ☐ No

Do you have experience of the treatment being appraised?

☐X Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

NA

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- Crizotinib is given to patients with the ALK positive receptors. It is given in tablet form which much easier for the patients to take. And the side effects for patients appear to be minimal.
- Because the treatment is in tablet form at home, the patients only have to attend an appointment with the oncologist once a month, this is vastly reduced from the alternative treatments.
- Family members are better able to support patients to administer a tablet at home.
- Patients will have less travelling to hospital appointments
- Alternative treatments have more side effects and patients are offer hospitalised to manage the side effects.
- Psychologically patients taking this treatment seem to accept it as a therapy much easier as it is included in their daily routine of medicines management at home.
- Patients also have the benefit of knowing they have a treatment that is completely targeted to their disease.

- Overall the quality of life for patients who are able to receive the treatment appears to be improved
- There are only a few patients in the total population of NSCLC patients who will have the ALK receptor to target so the treatment will not by the nature of numbers be a common treatment given, however the outcomes could be significant in terms of disease free progression, but more over the quality of life of palliative patients.

Please list the benefits that you expect to gain from using the treatment being appraised.

Patients will have a better quality of life and less side effects so the specialist nurse wil need to give less patient support

Please explain any advantages that you think this treatment has over other NHS treatments in England.

see above

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- It is difficult to find any disadvantages, other than this drug will only be appropriate for the few patient who have an ALK receptor

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than

others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

yes

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

yes

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that I am aware of

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes X☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

no

9. Other issues

Do you consider the treatment to be innovative?

☐X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This treatment only targets patients who have the ALK positive receptor

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Tablet form,
- Less side effects
- Improved quality of life
- Improved life psychologically and for the family
- Less hospital appointments and less inpatient stays for patients and their family.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296) [ID1010]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by the Roy Castel Lung Cancer Foundation and consequently I will not be submitting a personal statement.

Name: .....[redacted].....

Signed: .....[redacted].....

Date: .....20th September 2016.....

ERG review of the submission for the reconsideration of crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene under the proposed new CDF criteria

Produced by CHE and CRD Technology Assessment Group, University of York

Authors Mathilde Peron, Research Fellow, CHE

Stephen Palmer, Professor, CHE

Date 01/09/2016

1 Introduction

NICE did not recommend crizotinib for treating adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) (TA296, September 2013). The Committee concluded that the ICER on which to base a decision for crizotinib compared with docetaxel would be more than £100,000 per QALY gained, and for crizotinib compared with best supportive care would be more than £50,200 per QALY gained.

Crizotinib is currently funded through the previous Cancer Drugs Fund (CDF) and is now being re-considered by NICE under the new proposed CDF criteria. The company has proposed a Commercial Access Agreement (CAA) based on a simple confidential discount. The company also includes a revised economic analysis taking into account the Committee's preferred assumptions identified in TA296. Unit costs are updated to reflect 2016 prices and a more mature dataset from PROFILE 1007 is used to re-estimate the treatment effect of crizotinib on overall survival.

The Evidence Review Group (ERG) was requested by NICE to provide additional commentary and validity checks on the new submission.

2 Commercial access agreement implementation

The commercial access agreement (CAA) is a simple confidential discount [redacted]

3 Cost effectiveness analysis: model changes

Full details of the proposed model changes are summarised in Table 2 (p13) of the company's submission. The company considers the Committee's preferred assumptions outlined in TA296 and provides ICERs that reflect two scenarios regarding treatment duration for crizotinib: (i) until radiographic progression (new base-case analysis) and (ii) beyond radiographic progression (scenario analysis). As regards data inputs, unit costs have been updated to reflect 2016 prices. The new base case analysis also includes an update to the overall survival data using more mature data from PROFILE 1007. All other clinical outputs are unchanged and reflect the Committee's preferred assumptions. However, it is important to note that the use of more mature data requires a change in crossover adjustment methods. As a result, the revised cost-effectiveness analysis is more than just a simple update of the 2013 submission and includes significant changes to the estimate of the treatment effect of crizotinib on overall survival.

3.1 Treatment beyond radiographic progression

In TA296, the Committee stated a preference for ICER estimates based on treatment with crizotinib beyond radiographic progression. The Committee discussed whether crizotinib would be discontinued at radiographic progression in clinical practice and heard from the clinical specialists that if a tumour has progressed, it would indicate reduced sensitivity to treatment and there would be a need to switch to another therapy. However, in the absence of a standard third-line therapy available at the time of TA296, the Committee concluded that symptomatic progression, rather than radiographic progression, was likely to be the trigger for treatment change or discontinuation.

The company acknowledges the Committee's previous preference for ICER estimates that assumed treatment with crizotinib beyond radiographic progression, given the lack of availability of a standard third-line therapy at the time of TA296. However, the company also highlights that NICE has now recommended ceritinib (another ALK-inhibitor) for use post-crizotinib (TA395). For this reason the company now considers it reasonable to assume that treatment with crizotinib would be unlikely to continue beyond radiographic progression in routine clinical practice. The company cites UK clinical experts who confirm that treatment beyond radiographic progression would no longer be expected, with one expert stating that treatment beyond progression may be a maximum of 1 month in some cases. For this reason, the company's revised base-case analysis now assumes that crizotinib treatment is stopped at radiographic progression.

The impact of assuming treatment costs beyond radiographic progression is now presented as a separate scenario. Within this scenario, the cost of crizotinib is estimated from the treatment duration Kaplan-Meier curve (based on a Weibull parametric function), instead of the Kaplan-Meier progression-free survival (PFS) curve. The treatment duration (median = 11 months, mean = 15.5 months) therefore exceeds PFS (median = 7.9 months, mean =10.1 months). The company assumes

that continued treatment with crizotinib beyond radiographic progression does not affect patients' utility (i.e. the company assumes the same utility for crizotinib and docetaxel after radiographic progression) and only impacts on costs. As a result, the company argues that ICERs assuming treatment beyond progression are likely to represent a conservative upper-bound of the 'true' cost-effectiveness of crizotinib.

3.2 Costs update

The company follows the Committee's preference from the 2013 appraisal and includes an administration cost for crizotinib. This estimate is based on the cost of administering oral chemotherapy (HRG code SB11Z; 2016 prices = £164 per cycle). However, the company previously argued in the 2013 appraisal that it was not appropriate to apply the cost of oral chemotherapy administration to crizotinib and restates this position in their latest submission. The company also identifies potential inconsistencies regarding the appropriate administration costs used in more recent NICE appraisals, including the use of a lower pharmacy dispensing cost as a proxy for administration costs in the appraisal of ceritinib for ALK-positive NSCLC. Despite these concerns, the company subsequently incorporates the cost of £164 per cycle within the new base case on the grounds of simplicity and consistency with the Committee's original preferences. However, the company notes that the resulting ICERs should be considered conservative.

The costs of administering docetaxel, the cost of generic docetaxel (eMIT costs) as well as the costs of IHC ALK-testing and FISH testing have also been increased to reflect 2016 prices (see Table 1).

Table 1: Costs inputs applied in TA296 and the new 2016 submission

COSTS	Original company submission (TA296)	Company submission 2016
Administration cost Crizotinib	£0	£164
Administration cost Docetaxel	£102.11	£251
IHC ALK-testing	£25	£75
FISH testing	Confidential	£120
Total cost of testing per patient receiving crizotinib	£630.06	£1638.12
Docetaxel	MIMS (cost not stated)	£17.7

3.3 New data on overall survival

Since the publication of TAG296, more mature overall survival data from PROFILE 1007 are now available and additional crossover adjustment analyses are presented and included in the new base case. The median follow-up is significantly longer for crizotinib (51 months versus 12.2 months in 2013) and for chemotherapy (53.1 months versus 12.2 months). 67% of patients have died in the crizotinib arm, 73% in the chemotherapy arm. However, the longer follow-up results in increasing switching rate (87% versus 64% previously) from chemotherapy to crizotinib (see Table 2).

Table 2: Main features of data used in TA296 and the new 2016 submission

DATA		Original company submission (TA296)	Company submission 2016
Crizotinib	Median follow-up (months)	12.2	51
	Have died (%)	28	67
Chemotherapy	Median follow-up (months)	12.2	53.1
	Have died (%)	27	73
Crossover	Switching from chemo (%)	64	87
	Switching to chemo (%)	Confidential	23

Due to the higher switching rates, the company now argues that the Committee's preferred method for crossover adjustment assumed in TA296, the Inverse Probability of Treatment and Censoring Weighted (IPTCW) method, is no longer appropriate. Therefore, in order to take into account for the higher switching rate in the more mature dataset, crossover adjustment analyses have been re-conducted with different methods considered including the Rank-Preserving Structural Failure Time Model (RPSFTM) and the Inverse Probability of Censoring Weighting (IPCW).

The company reports that the feasibility of the IPTCW and IPCW methods was assessed and neither considered appropriate given the higher variation in post-progression therapies in the mature OS dataset, such that the required assumptions for these methods were no longer considered likely to hold. The company therefore based their revised crossover analyses on the RPSFTM, which is more appropriate given the high switching rates. Three alternative approaches for the RPSFTM were used: the log-rank, Wilcoxon and Cox model-based Wald tests.

The crossover adjusted results for all three approaches resulted in a statistically significant improvement in OS for the crizotinib arm compared to the pooled chemotherapy arm. These are summarised in Table 3 together with the ITT results and the HR results previously reported in TA296 based on the less mature evidence. It is important to note that that the use of updated overall survival data together with a change in crossover adjustment methods result in significantly lower hazard ratios than those estimated for TA296.

In the absence of any clear methodological or clinical reasons to support the selection of one of the RPSFTM methods, the company selects the RPSFTM log-rank crossover adjustment method within the base-case analysis arguing that the estimated hazard ratio (0.38) provides a mid-range value compared to those derived from the Wilcoxon (0.402) and the Wald tests (0.35).

Table 3: Estimated hazard ratios in TA296 and the new 2016 submission

HR Overall Survival	Original company submission (TA296) Mean [95% CI]	Company submission 2016 Mean [95% CI]
ITT	1.02 [0.68,1.54]	0.854 [0.661,1.104]

IPTCW2	0.79 [0.45,1.40]	--
RPSFTM Log-rank	0.83	0.38 [0.04,0.99]
RPSFTM Wilcoxon	--	0.40 [0.07,0.97]
RPSFTM Wald	--	0.35 [0.04,0.85]

4 The company's submission

The company presents deterministic and probabilistic analysis (PSA) for a base case scenario which compares the use of crizotinib as a second-line treatment versus pooled chemotherapy, where 42% of patients received docetaxel and 58% received pemetrexed. The comparisons with docetaxel only and best supportive care are also discussed though not formally assessed with ICERs because of a lack of robust data.

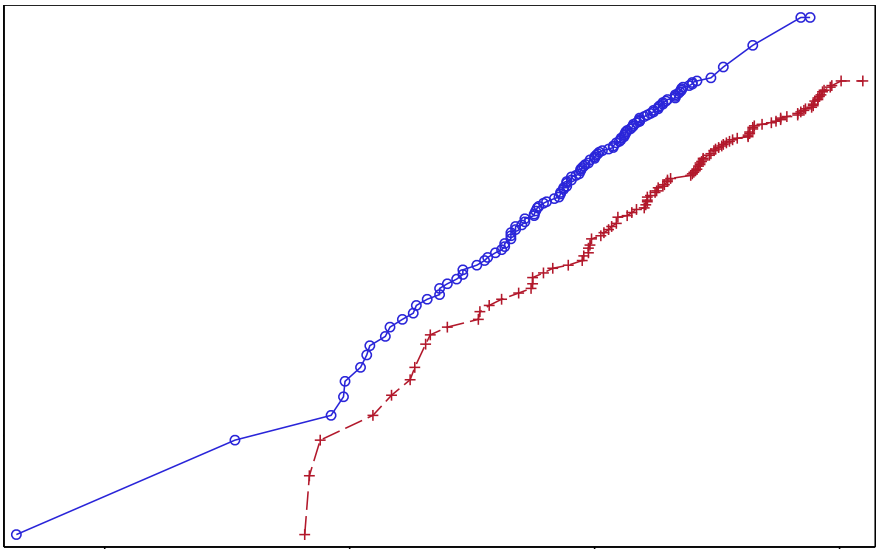
4.1 Crizotinib versus chemotherapy: base case scenario

The base-case results presented by the company in the 2016 submission are based on the more mature data from PROFILE 1007 and include the following assumptions:

- treatment continued until radiographic progression;
- crossover adjustment method: RPSFTM log-rank (Hazard ratio = 0.38 [95% CI 0.04, 0.99]);
- proportional hazards model;
- overall survival for crizotinib and chemotherapy is assumed to follow an exponential distribution

The validity of the proportional hazards assumption is assessed with a log hazard plot of the survivor functions for crizotinib and chemotherapy, adjusted for crossover. The plot does not show a departure from parallel lines and therefore does not invalidate the PH assumption (see Figure 1). An alternative scenario based on independent curves is also presented in the submission.

Figure 1: Log of negative log of estimated survivor functions for the RPSFTM log-rank (replication of Figure 2, company submission)



Crossover adjusted overall survival for crizotinib and chemotherapy is assumed to follow an exponential distribution. Although the log-logistic distribution appeared to provide the best statistical fit (see Table 4), the company subsequently excludes this distribution on the grounds of face validity. The company argues that fitting the chemotherapy curve with a log-logistic distribution yields a mean OS that exceeds 24 months, which seems implausible considering clinical opinion and historical estimates of docetaxel effect on OS (consistently reported to be less than 10 months). As a result, the exponential distribution is selected on the grounds of statistical goodness of fit (the lowest BIC and the second lowest AIC after the log-logistic) and face validity.

Table 4: AIC and BIC for OS curves (replication of Table 4, company submission)

Parametric model	AIC	BIC
Exponential	1924.47	1932.17
Generalised Gamma	1923.81	1939.20
Gompertz	1924.51	1936.06
Log-logistic	1921.66	1933.21
Log-normal	1926.73	1938.28
Weibull	1926.37	1937.92

In order to separate the respective effects of the new mature OS data and the confidential discount in the ICER changes, Table 5 compares the base-case results of the company's original submission

(immature data) based on list prices with results based on the 2016 submission (mature data), with and without the confidential discount.

Table 5: Base case company results with data from 2013 and data from 2016, with and without the CAA

	Original Company submission (TA296), without CAA and updated costs		**Company submission 2016, without CAA, updated costs and updated OS data**		**Company submission 2016, with CAA, updated costs and updated OS data**	
	Crizotinib	**Chemotherapy**	**Crizotinib**	**Chemotherapy**	**Crizotinib**	**Chemotherapy**
Intervention cost (£)	[redacted]	76	[redacted]	76	[redacted]	76
Other costs (£)	12,781	9,236	14,735	7,939	14,735	7,939
Total costs (£)	[redacted]	9,312	[redacted]	8,015	[redacted]	8,015
Difference in total costs (£)	[redacted]	NA	[redacted]	NA	[redacted]	NA
LYG	2.40	1.94	3.41	1.30	3.41	1.30
LYG difference	0.46	NA	2.11	NA	2.11	NA
QALYs	[redacted]	1.24	[redacted]	0.84	[redacted]	0.84
QALY difference	[redacted]	NA	[redacted]	NA	[redacted]	NA
ICER (£)	**96,254**	NA	[redacted]	NA	[redacted]	NA

Based on the "immature data" from 2013, the ICER of crizotinib is £96,254 per QALY. The use of more mature data, together with a change in crossover adjustment methods, increases the difference in life years gained (LYG) from 0.46 to 2.11 and reduces the ICER of crizotinib to [redacted] per QALY. The proposed CAA reduces the total cost of crizotinib from [redacted] to [redacted] and further reduces the base-case ICER of crizotinib to [redacted] per QALY.

The sensitivity of the base-case ICER is assessed for alternative assumptions based on a series of deterministic scenario and univariate sensitivity analyses. The cost-effectiveness of crizotinib is reported in Table 6 considering three scenarios: (i) treatment beyond progression, (ii) alternative methods for crossover adjustment and (iii) avoiding the proportional hazards assumption by fitting OS curves independently for each treatment.

Table 6: Results of deterministic scenario analyses with new discount (replication of Table 10, Company submission)

Input data or assumption	**Sensitivity analyses**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY)**
Base case ICER		[redacted]	[redacted]	[redacted]
Choice of crossover-adjusted hazard ratio	RPSFTM Wilcoxon test (HR=0.40)	[redacted]	[redacted]	[redacted]
	RPSFTM Wald test (HR=0.35)	[redacted]	[redacted]	[redacted]
Parametric model for OS	Independent curve selection*	[redacted]	[redacted]	[redacted]

Treatment beyond progression (TBP)	TBP included (additional cost only)	[redacted]	[redacted]	[redacted]

- When treatment continues beyond progression, the incremental cost of crizotinib increases to £[redacted]. QALY estimates do not change with this assumption. As a result, the deterministic ICER of crizotinib assuming treatment beyond progression (TBP) with the CAA is [redacted].
- Three methods are tested to adjust the hazard ratio for crossover (technically, it is more accurate to consider these as three different ways to implement the same method – see section 5.2) and give slightly different estimates for the hazard ratio (HR). HR estimates range from 0.35 (RPSFTM with Wald test) to 0.40 (RPSFTM with Wilcoxon test) and result in ICERs from £[redacted] to £[redacted] per QALY.
- When OS curves are fitted independently, the ICER of crizotinib decreases to £[redacted] per QALY.

A 'tornado' plot also reports separate univariate sensitivity analyses (see Figure 2). The univariate deterministic sensitivity analyses are presented for the base case and give evidence of small variations of the ICER. The most important variation is on treatment utility values for crizotinib but stays within £1,200 per QALY of the base case.

Figure 2: 'Tornado' diagram illustrating sensitivity of ICER to one-way parameters (replication of Figure 6, Company submission)


[redacted]

The company additionally conducts probabilistic sensitivity analysis (PSA) on the base case. The probabilistic ICER ([redacted] per QALY) is reported to be very close to the deterministic

ICER ([redacted] per QALY). The PSA results (10,000 simulations) suggest that crizotinib has a [redacted]% probability of being cost-effective at the £50,000 per QALY threshold.

4.2 Crizotinib versus docetaxel only

The mature crossover adjusted analyses are based on the pooled chemotherapy arm (42% of patients received docetaxel and 58% received pemetrexed). Data from PROFILE1007 preclude robust analyses assuming docetaxel only as a comparator: the subgroup is considered too small (n=72 vs the entire pooled arm n=174) and the study was not pre-stratified to measure OS for the docetaxel only subgroup. However, the company notes that the control group appears to respond better to pemetrexed than docetaxel; the mature trial data suggests that the 12 month survival probability is [redacted] with pemetrexed versus [redacted] with docetaxel.

As a result, the company expects the crossover adjusted hazard ratio to be lower for docetaxel only and argues that the base case ICER versus pooled chemotherapy subsequently overestimates the true ICER of crizotinib versus docetaxel.

4.3 Crizotinib versus best supportive care

The company does not present any new evidence as regards the cost-effectiveness of crizotinib versus BSC. The company relies on the estimates from the original submission where the hazard ratio for OS for crizotinib versus BSC was 0.37 (0.12, 0.89); which was much lower than the hazard ratio versus docetaxel. The company therefore argues that if crizotinib demonstrates it is cost-effective versus docetaxel, it should be cost-effective versus BSC by transitivity.

5 ERG review

5.1 ERG verification checks

The ERG undertook a series of verification checks in relation to the new analysis performed and successfully replicated the base case results and scenario analyses.

The ERG identified some potential confusion, mostly semantic, regarding the implementation of Proportional Hazards (PH) models. The company suggests two alternative models and argues that one assumes PH, whereas the other avoids the PH assumption by fitting independent curves separately to each treatment. For each of these models the company provides parametric estimations using six different distributions: Exponential, Weibull, Gompertz, Log-Normal, Log-Logistic and Generalised Gamma.

Theoretically, the methodology presented by the company is not a choice between a PH model and a non-PH model. Rather the choice is between fitting one parametric model to the whole dataset (with a covariate for treatment) or fitting a specific parametric model to each treatment arm separately. When

the first method is preferred, the company actually relies either on the *PH assumption* when Exponential, Weibull or Gompertz distributions are used or on the *Accelerated Failure Time* (AFT) assumption when Log-logistic, Log-Normal or Gamma distributions are used. It is important to notice that the different models are still correctly implemented in the economic model and the ERG's further remarks do not question the internal validity of the company's results. However, the methodology, as it is described by the company, is not accurate and the interpretation of the treatment effects can be misleading.

Indeed, when modelling the effect of a treatment on overall survival between two groups of patients, one can either assume that the effect of treatment is proportional - in which case a proportional hazards model will be preferred - or consider that the proportionality assumption does not hold and favour an accelerated failure time (AFT) model. These two models differ mainly on three dimensions: (i) the underlying assumption on the treatment effect; (ii) the interpretation of the treatment effect; (iii) the range of distributions "available" to parametrise the model.

Under a PH model, the treatment is assumed to act proportionally on the hazards of death, independently of the time scale. The treatment effect, ψ, is called a hazard ratio and must be interpreted as follows: at any time, the hazards of death is ψ times higher for an individual receiving the new treatment than for an individual receiving the standard treatment. When parametrising the model, the choice of distributions that allow for a PH model is quite restrictive: only the Exponential, the Weibull and the Gompertz distributions can be used.

Under an AFT model, the treatment acts multiplicatively on the time scale. The treatment effect, ϕ^{-1}, is called an acceleration factor and must be interpreted as follows: the lifetime of an individual receiving the new treatment is ϕ times the lifetime of an individual on standard treatment. An interpretation referring to any percentile (including the median) is also valid: the median survival time of an individual receiving the new treatment is ϕ times higher than the median survival time for an individual receiving the standard treatment. AFT models can be parameterised with Exponential and Weibull distributions (which have both PH and AFT properties) as well as Log-Normal, Log-Logistic and Gamma distributions.

Independent estimation of both arms avoids both PH and AFT assumptions but is more costly in terms of parameter estimation.

This potential confusion does not call into question the actual implementation of the assumptions with the executable model and the subsequent results. Rather the ERG considers that there is a lack of clarity in the submission regarding the procedure used to derive the stated cross-over adjusted hazard ratio of 0.38 (i.e. whether based on a fully parametric or semi-parametric approach) and specific

reference to how this hazard ratio actually relates to the economic model. For example, the crossover-adjusted hazard ratio of 0.38 (95% CI 0.042 to 0.991) stated by the company to be used in the updated base-case analysis clearly does not make any theoretical sense in the case of an AFT model when Log-logistic, Log-Normal or Gamma distributions are used. Furthermore, it is not clearly highlighted within the submission that both the interpretation of the treatment effect (i.e. whether the effect estimate used is a hazard ratio or acceleration factor) and the magnitude of the actual treatment effect applied within the economic model differ according to the specific parametric assumptions applied. Hence, instead of there being a single effect as referred to in the company submission, the implementation of economic model across the range of different parametric distributions is actually based on a range of different effect estimates all apparently derived from the same log-rank cross-over adjusted method.

Based on the distributions' parameters used by the Company, the ERG was able to summarise the different hazard ratios or acceleration factors that are actually used with the economic model for the treatment effect of crizotinib on OS (see Table 7). For instance, the hazard ratio applied to the baseline function, estimated through the RPSFTM log-rank method and parametrised with an exponential distribution (base case scenario), is actually 0.34; which is equivalent to an inverse of the acceleration factor of 2.94. In contrast, the Log-Logistic distribution is associated with a significantly lower inverse acceleration factor of 2.72[1].

The ERG concludes that the difference between the stated hazard ratio estimate and those actually applied in the model are simply due to differences in the estimation procedure of the RPSFTM method across the different parametric distributions, rather than this being an issue of factual accuracy.

Table 7: Parametric estimates of the treatment effect

Crossover method	Distribution	Hazard Ratio ψ	1/Acceleration factor ϕ
RPSFTM Log rank	Exponential	0.34	2.94
	Weibull	0.33	2.94
	Gompertz	0.38	NA
	Log-Logistic	NA	2.72
	Log-Normal	NA	2.64
	Gamma	NA	2.81
RPSFTM Wilcoxon	Exponential	0.36	2.78
RPSFTM Wald	Exponential	0.32	3.14
IPTCW2	Exponential	0.79	1.27

5.2 ERG further validation and critique

[1] For interpretation of the inverse of the acceleration factor, recall that $\phi = \frac{Median\ OS\ Crizotinib}{Median\ OS\ Chemo}$.

Although mature data present longer follow-up and possibly more accurate data on overall survival, they are also increasingly affected by crossover. The randomisation design implemented in PROFILE 1007 has almost vanished since 87% of the original control group has eventually had access to crizotinib. Such high crossover rates, despite the attempts to control for it, are likely to introduce significant uncertainty around the estimates of the treatment effect.

Issue 1: Uncertainty around crossover adjustment methods

There are several methods available to deal with data affected by crossover, each has its own limitations, but the common objective is to create a "counterfactual", i.e. to reconstruct data for the control arm as if crossover had not occurred. This "reconstruction" is obviously not neutral on the final estimates of the treatment effect and creates three levels of uncertainty. The first level of uncertainty arises from the choice of crossover adjustment method. The second level concerns the estimation of the counterfactual baseline function. The third level arises from the parametrisation of the survivor function and the estimate of the hazard ratio. The ERG notes that although the third level of uncertainty is correctly assessed by the company through the Probabilistic Sensitivity Analysis, the first two sources of uncertainty do not seem to be fully taken into account.

As regards the methods available, the more commonly used are the IPTCW and the RPSFTM.

The IPTCW method uses patients from the control group that never switched to create a counterfactual control group. However, as argued by the Company, the number of patients who remained in the control arm ([redacted]) is too low to implement the method.

The company therefore uses the RPSFTM method to create a counterfactual output, a crossover adjusted baseline function. This method relies on a structural model where the observed overall survival and the counterfactual (the overall survival that would have been observed if crossover had not occurred) are related by a constant acceleration factor. It then uses the fact that, due to initial randomisation, the counterfactual should be the same between control and treatment groups. Therefore, the estimation procedure consists in computing the counterfactual for different values of the acceleration factor and testing for equality of the counterfactual across the two groups until the test p-value reaches its maximum. Different tests of equality are available. The company has conducted the estimations using three different tests: the log-rank, the Wald and the Wilcoxon tests. However, the impact of the test of equality used has to be marginal on the estimates: the only difference is the distribution used to build the test statistic. However, the estimation procedure and more importantly the structural assumptions remain exactly the same. Consequently, the three "methods" presented by the company are actually the same RPSFTM method but based on three different tests of equality. As a result, the "consistency of the estimates" reported by the company

cannot be considered as sufficient evidence of low uncertainty as regards the estimation of the treatment effect. The uncertainty around the choice of crossover adjustment method can only be assessed by the use of alternative methods. Although the IPTCW is not recommended in this case, there are other methods that could have been implemented such as the 2-stage or the iterative parametric estimation methods (IPE) [1]. The company does not provide any discussion regarding the feasibility or appropriateness of these alternative methods. However, the ERG notes that both IPE and the 2-stage methods were investigated by the company in the recent appraisal of crizotinib in previously untreated patients (NICE ID865), with the 2-stage method being selected in the base-case analysis.

The second level of uncertainty arises from the estimates of the counterfactual baseline function. Under the RPSFTM method, regardless of the equality test that is used, the estimated "acceleration factor" which links the observed overall survival to the counterfactual, and consequently drives the estimate of the baseline function, is also subject to uncertainty. It would have been necessary to compute a confidence interval as well as a p-value for this parameter. It is also important to notice that the acceleration factor parameter is different from the hazard ratios reported by the company, which are estimated considering the counterfactual as the "true" baseline function. The uncertainty around the hazard ratio (the third level of uncertainty), correctly assessed by the company's probabilistic sensitivity analysis, does not take into account the uncertainty coming from the counterfactual estimates.

The ERG is concerned that the estimation procedure of the RPSFTM method had been "black boxed" and the confidence interval of the estimated acceleration factor was not reported by the company. Furthermore, there is no evidence of recensoring following the implementation of the RPSFTM method. Indeed, counterfactual events that fall beyond the time horizon have to be censored, which might be costly especially with a small sample.

In the presence of these various uncertainties, the ERG considers that the resulting estimates of the treatment effect of crizotinib should be considered highly uncertain. Given the magnitude of the difference between the effect estimates based on the more mature data and those previously reported in TA296, the ERG considers that the robustness of the estimates should have been further explored by the company using alternative methods and further information provided regarding the estimation procedure of the RPSFTM method and the confidence interval of the estimated acceleration factor.

The company presents additional evidence to support the validation of the OS modelling. This evidence includes recent UK audit data from the [redacted] The UK audit data of previously treated ALK-positive patients who were then treated with an ALK-inhibitor ([redacted]) appears to show similar median OS estimates ([redacted]) as that

derived from the exponential survival distribution for crizotinib based on the RPSFTM log-rank method (median = 32 months). Comparable estimates are also reported for the 10 ALK-positive patients from the UK audit data that were not subsequently treated with an ALK-inhibitor ([redacted] vs 10.9 months based on exponential survival distribution for the pooled chemotherapy arm). Although the ERG acknowledges the similarity in the estimates, the ERG considers that the UK audit provides useful supportive information as opposed to representing a formal validation approach. No data are provided on the patient characteristics from the UK audit data or on whether the groups were balanced or not. Consequently, the ERG does not consider that the audit data provides a robust basis to determine the validity of the current results and that significant uncertainty still remains concerning the treatment effect of crtizotinib on OS.

In the absence of any alternative crossover methods presented by the company, the ERG undertook additional scenario analyses to consider the robustness of the ICER estimates to the inevitable uncertainties arising from the high levels of crossover. The ERG used the exponential distribution based on the new mature data and explored additional scenarios based on two alternative hazard ratio estimates for OS. In the absence of alternative crossover methods reported by the company or access to the individual patient data, the ERG was restricted to considering plausible estimates based on external evidence and assumptions.

- The first ERG scenario assumes the same hazard ratio for OS as reported in the original trial publication for progression free-survival (PFS); HR1= 0.49 (0.37-0.64) [2]. The rationale for this scenario is that the effect estimate for PFS is not affected by crossover and generally (although not universally) hazard ratios for OS are normally not greater than for PFS. A recent analysis by the FDA explores trial-level and patient-level associations between progression-free survival (PFS), and overall survival (OS) in 14 advanced NSCLC trials (including crizotinib [3]). A relationship between PFS and OS was not established at a trial level, with the authors indicating that this was possibly because of cross-over and longer survival after progression in the targeted therapy and first-line trials. However, in the patient-level responder analyses of the 14 trials, patients who achieved a response had better PFS and OS compared with nonresponders and the same HR was reported for both PFS and OS (PFS: HR, 0.40; 95% CI, 0.38 to 0.42; OS: HR, 0.40; 95% CI, 0.38 to 0.43). Consequently, the ERG considered assuming the same HR for both PFS and OS to be a plausible alternative scenario.
- The second scenario assumed the same crossover hazard ratio for OS reported for crizotinib in previously untreated patients, estimated through RPSFTM method with the Wilcoxon test: HR2= 0.60 (0.27-1.42) [4]. The rationale for this scenario was to ensure consistency in the treatment effect estimates assumed for both previously untreated and previously treated patients.

Table 9 summarises the variation in the median and mean OS across the different approaches, demonstrating the marked impact that different estimates of the HR has on subsequent OS estimates.

Table 8: Median and mean OS for cizotinib versus chemotherapy using alternative hazard ratios - base case with PAS, updated costs and mature data

Approach	HR	Median OS			Mean OS		
		Criz	Chemo	Gain	Criz	Chemo	Gain
RPSFTM Log-rank	0.38	[redacted]	[redacted]	21.1	[redacted]	[redacted]	29.6
RPSFTM Wilcoxon	0.40	[redacted]	[redacted]	20.2	[redacted]	[redacted]	28.3
RPSFTM Wald	0.35	[redacted]	[redacted]	22.4	[redacted]	[redacted]	31.2
Scenario 1: HR=PFS	0.49	[redacted]	[redacted]	11.3	[redacted]	[redacted]	16.2
Scenario 2: Previously untreated HR (RPSFTM)	0.60	[redacted]	[redacted]	7.3	[redacted]	[redacted]	10.4

Table 10 reports the ICER estimates based on the alternative scenarios conducted by the ERG based on the assumption that crizotinib is stopped at the point of radiographic progression. Assuming a HR for OS of 0.49 (i.e. the same as PFS) increases the ICER from [redacted] to [redacted]. Assuming a HR for OS of 0.60 (i.e. the same as reported for previously untreated patients) increases the ICER to £[redacted] per QALY.

Table 9: ERG's estimates of crizotinib ICER using alternative hazard ratios - base case with PAS, updated costs and mature data, <u>treatment until progression</u>.

	HR1=0.49 Progression in the original trial		HR2=0.60 Previously untreated	
	Crizotinib	Chemotherapy	Crizotinib	Chemotherapy
Intervention cost (£)	[redacted]	76	[redacted]	76
Other costs (£)	12,939	7939	12,118	7939
Total costs (£)	[redacted]	8015	[redacted]	8015
Difference in total costs (£)	[redacted]	NA	[redacted]	NA
LYG	2.48	1.30	2.07	1.30
LYG difference	1.18	NA	0.77	NA
QALYs	[redacted]	0.84	[redacted]	0.84
QALY difference	[redacted]	NA	[redacted]	NA
ICER (£)	[redacted]	NA	[redacted]	NA

Issue 2: Treatment duration

The ERG considers the company's reasoning regards the use of crizotinib beyond progression reasonable and that a scenario which crizotinib is discontinued at progression is likely to be more representative of how patients will now be treated in routine clinical practice. The ERG, however, has significant concerns regarding the base-case analysis carried out by the company and does not consider it is representative of the counterfactual scenario where patients do not receive crizotinib

post progression. This is because the scenario presented by the company considers only the implication of stopping treatment beyond radiographic progression on treatment costs and not on OS. The OS benefit assumed in the model is partially attributable to differences in treatment received by crizotinib and chemotherapy patients post progression. Hence, it does not appear reasonable to continue to assume that these OS benefits are realised without any additional costs (i.e. whether these costs relate to continued use of crizotinib or to a subsequent ALK inhibitor). For this reason, the ERG considers that the base-case assumption that assumes the cost of crizotinib is stopped at the point of radiographic progression is likely to result in overly optimistic estimates of the ICER.

Table 10 reports the ICER estimates based on the alternative scenarios conducted by the ERG based on the assumption that crizotinib is continued beyond progression. Assuming a HR for OS of 0.49 (i.e. same as PFS) increases the ICER from [redacted] to [redacted] per QALY. Assuming a HR for OS of 0.60 (i.e. same as reported for previously untreated patients) increases the ICER to £[redacted] per QALY.

Table 10: ERG's estimates of crizotinib ICER using alternative hazard ratios - base case with PAS, updated costs and mature data, <u>treatment beyond progression.</u>

	HR1=0.49 Progression in the original trial		**HR2=0.60 First line submission**	
	Crizotinib	**Chemotherapy**	**Crizotinib**	**Chemotherapy**
Intervention cost (£)	[redacted]	76	[redacted]	76
Other costs (£)	13,768	7939	12,947	7939
Total costs (£)	[redacted]	8015	[redacted]	8015
Difference in total costs (£)	[redacted]	NA	[redacted]	NA
LYG	2.48	1.30	2.07	1.30
LYG difference	1.18	NA	0.77	NA
QALYs	[redacted]	0.84	[redacted]	0.84
QALY difference	[redacted]	NA	[redacted]	NA
ICER (£)	[redacted]	NA	[redacted]	NA

5.3 ERG summary and conclusions

The ERG is satisfied that the company appropriately implemented the confidential discount scheme and the specific adjustments that the NICE AC considered to be most plausible. The ERG successfully replicated the company base-case and the main scenario analyses.

The key areas of uncertainty identified by the ERG relate to the re-estimation of the treatment effect of crizotinib on OS based on the more mature data from PROFILE 1007 and the revised assumption employed in the new base case analysis that treatment with crizotinib is stopped at the point of radiographic progression.

The ERG accepts the company's rationale for using an alternative method (RPSFTM) for adjusting for crossover given the very high rate of switching evident in the more mature data now available. Although the company presents three approaches for the RPSFTM, the ERG does not concur with the company conclusions that the narrow range in the subsequent hazard ratio estimates (0.35 to 0.40) are sufficient to conclude a consistent improvement on the interim immature analyses. The three approaches are actually based on the same RPSFTM method and simply use different tests of equality. Consequently, the impact of the different approaches is marginal as would be expected. The ERG considers that uncertainty around the choice of crossover adjustment method can only be assessed by comparing the use of alternative methods. Given the magnitude of the difference between the effect estimates based on the more mature data and those previously reported in TA296, the ERG considers that the robustness of the estimates should have been further explored by the company using alternative methods (e.g. 2-stage and IPE) and providing further information regarding the estimation procedure of the RPSFTM method and the confidence interval of the estimated acceleration factor.

Additional exploratory scenarios were therefore undertaken by the ERG to further assess the robustness of the base-case ICER presented by the company ([redacted] per QALY) based on the assumption that crizotinib is stopped at radiographic progression. The ERG scenarios were selected based on plausible alternative estimates both of which were less favourable than assumed by the company assumed by the company. These alternative scenarios increased the ICER to between [redacted] and [redacted]. Importantly, neither of these scenarios is considered by the ERG to represent an alternative 'ERG base-case' but rather these scenarios are presented to consider the impact on the base-case ICER estimate to alternative effect estimates which would appear equally plausible. Indeed, the ERG also notes that the HR for OS for responders vs non-responders (HR=0.40) reported from the individual patient analysis of 14 NSCLC trials is close to the base-case HR estimate assumed by the company (HR = 0.38) for all patients receiving crizotinib. Consequently, the effect estimate applied in the model is similar to that which would have been predicted from the 14 trials based on a 100% response difference between treatments.

A further important source of uncertainty relates to the revised assumption employed in the new base-case analysis regarding the treatment duration of crizotinib. Given the recent positive recommendation of ceritinib, the ERG accepts the company's reasoning that the discontinuation of crizotinib at radiographic progression is now more likely to representative of how patients will now be treated in routine clinical practice. However, the ERG does not consider it reasonable to conclude that the same OS benefits are realised without any additional costs being incurred. For this reason, the ERG considers that the base-case assumption that assumes the cost of crizotinib is stopped at the point of radiographic progression is likely to result in overly optimistic estimates of the ICER. Consequently, the ERG considers that the 'true' ICER of crizotinib is likely to lay between the two

treatment duration scenarios (company ICER estimates of [redacted] and [redacted]). The alternative ICERs presented by the ERG range from [redacted] to [redacted] (treatment stopped at radiographic progression) and £[redacted] - [redacted] (treatment continued beyond progression) demonstrating the potential sensitivity of the ICER to the uncertainties surrounding the treatment duration and magnitude of the effect on OS. However, the ERG scenarios suggest that the ICER for crizotinib is likely to remain below £50,000 per QALY for both treatment duration scenarios when HR for OS for crizotinib is assumed to be at least equal to that previously reported for PFS (i.e. HR for OS ≤0.49).

The ERG appreciates that the company has sought to provide additional external evidence to demonstrate the validity of their estimates. Although the ERG acknowledges the similarity in the estimates, the ERG considers that the UK audit provides useful supportive information as opposed to representing a formal validation approach. The ERG also acknowledges that the company has employed conservative assumptions with respect to the administration costs of crizotinib (i.e in light of the lower cost proxy estimates based on pharmacy dispensing costs used in a more recent appraisal of another ALK inhibitor), the use of pooled chemotherapy data for the control group and assumptions concerning health utility in the post-progression period for crizotinib (treatment beyond progression scenario).

References

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2. Shaw, A.T., et al., *Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.* New England Journal of Medicine, 2013. **368**(25): p. 2385-2394.
3. Blumenthal, G.M., et al., *Overall Response Rate, Progression-Free Survival, and Overall Survival With Targeted and Standard Therapies in Advanced Non–Small-Cell Lung Cancer: A US Food and Drug Administration Trial-Level and Patient-Level Analyses.* Journal of Clinical Oncology, 2015: p. JCO. 2014.59. 0489.
4. Solomon, B.J., et al., *First-line crizotinib versus chemotherapy in ALK-positive lung cancer.* New England Journal of Medicine, 2014. **371**(23): p. 2167-2177.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296) [ID1010]

You are asked to check the ERG report from the Centre for Reviews and Dissemination - York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 09 September 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Correct scheme terminology for discount

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 1 and following: Discount cited as “Commercial Access Agreement (CAA)”.	Change CAA to PAS	Our original submission did contain a CAA [redacted].	Corrected in the erratum document on pages 1,7 and 8.

Issue 2 CIC change

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 5: The “76” for intervention costs need not be CIC	Remove CIC on “76”	No confidentiality needed; expected this was just a typo on shading.	CIC removed or “76” in erratum document on page 7.

ERG review of the submission for the reconsideration of crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene under the proposed new CDF criteria

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Date 01/09/2016

1 Introduction

NICE did not recommend crizotinib for treating adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) (TA296, September 2013). The Committee concluded that the ICER on which to base a decision for crizotinib compared with docetaxel would be more than £100,000 per QALY gained, and for crizotinib compared with best supportive care would be more than £50,200 per QALY gained.

Crizotinib is currently funded through the previous Cancer Drugs Fund (CDF) and is now being re-considered by NICE under the new proposed CDF criteria. The company has proposed a Patient Access Scheme (PAS) based on a simple confidential discount. The company also includes a revised economic analysis taking into account the Committee's preferred assumptions identified in TA296. Unit costs are updated to reflect 2016 prices and a more mature dataset from PROFILE 1007 is used to re-estimate the treatment effect of crizotinib on overall survival.

The Evidence Review Group (ERG) was requested by NICE to provide additional commentary and validity checks on the new submission.

2 Patient Access Scheme (PAS)

The PAS is a simple confidential discount [redacted]

(immature data) based on list prices with results based on the 2016 submission (mature data), with and without the confidential discount.

Table 1: Base case company results with data from 2013 and data from 2016, with and without the PAS

	Original Company submission (TA296), without PAS and updated costs		**Company submission 2016, without PAS, updated costs and updated OS data**		**Company submission 2016, with PAS, updated costs and updated OS data**	
	Crizotinib	**Chemotherapy**	**Crizotinib**	**Chemotherapy**	**Crizotinib**	**Chemotherapy**
Intervention cost (£)	[redacted]	76	[redacted]	76	[redacted]	76
Other costs (£)	12,781	9,236	14,735	7,939	14,735	7,939
Total costs (£)	[redacted]	9,312	[redacted]	8,015	[redacted]	8,015
Difference in total costs (£)	[redacted]	NA	[redacted]	NA	[redacted]	NA
LYG	2.40	1.94	3.41	1.30	3.41	1.30
LYG difference	0.46	NA	2.11	NA	2.11	NA
QALYs	[redacted]	1.24	[redacted]	0.84	[redacted]	0.84
QALY difference	[redacted]	NA	[redacted]	NA	[redacted]	NA
ICER (£)	**96,254**	NA	[redacted]	NA	[redacted]	NA

Based on the "immature data" from 2013, the ICER of crizotinib is £96,254 per QALY. The use of more mature data, together with a change in crossover adjustment methods, increases the difference in life years gained (LYG) from 0.46 to 2.11 and reduces the ICER of crizotinib to [redacted] per QALY. The proposed PAS reduces the total cost of crizotinib from [redacted] to [redacted] and further reduces the base-case ICER of crizotinib to [redacted] per QALY.

The sensitivity of the base-case ICER is assessed for alternative assumptions based on a series of deterministic scenario and univariate sensitivity analyses. The cost-effectiveness of crizotinib is reported in Table 6 considering three scenarios: (i) treatment beyond progression, (ii) alternative methods for crossover adjustment and (iii) avoiding the proportional hazards assumption by fitting OS curves independently for each treatment.

Table 2: Results of deterministic scenario analyses with new discount (replication of Table 10, Company submission)

Input data or assumption	**Sensitivity analyses**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY)**
Base case ICER		[redacted]	[redacted]	[redacted]
Choice of crossover-adjusted hazard ratio	RPSFTM Wilcoxon test (HR=0.40)	[redacted]	[redacted]	[redacted]
	RPSFTM Wald test (HR=0.35)	[redacted]	[redacted]	[redacted]
Parametric model for OS	Independent curve selection*	[redacted]	[redacted]	[redacted]
Treatment beyond progression	TBP included (additional	[redacted]	[redacted]	[redacted]

(TBP)	cost only)			

- When treatment continues beyond progression, the incremental cost of crizotinib increases to [redacted]. QALY estimates do not change with this assumption. As a result, the deterministic ICER of crizotinib assuming treatment beyond progression (TBP) with the PAS is [redacted].
- Three methods are tested to adjust the hazard ratio for crossover (technically, it is more accurate to consider these as three different ways to implement the same method – see section 5.2) and give slightly different estimates for the hazard ratio (HR). HR estimates range from 0.35 (RPSFTM with Wald test) to 0.40 (RPSFTM with Wilcoxon test) and result in ICERs from £[redacted] to £[redacted] per QALY.
- When OS curves are fitted independently, the ICER of crizotinib decreases to £[redacted] per QALY.

A 'tornado' plot also reports separate univariate sensitivity analyses (see Figure 2). The univariate deterministic sensitivity analyses are presented for the base case and give evidence of small variations of the ICER. The most important variation is on treatment utility values for crizotinib but stays within £1,200 per QALY of the base case.

Figure 1: 'Tornado' diagram illustrating sensitivity of ICER to one-way parameters (replication of Figure 6, Company submission)

The company additionally conducts probabilistic sensitivity analysis (PSA) on the base case. The probabilistic ICER ([redacted] per QALY) is reported to be very close to the deterministic ICER ([redacted] per QALY). The PSA results (10,000 simulations) suggest that crizotinib has a [redacted]% probability of being cost-effective at the £50,000 per QALY threshold.