NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

Pre-meeting briefing

Crizotinib for ROS1-positive advanced non-small cell lung cancer

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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Key issues (1): Decision Problem

- Company did not include following comparators which were stated in the scope
  - first line
    - Third generation chemotherapy plus platinum (cisplatin/carboplatin)
    - Single agent chemotherapy
    - Pemetrexed monotherapy
  - second line
    - Docetaxel plus nintedanib
    - Best supportive care

  Is it appropriate for the company to exclude these comparators?

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Key issues (2): Companion diagnostics

- How would ROS1 positivity be tested in the clinical practice? Company proposes
  - an initial test by Immunohistochemistry (IHC) followed by
  - a confirmatory test, in those detected positive by IHC, through a more expensive and 100% accurate Fluorescence In Situ Hybridization (FISH) test.

  Is that correct?
- Company envisages that
  - all patients with non-squamous NSCLC will be tested for ROS1 upfront alongside EGFR and ALK,
  - also explored sequential testing i.e. ROS1 tested only in those tested negative for EGFR and ALK.

Which strategy is more likely to happen in the clinical practice?

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Key issues (3): Clinical effectiveness

- Is it appropriate for the company to use outcome data from patients with ALK-positive advanced NSCLC as a proxy for the outcome data of patients with ROS1-positive advanced NSCLC?

  The ERG stated that the following 2 assumptions must hold for the company's approach to be valid:

  - ROS1-positive advanced NSCLC and ALK-positive advanced NSCLC patient populations must be comparable in terms of baseline characteristics
  - Patients recruited to the ALK-positive advanced NSCLC trials must be representative of the ALK-positive advanced NSCLC patient population (and consequently the ROS1-positive advanced NSCLC patient population, if assumption 1 holds) that would be seen in NHS clinical practice
- Do the 2 required assumptions hold?

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Key issues (4): Clinical effectiveness

- Company's view:
  - cited clinical and biological plausibility
  - Company stated '*Based on the similarities between ROS1- and ALK-positive NSCLC, the generalisability of data from ALK-positive patients to the ROS1-positive patients has been recognised by the European Medicines Agency (EMA) in their approval of crizotinib and is supported by 12 UK leading clinical experts from a recent UK advisory board.*'
- ERG's comments:
  - Clinical advice to ERG suggests that ROS1-positive advanced NSCLC and ALK-positive advanced NSCLC patient populations are comparable in terms of baseline characteristics (assumption 1)
  - Clinical advice to the ERG suggests that patients in PROFILE 1001 and patients in PROFILE 1014 and 1007 have similar baseline characteristics and broadly represent patients likely to be treated in the NHS (assumption 2)
  - ERG noted that the median PFS varied across PROFILE 1001, 1014 and 1007. The ERG stated that the variation in PFS brings into question the comparability of the ALK-positive and ROS1-positive patient populations (assumption 1)
  - ERG noted that a previous appraisal patients in PROFILE 1014 were considered by a previous Appraisal Committee (TA406) not be representative of patients likely to be treated with crizotinib in the NHS (assumption 2)

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Key issues (5): Clinical effectiveness

- How robust is the PFS data from PROFILE 1014 and 1007?
  - ERG concluded that the proportional hazards assumption was not valid for PFS, and that the hazard ratios for PFS data from both trials should be interpreted with caution
- How robust is the OS data from PROFILE 1001, 1014 and 1007?
  - OS data from PROFILE 1001 were immature, with only 30% of patients having died at the latest data cut-off date (2014)
  - ERG considers the RPSFTM-adjusted hazard ratios for OS in PROFILE 1014 are unlikely to be valid and should be interpreted with caution
  - ERG considers the PFS hazard ratio in PROFILE 1001 is likely to be closer to the true OS hazard ratio than the RPSFTM-adjusted OS hazard ratio. However, the ERG also noted that the true OS hazard ratio may still be less than the PFS hazard ratio, and that the company's hazard ratio for "crossover-adjusted" OS should be interpreted with caution

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Key issues (6): Cost effectiveness

- Is the company's economic model appropriate for determining the cost effectiveness of crizotinib for ROS1-positive advanced non-small cell lung cancer?
  - The evidence underpinning the base case first- and subsequent-line models is from a proxy population (ALK-positive advanced NSCLC) rather than the population of interest (ROS1-positive advanced NSCLC). ERG stated that the impact of this assumption on cost effectiveness estimates is unknown, since the evidence for the ROS1-positive advanced NSCLC population is severely limited
- How appropriate are the assumptions in the company's economic model?
  - ERG stated that the company submission relies heavily on the assumptions and modelling approaches used in three previous STAs (TA406, TA422 and TA296) and company has not provided sufficient justification for use of these assumptions and approaches, except that they were previously accepted.
  - The ERG was unable to investigate the effects of specific key assumptions in the model as a result of the limited functionality of the model

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Key issues (7): Cost effectiveness

- How robust are the company's estimates of post progression survival ?
  - Estimates of post progression survival gain in the first- and subsequent-line base cases are substantially greater than estimates of progression-free survival gain. This means that treatment effect on overall survival is greater than treatment effect on progression-free survival, which the ERG does not consider to be supported by the evidence available
- ERG explored 2 additional scenarios for overall survival modelling
  - assuming continued treatment effect on survival (as seen in pre-progression stage) after progression
  - assuming no benefit of crizotinib after progression

  Which is the committee's preferred method?
- How robust are the company's progression-free survival utility values?
  - For patients who received treatment with pemetrexed + platinum in the first-line model?
    - ERG was concerned that the progression-free survival utility value may not be representative of the whole time that these patients spend in the progression-free state, as it is based on EQ-5D responses collected only whilst patients are on treatment

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Key issues (8): Cost effectiveness

- How robust is the company's PROFILE 1001 scenario analysis?
  - The ERG stated that estimates of overall survival, progression-free survival and time to treatment discontinuation were based on parametric models with low levels of face validity and clinical plausibility.
- Costing: ERG identified that in the company's analyses
  - Cost of treating pulmonary embolism is underestimated
  - For subsequent-line, ROS1+ positivity should only be tested only in those who have not been tested positive for ALK and EGFR mutation (sequential test)
  - For upfront testing, NHS may get a discount when testing for more than one mutation at the same time

  ERG consider them to have small effect on the ICER.
- What are the most plausible ICERs for crizotinib for treating ROS1-positive advanced NSCLC?

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Crizotinib (Xalkori, Pfizer)

Mechanism of action		Tyrosine kinase inhibitor inhibits • ROS1 proto-oncogene receptor tyrosine kinase **and** • anaplastic lymphoma kinase (ALK) which lead to the inhibition of tumour cell growth
Administration and dosage		Oral 250 mg twice daily (a total of 500 mg daily)
Marketing authorisation	**New (subject of this appraisal)**	• on 25th August 2016: 'for the treatment of adults with ROS1-positive advanced NSCLC.'
	Existing licensed indications	• first-line treatment of ALK-positive advanced NSCLC (November 2015) recommended in NICE TA 406 • for the previously treated ALK-positive advanced NSCLC (October 2012) recommended in NICE TA 422
Companion diagnostic		accurate and validated assay for either ROS1 or ALK
List price		£4,689.00 for 60 capsules of 200 mg or 250 mg
PAS discount		simple discount (magnitude: commercial in confidence)

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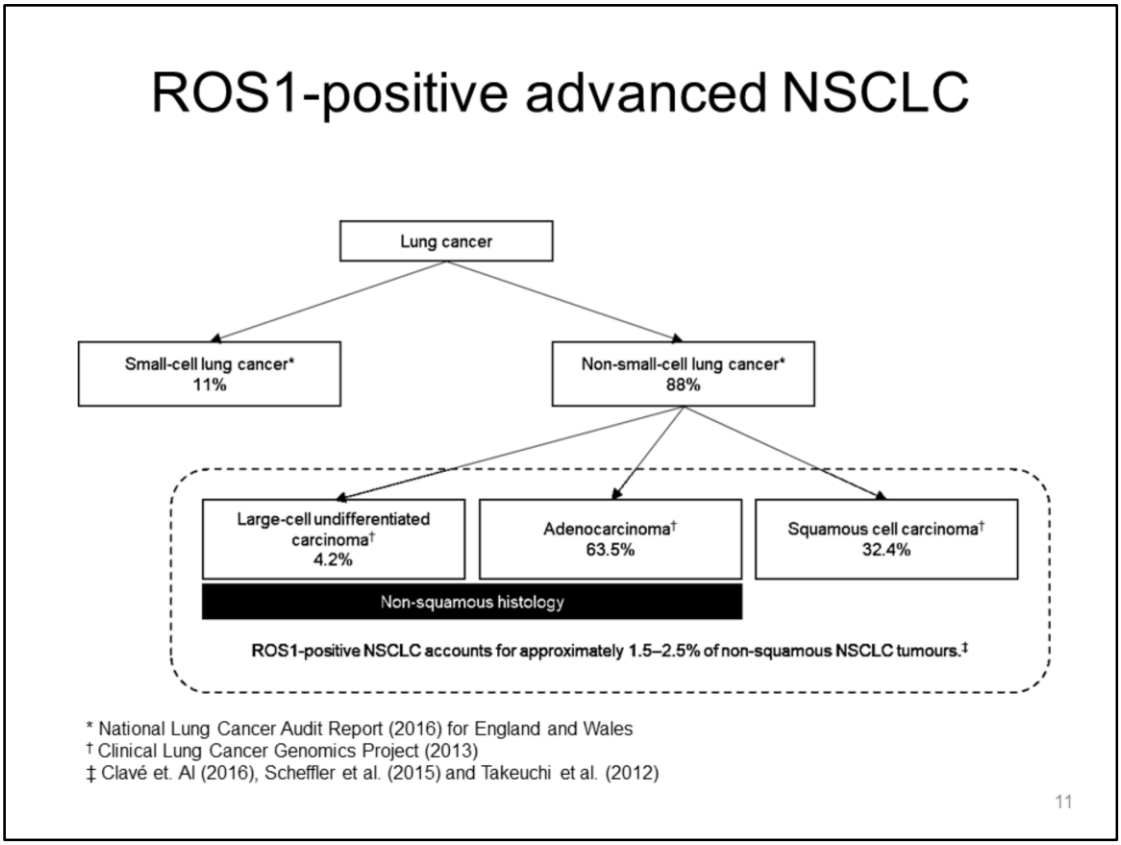

Source: Company's submission, Figure 1 page 17

ROS1-positive advanced NSCLC

- ROS1-positivity occurs in only 1.1–1.8% of NSCLC patients
  - exclusively in **non-squamous tumours**
  - predominantly in **adenocarcinoma** tumour types
- ROS1 is mutually exclusive to other oncogenic markers such as ALK or EGFR or KARS
- Similar to ALK-positive NSCLC, ROS1-positive NSCLC is more prevalent among
  - **younger patients , never-smokers**
- Diagnostic testing for ROS1-positivity is not established
- Patients with ROS1-positive advanced NSCLC do not have access to any targeted therapy
- Estimated number of patients with ROS1-positive advanced NSCLC in England and Wales
  - Company 289, ERG 307

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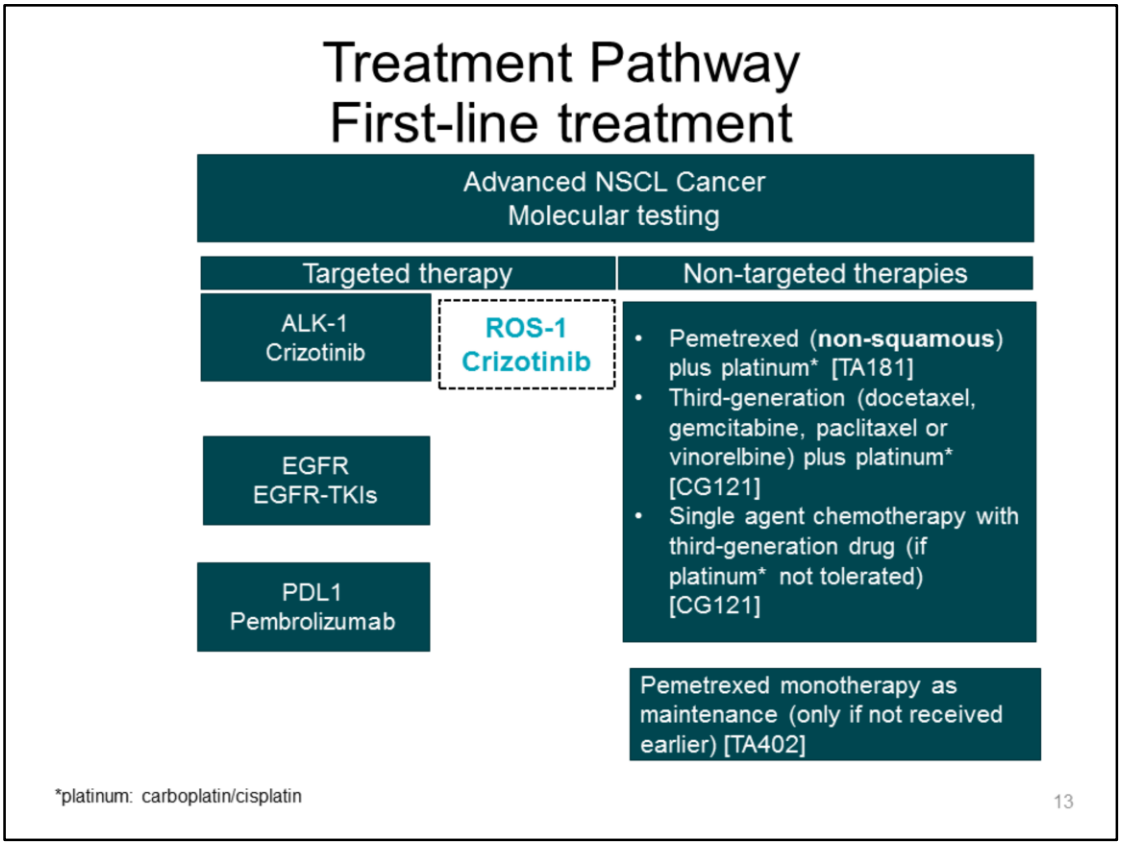
Treatment Pathway
First-line treatment
Advanced NSCL Cancer
Molecular testing
Targeted therapy
Non-targeted therapies
ALK-1
Crizotinib
ROS-1
Crizotinib
EGFR
EGFR-TKIs
PDL1
Pembrolizumab
• Pemetrexed (non-squamous) plus platinum* [TA181]
• Third-generation (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus platinum* [CG121]
• Single agent chemotherapy with third-generation drug (if platinum* not tolerated) [CG121]
Pemetrexed monotherapy as maintenance (only if not received earlier) [TA402]
*platinum: carboplatin/cisplatin
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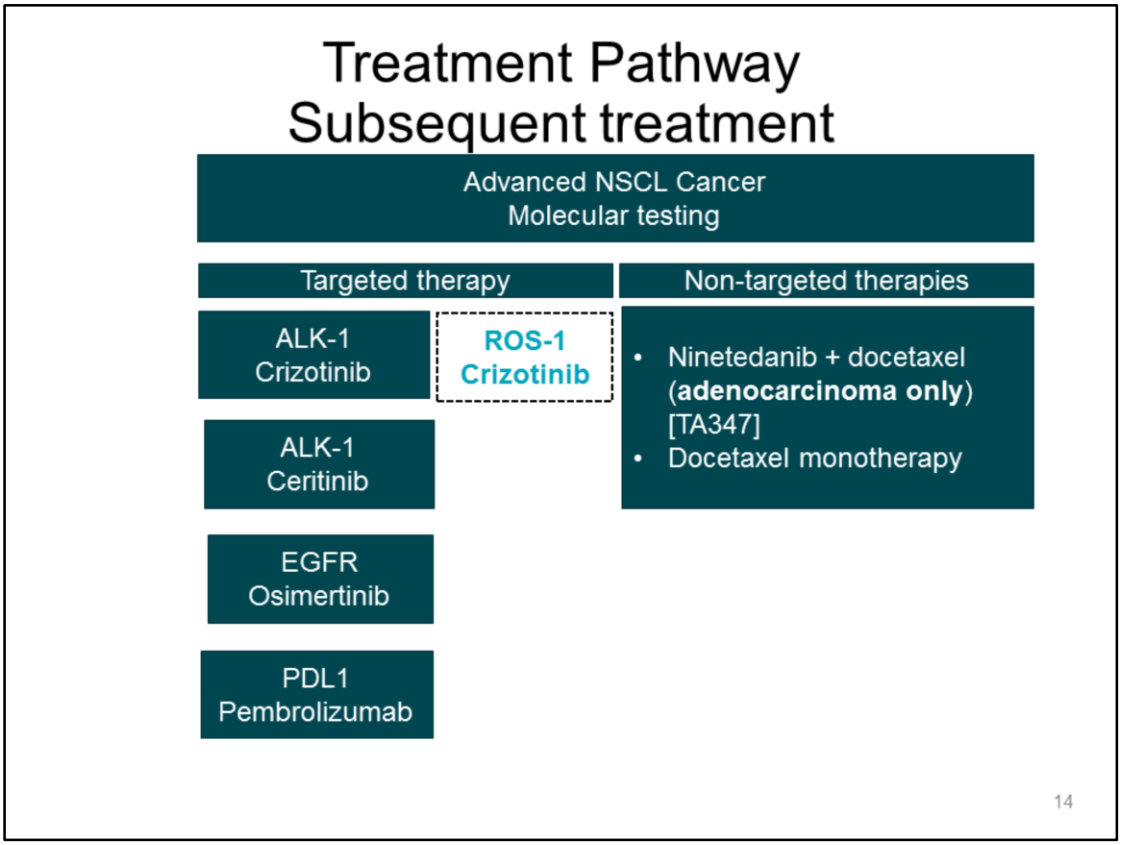
Treatment Pathway
Subsequent treatment
Advanced NSCL Cancer
Molecular testing
Targeted therapy
Non-targeted therapies
ALK-1
Crizotinib
ROS-1
Crizotinib
ALK-1
Ceritinib
EGFR
Osimertinib
PDL1
Pembrolizumab
• Ninetedanib + docetaxel (adenocarcinoma only) [TA347]
• Docetaxel monotherapy
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Professional perspective (1)

- Improving survival, progression-free survival, and quality of life are main aims of treatment in ROS1-positive advanced NSCLC
- ROS1 is not routinely tested. No provision of ROS1-directed therapies in the NHS at present.
  - First-line chemotherapy depends on tolerability and consists usually of 4 cycles of cisplatin-pemetrexed followed by maintenance pemetrexed chemotherapy (as per TA402).
  - On progression combination docetaxel-nintedanib (TA347) or if unsuitable best supportive care.
  - first or second lines with pembrolizumab (TA428) is **not** routine
- American Society of Clinical Oncology recommends crizotinib for ROS1-positive NSCLC.

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Professional perspective (2)

- Clinically significant difference in effectiveness from existing treatment would be
  - a response rate of 40% for first line
  - equivalent response rate (30% for first line and 10% for second line) but with reduction in toxicities
  - progression-free survival more than chemotherapy (around 5 months for the first line and 3 months for second line).
- Crizotinib is taken orally, therefore resource saving in terms of clinician, pharmacy, nursing, day unit time, and radiology time
  - ROS1 testing will need to be implemented but hospitals have established diagnostics pathways
- Crizotinib represents a 'step change' for the treatment of ROS1-positive advanced NSCLC

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Impact on Patients and Carers

- People with advanced or metastatic non-small cell lung cancer often debilitated by multiple and distressing symptoms, e.g. breathlessness difficult to manage
- Recent addition of targeted therapies and immunotherapy has given active treatment options: availability of new targets & therapy choices important
- Since outlook for these patients is poor, improved QoL and even small extension of life is significant for patients & family

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Patient/carer views on Crizotinib

- Crizotinib has been standard practice for ALK+ patients for some time so side effect profile well known.
- Wide range of side effects, but all appear to be well tolerated, especially compared with standard cytotoxic therapies
- Diagnostic testing ensures segmentation of therapy
- Patient group highlights importance of End of Life considerations for these patients

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Innovation: Company

- A first-in-class targeted therapy for patients with ROS1-positive NSCLC
- Received "Breakthrough Therapy Designation" and was granted through "Priority Review" by US FDA
- EMA approved crizotinib for ROS1-positive NSCLC based on the strength of the single-arm study
- Available orally therefore greater autonomy for patients
- Crizotinib addresses current clinical unmet need in terms of
  - Response to treatment
  - Progression-free survival
  - Decrease in tumour size
  - Quality of life
  - Extension of life
  - Wider societal benefit: typically younger patients (median age in mid-50s) crizotinib may allow working-age patients to return to employment; burden on carers in terms of quality of life and cost is substantial

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Decision Problem (1)

	Scope	Company's decision problem and justification
Population	People (adults) with ROS1-positive advanced non-small cell lung cancer	Clinical evidence available only from a single arm study of 53 patients with ROS1+ advanced NSCLC. Company extrapolated the data on clinical effectiveness of crizotinib from patients with ALK+ advanced NSCLC for the economic analysis

ERG 'the company has met the population parameter specified in the decision problem only if the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC'

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Decision Problem (2)

	Scope	Company's decision problem and Justification
Comparator	**Untreated:** • Chemotherapy* plus platinum** For people with non-squamous NSCLC only • Chemotherapy* plus platinum** with pemetrexed maintenance treatment For people with adenocarcinoma or large cell carcinoma (non-squamous cell) only • Pemetrexed plus platinum** • Pemetrexed plus platinum with pemetrexed maintenance (if received first-line) cisplatin) For people who cannot tolerate platinum • Single agent chemotherapy*	No data for effectiveness of comparators available in people with ROS1 positive NSCLC • For comparison company extrapolated data from patient with ALK positive NSCLC for pemetrexed+ platinum** **Excluded** • Pemetrexed maintenance (rationale: only small proportion [~15%] being eligible and insufficient evidence) • Chemotherapy* plus platinum** (rationale: clinical opinion against use in non-squamous NSCLC) • Single agent chemotherapy (rationale: unavailability of evidence)

- *chemotherapy: (docetaxel, gemcitabine, paclitaxel or vinorelbine)
- **platinum: carboplatin/cisplatin

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Decision Problem (3)

	Scope	Company's decision problem and justification
Comparator	Treated: • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care	Docetaxel monotherapy Excluded (rationale: unavailability of evidence) • Docetaxel with nintedanib (for adenocarcinoma histology) • Best supportive care

ERG agreed with company's rationale for excluding the comparators specified in the scope

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Decision Problem (4)

	Scope	Company's decision problem
Outcome	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	In ROS1 positive NSCLC evidence available for • Progression-free survival • Objective response rate • Overall survival • Adverse events Health related quality of life (not available)

ERG: clinical effectiveness analyses presented by the company based on use of crizotinib in ALK+ advanced NSCLC as a proxy for ROS1+ advanced NSCLC.
OS in ALK+ advanced NSCLC are unreliable due high levels of crossover

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Clinical evidence

- Direct evidence in people with ROS1-positive NSCLC
  - PROFILE 1001 study (small, single arm study)
    - Main source of evidence in submission and for regulatory approval
  - Supplementary
    - EUCROSS study (small, single arm study). Not used in the economic analysis as OS data were not available at the time of the economic analysis
    - [redacted]
- Proxy evidence from people with ALK-positive NSCLC
  - Data from PROFILE 1014 (first-line) and PROFILE 1007 (subsequent-lines) used as proxy to provide comparative evidence of crizotinib versus chemotherapy and as supplementary evidence to PROFILE 1001
  - Data from PROFILE 1014 and 1007 considered by the EMA when it approved the marking authorisation for crizotinib for ROS1-positive NSCLC

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Can data from ALK+ be extrapolated to ROS1+? Company's view

- ROS1+ and ALK+ advanced NSCLC are similar in terms of
  - structure of their receptor tyrosine kinases: kinase domains for both have 77% common amino acids within the ATP-binding site (where crizotinib binds)
  - in clinical behaviour, including response to crizotinib
  - patient characteristics (tend to be non-smokers and younger than unselected NSCLC)
  - Histology (predominantly adenocarcinoma)
- European Medicines Agency (EMA) recognised the generalisability of data from ALK+ to the ROS1+
- 12 UK clinical experts from a company sponsored advisory board supported generalisability of clinical effectiveness data from ALK+ to ROS1+ patients
  - during clarification, company reconfirmed it with a targeted mutation specialist clinician
- RCT of crizotinib in ROS1+ is unlikely, given the small number of ROS1+ and the clinical efficacy from PROFILE 1001 study, clinical equipoise is not feasible, therefore, unethical to conduct an RCT

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Can data from ALK+ be extrapolated to ROS1+? EPAR

- Information on natural history of ROS1+ NSCLC is currently limited, but several retrospective analyses suggest that ROS1 positivity is unlikely to be a favourable prognostic factor similar to what has previously been shown in ALK+ NSCLC
- Due to limited and in some cases conflicting results provided by retrospective analyses, it is not possible to conclude on the prognostic value of ROS1 positivity. Thus the rational and benefit of a therapy selectively addressing ROS1-positive NSCLC patients is at present not fully evaluable.
- Activity of crizotinib is undisputable, at least in previously treated ROS1+ patients.
- Limitations in benefit/risk assessment of crizotinib as single agent in previously untreated patients because of the non-comparative data and sample size
- Since ROS1+ represents rare, serious and life-threatening distinct molecular subset of NSCLC with no currently approved targeted therapies, pre-clinical and clinical ancillary data show efficacy both in patients with ROS1 and ALK mutations (including efficacy in first line setting), a large indication is considered acceptable.

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Can data from ALK+ be extrapolated to ROS1+? ERG's view

- ERG accepts the company's view that biological and clinical similarities exist between ROS1+ and ALK+ advanced NSCLC and that there are similarities between patients with ROS1+ and ALK+ advanced NSCLC.
- Clinical advice to the ERG
  - uncertain if the currently documented similarities between ROS1+ and ALK+ will be supported as more patients with ROS1+ are identified
  - small number of ROS1+ patients so far identified does not allow robust comparisons between the outcomes from patients with ROS1+ and ALK+ treated with crizotinib

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Can data from ALK+ be extrapolated to ROS1+ ? Clinical expert's view

- ROS1+ NSCLC would behave in a similar manner as ALK+ NSCLC.
  - Both tend to present with metastatic disease, at a younger age than average NSCLC, and usually in never-smokers.
  - Both have similar symptoms and distribution of disease at presentation.
  - Both respond very well to crizotinib with rapid durable responses.
  - Quality of life is markedly improved in both ROS1 and ALK+ NSCLC with crizotinib to near baseline/premorbid status.

"My clinical experience is of ROS1+ patients gaining similar benefit of crizotinib as ALK+ patients and markedly superior to chemotherapy. Given the marked rarity of the ROS1 genotype it would be reasonable to generalize outcomes for the ROS1+ NSCLC group from that of the ALK+ group"

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PROFILE1001 (NCT00585195)

Study design	single-arm, open-label, phase 1 study
Location	8 locations across US, Australia and South Korea
Population	People with ROS1+ locally advanced or metastatic NSCLC N=53, 7 untreated and 46 had at least 1 prior chemotherapy 3 ALK-negative patients were included when retrospectively identified to be ROS1+ 2 patients retrospectively determined to be ROS1-negative
Intervention	250 mg of crizotinib twice daily until disease progression
Primary outcome	objective response rate (ORR): % of patients with complete or partial response (CR or PR) according to RECIST v1.0/v1.1*
Secondary outcome	disease control rate (DCR) at weeks 8 and 16, duration of response (DR), time to tumour response (TTR), progression-free survival (PFS), time to progression (TTP), time to treatment failure (TTF), overall survival (OS), safety
Duration	Recruitment: October 2010 to September 2013 Data cut-off: 30 November 2015/24 June 2014 * Median follow-up: 25.4 months

*for 3 patients who retrospectively identified as ROS1 positive

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PROFILE1014 (NCT01154140)

Study design	Randomised, open-label, active-controlled, cross-over, phase III study
Location	251 locations across USA, Canada, Mexico, Australia, Asia, Europe (9 UK sites) South America and South Africa
Population	Adults with ALK+ locally advanced or metastatic non-squamous NSCLC who had not had any treatment for advanced disease (n=343)
Intervention	250 mg of crizotinib twice daily (n=172) Patients allowed to continue crizotinib beyond RECIST-defined PD, at investigator's discretion
Comparator	pemetrexed, 500 mg/m^2, plus platinum-based therapy (cisplatin, 75 mg/m^2, or carboplatin, target AUC of 5–6 mg/mL/min); iv every 3 weeks for a maximum of 6 cycles (n=171)
Primary outcome	Progression-free survival: duration from randomisation to disease progression according to RECIST v1.1 (as by independent radiological review) or death
Secondary outcome	overall survival (OS), time to treatment failure (TTF), safety , health-related quality of life (EQ-5D)

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PROFILE1007 (NCT00932893)

Study design	Randomised, open-label, active-controlled, cross-over, phase III study
Location	North America, Australia, Brazil, China, Japan, Korea, Taiwan, Hong Kong and Europe (9 UK sites)
Population	People with ALK+ locally advanced or metastatic NSCLC that progressed after 1 platinum based therapy and considered eligible for additional chemotherapy
Intervention	250 mg of crizotinib twice daily (n=173)
Comparator	docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2 (n=174)
Primary outcome	Progression-free survival: duration from randomisation to disease progression according to RECIST v1.0
Secondary outcome	overall survival (OS), time to treatment failure (TTF), safety , health-related quality of life (EQ-5D)

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ERG's critique: design of studies

- The PROFILE 1001,1014 and 1007 trials were generally well designed and well conducted.
- PROFILE 1001
  - Population in the study matches the patient population specified in the final scope issued by NICE
  - Clinical advice to the ERG suggests that the eligibility criteria used in PROFILE 1001 are appropriate
  - Main limitations of the study are:
    - Small sample size (n=53)
    - no comparator arm to provide direct evidence of the effectiveness of crizotinib in comparison to a relevant comparator in the patient population of interest

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Base-line characteristics (1)

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
Age (years): median, (min, max)		55 (25–81)	52.0 (22–76)	54 (19–78)	51 (22–81)	49 (24–85)
Category (years) – no. (%)	<65	38 (71.7)	[redacted]	[redacted]	146 (84.4)	[redacted]
	≥65	15 (28.3)	[redacted]	[redacted]	27 (15.6)	[redacted]
Sex – no. (%)	Male	23 (43.4)	68 (39.5)	63 (36.8)	75 (43.4)	78 (44.8)
	Female	30 (56.6)	104 (60.5)	108 (63.2)	98 (56.6)	96 (55.2)
Race – no. (%)	White	30 (56.6)	91 (52.9)	85 (49.7)	90 (52.0)	91 (52.3)
	Black	2 (3.8)	[redacted]	[redacted]	2 (1.2)	3 (1.7)
	Asian	21 (39.6)	77 (44.8)	80 (46.8)	79 (45.7)	78 (44.8)
	Other	NR	4 (2.3)	2 (1.2)	2 (1.2)	2 (1.2)
Weight (kg)	Mean (SD)	71.9 (16.0)	[redacted]	[redacted]	65.3 (17.3)	[redacted]
	Median (range)	70.0 (48.0-106.3)	[redacted]	62.5 (35.8–151.6)[a]	62.0 (35.2-160.0)	[redacted]

a: One person's weight incorrectly reported as 151.6kg instead of 151.6 pounds

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Source: Table 11 company's submission page 48-49

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Base-line characteristics (2)

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
ECOG performance status	0	23 (43.4)	[redacted]	[redacted]	72 (41.6)	65 (37.4)
	1	29 (54.7)	[redacted]	[redacted]	84 (48.6)	95 (54.6)
	2	1 (1.9)	9 (5.2)	[redacted]	16 (9.2)	14 (8.0)
Smoking status – no. (%)	Never smoker	40 (75.5)	106 (61.6)	112 (65.5)	108 (62.4)	111 (63.8%)
	Ex-smoker	13 (24.5)	56 (32.6)	54 (31.6)	59 (34.1)	54 (31.0%)
	Current smoker	NR	10 (5.8)	5 (2.9)	5 (2.9)	9 (5.2%)
Histological classification – no. (%)	Adenocarcinoma	51 (96.2)	158 (91.9)	159 (93.0)	163 (94.2)	160 (92.0%)
	Non-adenocarcinoma	2 (3.8)	14 (8.1)	12 (7.0)	9 (5.2)	14 (8.0)
Prior radiation therapies – no. (%)	No	34 (64.2)	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	19 (35.8)	[redacted]	[redacted]	[redacted]	[redacted]

b Two patients in the crizotinib group did not report their prior radiation therapy status

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Source: Table 11 company's submission page 48-49

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Base-line characteristics (3)

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
Number of prior systemic therapy regimens:	0	7 (13.2)	172 (100)	171 (100)	[redacted]	[redacted]
	1	20 (37.7)	0	0	[redacted]	[redacted]
	2	13 (24.5)	0	0	[redacted]	[redacted]
	3	3 (5.7)	0	0	[redacted]	[redacted]
	>3	10 (18.9)	0	0	[redacted]	0
	Not reported	0	0	0	[redacted]	0
Extent of disease[c]- no. (%)	Locally advanced	NR	4 (2.3)	3 (2)	7 (4.0)	8 (4.6%)
	Metastatic	NR	168 (97.7)	168 (98.2)	165 (95.4)	166 (95.4%)
Prior surgeries – no. (%)		53 (100)	NR	NR	NR	NR
Brain metastases present – no. (%)		NR	45 (26.2)	47 (27.5)	60 (35)	
Time since first diagnosis median (months)		NR	1.2 (0–114.0)	1.2 (0–93.6)	[redacted]	[redacted]

C: Data missing for 4 patients in the crizotinib arm in the PROFILE 1007 trial

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Source: Table 11 company's submission page 48-49

ERG's critique: baseline characteristics (1)

- ERG stated that there were no important differences in baseline characteristics between the treatment arms in PROFILE 1014 and PROFILE 1007.
- ERG commented that the following 2 assumptions must hold if the company's approach of using results from PROFILE 1014 and PROFILE 1007 as estimates of the effectiveness of treatment with crizotinib for ROS1-positive advanced NSCLC patients in first-line and subsequent-line settings is to be valid:
  1. ROS1-positive advanced NSCLC and ALK-positive advanced NSCLC patient populations must be comparable in terms of baseline characteristics
  2. Patients recruited to the ALK-positive advanced NSCLC trials must be representative of the ALK-positive advanced NSCLC patient population (and consequently the ROS1-positive advanced NSCLC patient population, if assumption 1 holds) that would be seen in NHS clinical practice

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ERG's critique: baseline characteristics (2)

- For assumption 1, clinical advice to the ERG suggested that ROS1-positive advanced NSCLC and ALK-positive advanced NSCLC patient populations are comparable in terms of baseline characteristics
- For assumption 2, as noted in the development of TA406, patients in PROFILE 1014 tended to be younger than patients seen in clinical practice. However, clinical advice to the ERG suggested that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS

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ERG's critique: baseline characteristics (3)

- PROFILE 1001
  - Of the patients who had received previous treatment, 37% had not received treatment with pemetrexed + platinum in the first-line setting. Pemetrexed + platinum is the standard of care in the NHS as a first-line treatment for patients with tumours of adenocarcinoma histology
- PROFILE 1007
  - [redacted] of patients did not receive treatment with pemetrexed + platinum in the first-line setting. Pemetrexed + platinum is standard of care in the NHS as a first-line treatment for patients with tumours of adenocarcinoma histology
  - No patients received treatment with docetaxel + nintedanib in the second line setting (NHS standard care)

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Results (PROFILE1001)

Outcome		Result
Objective response rate (ORR) investigator (n=53)	ORR (%) (95% CI)	37 (**69.8** [55.7 to 81.7])
	Complete response (%)	5 (9.4)
	Partial response (%)	32 (60.4)
	Stable Disease (≥6 weeks) (%)	11 (20.8)
	Progressive Disease (%)	3 (5.7)
	Early death (%)	1 (1.9)
	Indeterminate (%)	1 (1.9)
ORR IRR (n=50)	ORR (%) (95% CI)	33 (**66.0** [51.2 to 78.8])
	Complete response (%)	1 (2.0)
	Partial response (%)	32 (64.0)
	Stable Disease (≥6 weeks) (%)	12 (24.0)
	Progressive Disease (%)	4 (8.0)
	Early death (%)	1 (2.0)
	Indeterminate (%)	0 (0.0)

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Source: table 14 Company's submission page 55

Results (PROFILE 1001)

Outcome		Result
Disease Control Rate (DCR)	DCR at Week 8 (%) (95% CI)	46 (86.8 [74.7 to 94.5])
	DCR at Week 16 (%) (95% CI)	42 (79.2 [65.9 to 89.2])
Duration of Response (n=37[a])	Median months (range)	NR (15.2 to NR)
Time to Tumour Response (n=37[a])	Median weeks (range)	7.9 (4.3 to 32.0)
Time to Treatment Failure	Median months (95% CI)	**23.2** (15.0 to NR)
Overall survival	Median months	NR
	HR (95% CI, p-value)	N/A
	Probability of survival at 6 months (95% CI)	90.6% (78.8 to 96.0)
	Probability of survival at 12 months (95% CI)	79.0% (65.3 to 87.8)
	Median duration of follow up months (95% CI)	25.4 (22.5 to 28.5)

a: Probability was determined by Kaplan-Meier estimate

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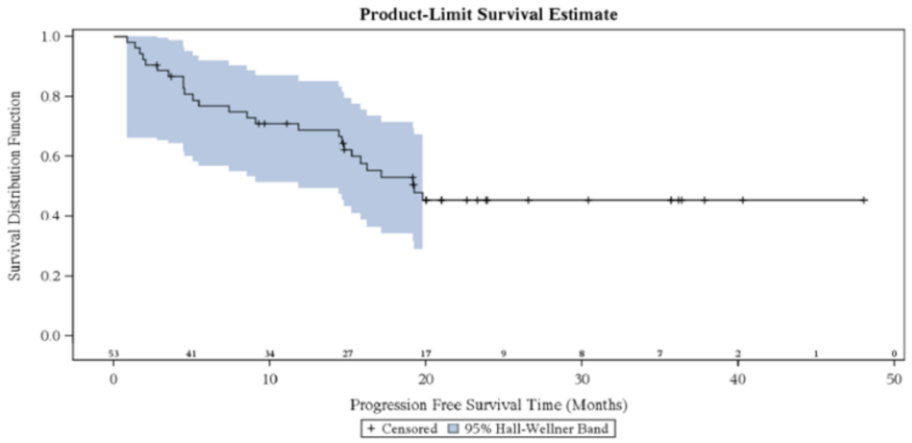
Source: table 14 Company's submission page 55

Progression-free survival (PROFILE 1001)



Progression free survival	Patients with event (%)	26 (49.1)
	Median months (95% CI)	**19.3** (14.8 to NR)
Time to Tumour Progression	Patients with event (%)	23 (43.4)
	Median months (95% CI)	**19.8** (15.2 to NR)

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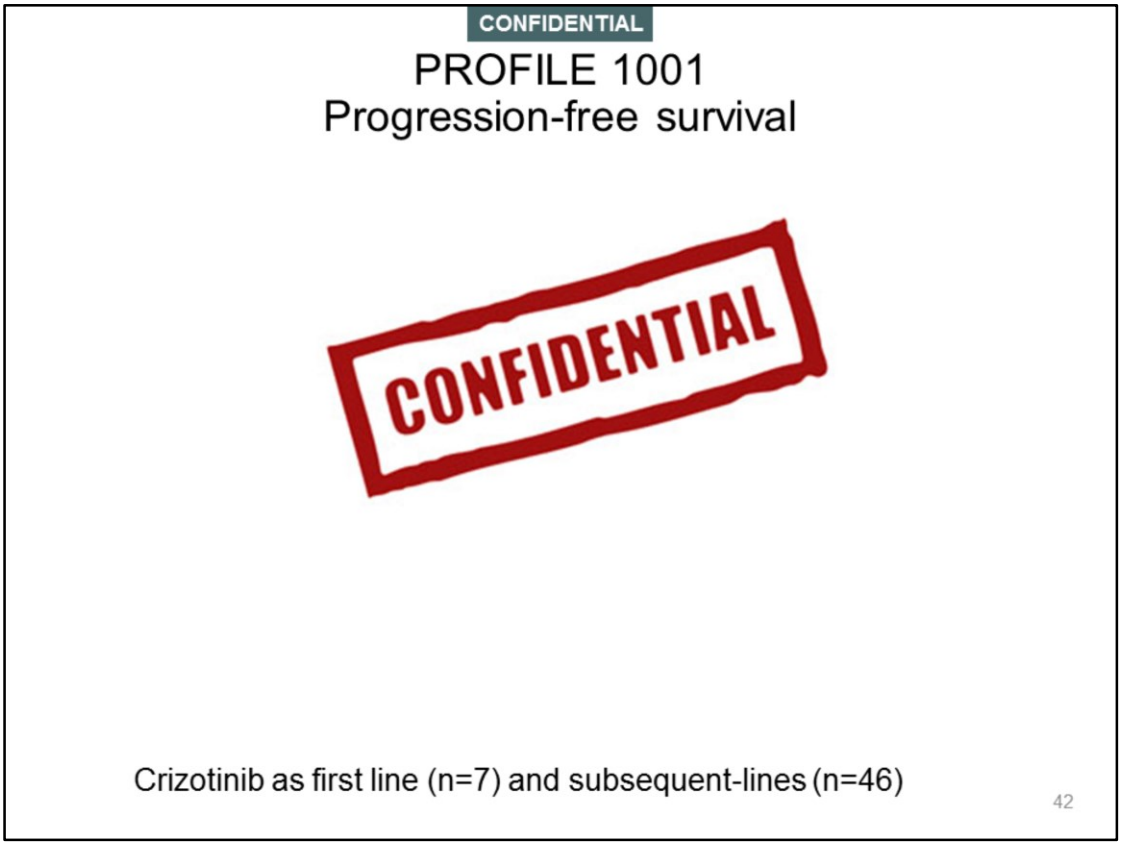
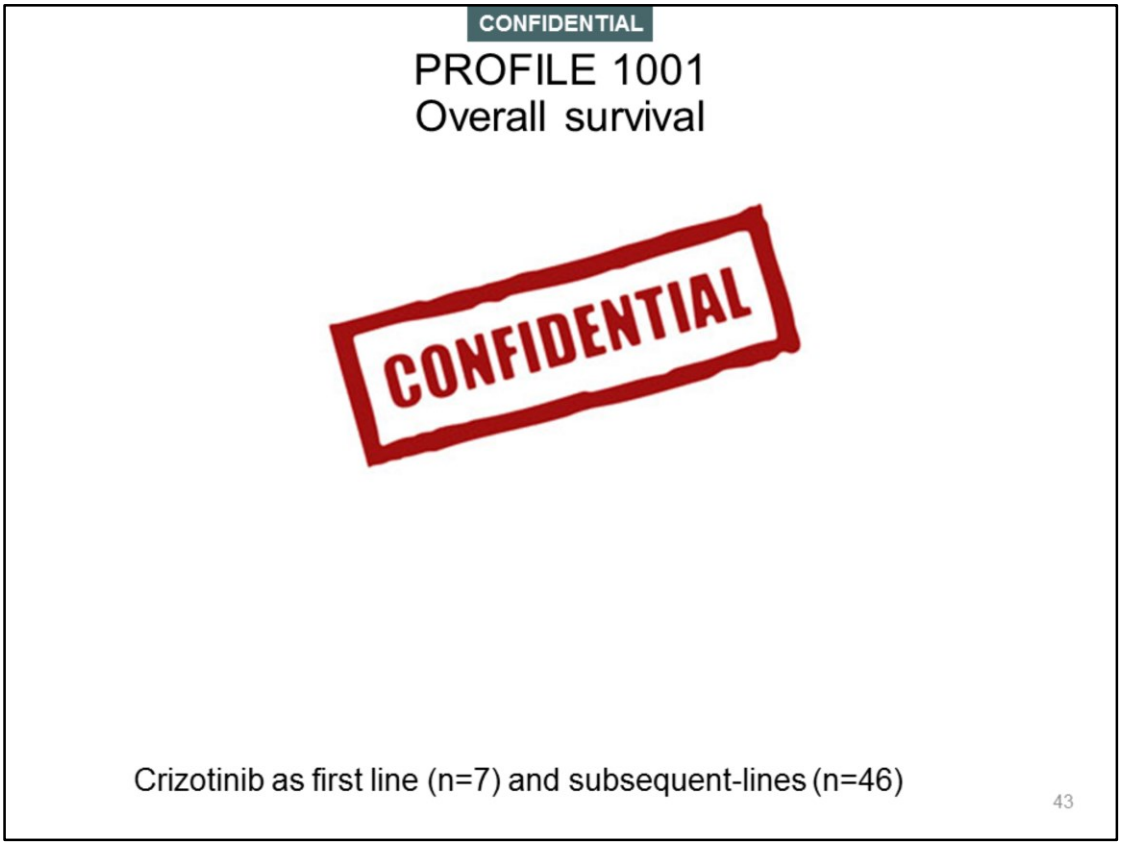
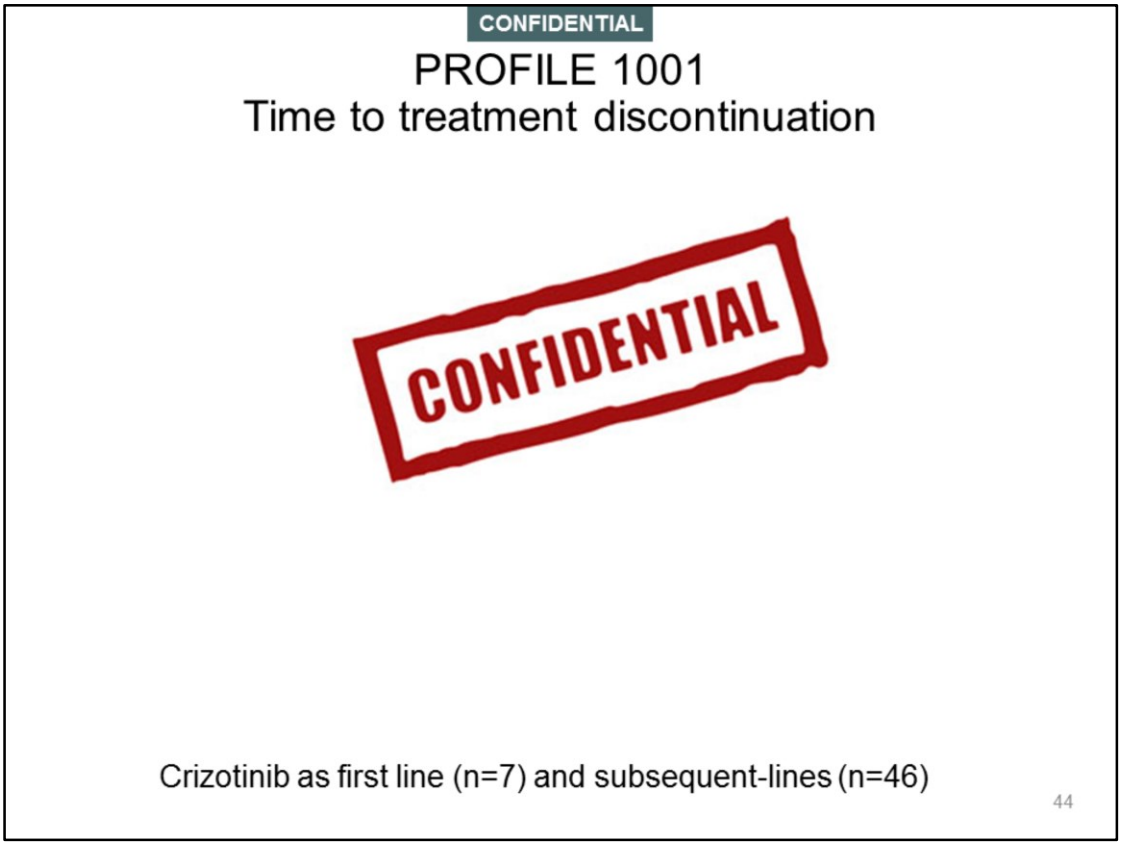
Source: Figure 5 and table 14 Company's submission page 61 and 55



Source: Figure 22 Company's submission (page 105)



Source: Figure 21 Company's submission (page 104)



Source: Figure 23 Company's submission (page 105)

Results (PROFILE 1014 & 1007)

Outcome	PROFILE 1014 (N=347)	PROFILE 1007 (N=343)
Median PFS		
Crizotinib, months (95% CI)	10.9 (8.3 to 13.9)	7.7 (6.0 to 8.8)
Chemotherapy, months (95% CI)	7.0 (6.8 to 8.2)	3.0 (2.6 to 4.3)
HR, (95% CI; p-value)	0.45 (0.35 to 0.60; p<0.001)	0.487 (0.371 to 0.638; p<0.0001)
Patients who crossed-over		
Crizotinib	33/172 (19.2%)	65/173 (37.6%)
Chemotherapy	144/171 (84.2%)	154/174 (88.5%)
		ORR
Crizotinib, no. of patients (%) [95%	128 (74.4 [67.2 to 80.8])	112 (65.3 [57.7 to 72.4])
Chemotherapy, no. of patients (%) [95% CI][c]	77 (45 [37 to 53])	34 (19.5 [13.9 to 26.2])
Median OS		
Crizotinib, months (95% CI)	[redacted]	21.7 (18.9 to 30.5)
Chemotherapy, months (95% CI)	[redacted]	21.9 (16.8 to 26.0)
Unadjusted HR, (95% CI, p-value)	[redacted]	0.854 (0.66 to 1.10; p=0.11)
Crossover adjusted HR, (95% CI, p-value)	[redacted]	0.383 (0.283–0.518)

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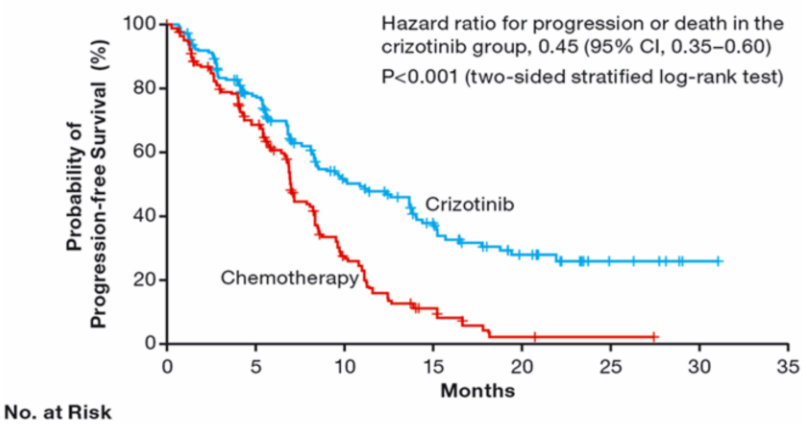
Source: table 15 Company's submission page 57

Progression-free survival in patients with untreated ALK-positive disease (PROFILE 1014)



No. at Risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

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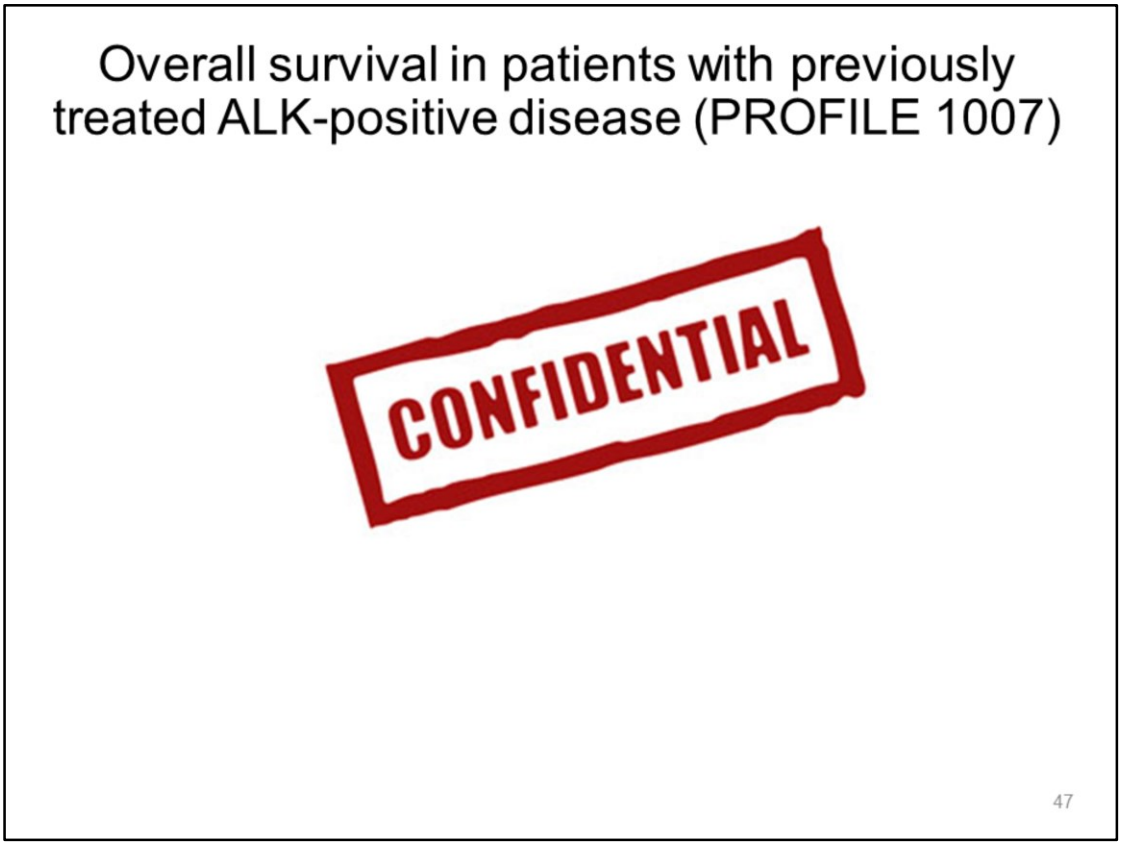
Source: Figure 6 Company's submission page 62



Source: Figure 8 Company's submission page 62

Crossover in PROFILE 1014 & 1007

PROFILE 1014 trial	PROFILE 1007 trial
• At interim analysis company used rank preserving structural failure time model (RPSFTM), iterative parameter estimation (IPE) and the two-stage method to adjust for switching from chemo to crizotinib (but not for those switching from the crizotinib chemo) • For the final analysis company considered 2 stage method inappropriate (due to the high level of patient crossover) and used only RPSFTM (2 variations of RPSFTM; log-rank and Wilcoxon)	Company did not give any explanation of how crossover-adjusted HR was calculated. **TA422** Company presented 3 adjusted OS using the RPSFTM with three different tests of equality, • log-rank • Wilcoxon and • Cox model-based Wald tests Company considered following methods not feasible • inverse probability of treatment and censoring weighted (IPTCW) • inverse probability of censoring weights (IPCW) ERG (TA422) presented 2 alternative method

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PROFILE 1007: results stratified by chemotherapy comparator

Outcome	Crizotinib (N=172)	Pemetrexed (N=99)	Docetaxel (N=72)
Tumour response, ORR			
No. of patients (%) [95% CI]	[redacted]	[redacted]	[redacted]
RR, crizotinib vs comparator (95% CI; p-value)		[redacted]	[redacted]
PFS			
PFS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR, crizotinib vs comparator (95% CI; p-value)		0.59 (0.43–0.80; p<0.001)[36]	0.30 (0.21 to 0.43; p<0.001)[36]
OS			
OS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR (not adjusted for crossover), crizotinib vs comparator (95% CI; p-value)		[redacted]	[redacted]

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Source: Company response to ERG clarification letter, Table 3

Health-related quality of life

- No direct HRQoL data for patients with ROS1-positive advanced NSCLC
  - not collected in PROFILE1001
- HRQoL data collected in PROFILE 1014 and 1007 using
  - EQ-5D-3L (summary result presented)
  - European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC-QLQ-C30) not included in the company's submission)
  - EORTC QLQ-Lung Cancer LC13 (not included in the company's submission)
  - Visual Symptom Assessment Questionnaire (VSAQ-ALK) questionnaire not included in the company's submission

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EQ-5D results (1)

PROFILE 1014	PROFILE 1007
Completion rates for crizotinib [redacted](over the first 30 of a total of 50 cycles) for chemotherapy [redacted] (over the maximum six cycles). Baseline data available for all ITT population except 8 patients in the crizotinib 7 patients in the chemotherapy group	Completion rates of all questions for crizotinib [redacted] for chemotherapy [redacted]
• In chemotherapy group: no statistically significant changes from baseline over 6 cycles • in crizotinib group a significant improvement from baseline [redacted]) in EQ-5D VAS general health status scores in cycles 3 to 16 and 18 to 21 In a mixed-model analysis, crizotinib was associated with a statistically significant greater improvement in EQ-5D VAS scores compared to chemotherapy ([redacted])	[redacted] absolute EQ-5D index scores were [redacted] The difference between groups became [redacted] only found to be statistically significant for Cycles 6 and 7

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EQ-5D results (2)

PROFILE 1014	PROFILE 1007
• In a mixed-model analysis the overall EQ-5D index score (utility) was found to be statistically significantly higher in the crizotinib group compared with chemotherapy ([redacted]); • Improvements from baseline in EQ-5D index scores were also statistically significantly greater in the crizotinib group relative to chemotherapy [redacted]	Absolute EQ-5D index scores [redacted]
Statistically significant improvements from baseline [redacted] in EQ-5D index scores were observed in some cycles in the crizotinib group (Cycles 2 to 20, 22, 24, 25, 29 and 30), but were not observed in any cycles in the chemotherapy group (Cycles 1 to 6)	

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ERG's critique: results from PROFILE 1001, 1014 and 1007

- **PROFILE 1001**
  - OS data were immature, with only 30% of patients having died at the latest data cut-off date (2014)
    - The ERG stated that there was no robust OS data available for patients with ROS1-positive advanced NSCLC
  - No HRQoL data were collected during the study
- **PROFILE 1014 and 1007**: The ERG concluded that the proportional hazards assumption was not valid for PFS, and that the hazard ratios for PFS data from both trials should be interpreted with caution
- Median PFS varied across **PROFILE 1001, 1014 and 1007**. ERG stated that the variation in PFS brings into question the comparability of the ALK-positive and ROS1-positive patient populations

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ERG's critique: adjusting for cross over PROFILE 1014 and 1007

- The ERG considered the RPSFTM-adjusted hazard ratios for OS in PROFILE 1014 was unlikely to be valid and should be interpreted with caution
- For the PROFILE 1007 trial, the company presented the PFS hazard ratio as a proxy for the true OS hazard ratio, instead of using the RPSFTM-adjusted OS hazard ratio.
  - The ERG considered the PFS hazard ratio to be most likely closer to the true OS hazard ratio than the RPSFTM-adjusted OS hazard ratio.
  - However, the ERG also noted that the true OS hazard ratio may still be less than the PFS hazard ratio, and that the company's hazard ratio for "crossover-adjusted" OS should be interpreted with caution
- The ERG stated that there are no reliable OS data available from either PROFILE 1014 or 1007 to support treatment with crizotinib

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Adverse events (PROFILE1001)

Adverse event, No. of patients (%)	Crizotinib (N=53)	
	All cause n (%)	Treatment-related n (%)
Number of patients		
With AEs	53 (100)	52 (98.1)
With Serious AEs	22 (41.5)	2 (3.8)
With Grade 3 or 4 AEs	28 (52.8)	16 (30.2)
With Grade 5 AEs	9 (17.0)	0
With AEs associated with:		
Permanent discontinuation	4 (7.5)	1 (1.9)
Dose reduction	6 (11.3)	6 (11.3)
Temporary discontinuation	24 (45.3)	13 (24.5)

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Source: CS, Table 18

Common treatment related adverse events (PROFILE1001)

AEs	% patients experiencing
Vision disorder	84.9
Nausea	49.1
Oedema	45.3
Diarrhoea	41.5
Vomiting	37.7
Constipation	34
Elevated aminotransferases	30.2

AEs	% patients experiencing
Bradycardia	20.8
Dysgeusia	18.9
Dizziness	18.9
Fatigue	18.9
Hypophosphataemia	15.1
Rash	13.2
Neutropenia	13.2
Decreased appetite	11.3
Neuropathy	9.4

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Source: Table 19 Company's submission (page 72)

Treatment related grade 3 or 4 adverse event (PROFILE 1001)

Grade 3 or 4 adverse event, No. of patients (%)	Crizotinib (N=53)
Hypophosphatemia	7 (13.2)
Neutropenia	5 (9.4)
Vomiting	1 (1.9)
Electrocardiogram QC prolonged	1 (1.9)
Elevated transaminases	2 (3.8)

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Source: Table 20, Company's submission page 73

Supportive evidence

EUCROSS

- a phase II single-arm study, 34 European ROS1+ NSCLC patients

- Preliminary results
  - ORR: [redacted]
  - Median PFS: [redacted] months ([redacted])
  - Probability of survival at 12 months: [redacted])
  - Probability of survival at 24 months: [redacted]).
- **Audit of ROS1-positive NSCLC from the** [redacted]
  - [redacted] patients [redacted] first-line pemetrexed + platinum and [redacted] received crizotinib
- Preliminary median PFS
  - Pemetrexed + platinum [redacted] months
  - Crizotinib [redacted] months
  - [redacted]
  - [redacted]

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Matched adjusted indirect comparison

- Company considered undertaking an unanchored matched adjusted indirect comparisons (MAIC) to compare the results from crizotinib treated ROS1-positive patients in PROFILE 1001 with the chemotherapy treatment arm of PROFILE 1014 and with the chemotherapy treatment arm of PROFILE 1007 in separate analyses.
- Company noted that the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 recommends that an unanchored MAIC should adjust for all effect modifiers and prognostic variables.
- Company considered it implausible to fit complex models including multiple variables given the small sample size in PROFILE 1001
- ERG agreed with the company's assessment.

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Cost effectiveness

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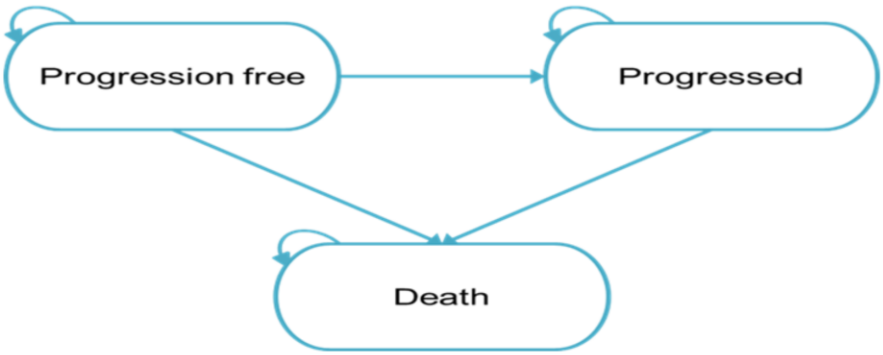
Model structure

- Partition survival model
- Based on the models considered in previous appraisals for crizotinib in ALK-positive NSCLC (TA406 and TA422)
- Same structure for first- and subsequent-line treatment with crizotinib
- 3 health states: progression-free disease, progressed disease and death
- Cycle length: 30-day and a half-cycle correction was implemented
- Time horizon 20 years, costs and benefits are discounted at a rate of 3.5% per annum, NHS and personal social services (PSS) perspective



61

How the model works?

- Patients begin in the progression-free state and are at risk of progression or death.
- Transitions to the death state can occur from either the progression free or progressed disease health states
- Progression free state was associated with a higher quality of life
- Progressed disease state captures the relatively poor quality of life following disease progression and prior to death
- For the crizotinib treatment arm, patients who continued to receive crizotinib beyond progression, assumed to have the same quality of life as in progression free state despite being in the progressed state
  - Progressed disease utility values applied after treatment discontinuation with crizotinib

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Model Population

- Clinical advisors to company suggested that patients in clinical practice may be less healthy and 5 to 10 years older (TA406)
  - Patients from a retrospective real-world, Western, cohort study conducted by Davis et al. (2015) considered to be more representative of patients seen in UK clinical practice
- Company conducted an analysis of key covariates by fitting Cox regression models to the patient-level trial data and evaluated effect of each of these factors on PFS and OS
- The company used parametric curves (OS, PFS and TTD) adjusted for patient characteristics in order to match Davis et al. (2015) for the following 6 covariates
  - Race [Asian vs. non-Asian]
  - Eastern Cooperative Oncology Group [ECOG] status [2 vs. 1 or 0]
  - Brain metastases [yes vs. no])
  - Age group (≥65 vs. <65)
  - Sex (male vs. female)
  - Smoking status (never smoked vs. former smokers or current smoker)
  - Adenocarcinoma (yes vs. no).

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Baseline characteristics for covariate-adjustment

Covariate	Real-world data (Davis et al. [2015])	Crizotinib (PROFILE 1014)	Pemetrexed plus platinum therapy (PROFILE 1014)	Pooled treatments (PROFILE 1014)
% non-Asian	87.6%	55.2%	53.2%	54.2%
% age ≥ 65	29.2%	13.4%	18.7%	16.0%
% male	67.9%	39.5%	36.8%	38.2%
% smoker or ex-smoker	62.8%	38.4%	34.5%	36.4%
% ECOG PS 0-1	78.1%	94.2%	95.3%	94.7%
% ECOG PS 2	21.9%*	5.8%	4.7%	5.3%
% with brain metastases	NR	26.2%	27.5%	26.8%
% non-adenocarcinoma	NR	6.4%	5.8%	6.1%

*16.8% were ECOG PS 2, and 5.1% were ECOG PS 3, only ECOG PS 0–1 and 2 included in the PROFILE 1014 trial, therefore n=7 (5.1%) ECOG PS 3 patients have been pooled into the ECOG PS 2 category.

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Source: Table 29 Company's submission, page 101

Modelling of clinical effectiveness

- In the base case analysis, company used effectiveness data from ALK-positive advanced NSCLC as a proxy for ROS1-positive advanced NSCLC for both first-line and subsequent-line treatment with crizotinib because
  - Data from ROS+ are limited and immature
  - Biological and clinical similarities between the ROS1 and ALK oncogenes
  - similarities in patient characteristics of ROS1- and ALK-positive NSCLC patients,
  - generalisability of ALK-positive data to ROS1-positive patients supported by 12 UK leading clinical experts
- Company used data from PROFILE 1001 (in ROS1+ NSCLC) as a scenario
- *ERG accepted company's view about biological and clinical similarities between ROS1+ and ALK+ advanced NSCLC and similarities between patients with ROS1+ and ALK+ advanced NSCLC*

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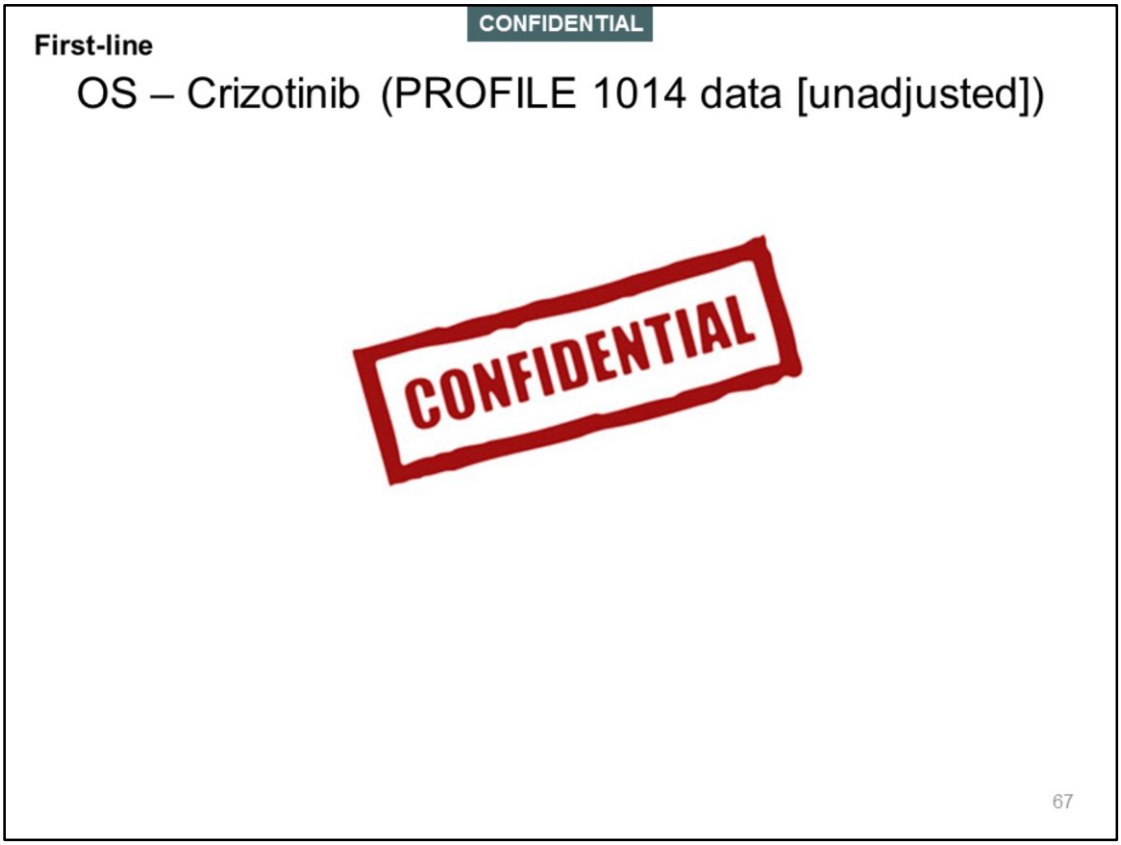
First-line

Overall survival

- Separate parametric survival curves were fitted to OS data from the latest data cut from PROFILE 1014 (2017), for crizotinib and pemetrexed plus platinum
  - OS data for pemetrexed plus platinum adjusted for crossover (RPFSTM: Wilcoxon)
- Based on; visual inspection, Akaike information criterion (AIC) & Bayesian information criterion (BIC) and clinical plausibility of expected survival from long-term extrapolation, the company chose
  - Exponential curves for its base case
  - Alternative curve fits are tested in sensitivity analysis
- Selected curves adjusted for patient characteristics

66



Source: Figure 10 Company's submission, page 102

Source: Figure 12 Company's submission, page 104

First-line

Overall survival extrapolation Goodness of fit

	Crizotinib		Pemetrexed plus platinum	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	**1203.6**	**1228.8**	**1141.6**	**1166.7**
Generalised Gamma	1207.3	1238.8	1138.9	1170.3
Gompertz	1205.6	1234.0	1143.1	1171.4
Log-logistic	1205.2	1233.6	1135.0	1163.3
Log-normal	1209.4	1237.8	1137.3	1165.6
Weibull	1205.6	1233.9	1142.5	1170.7

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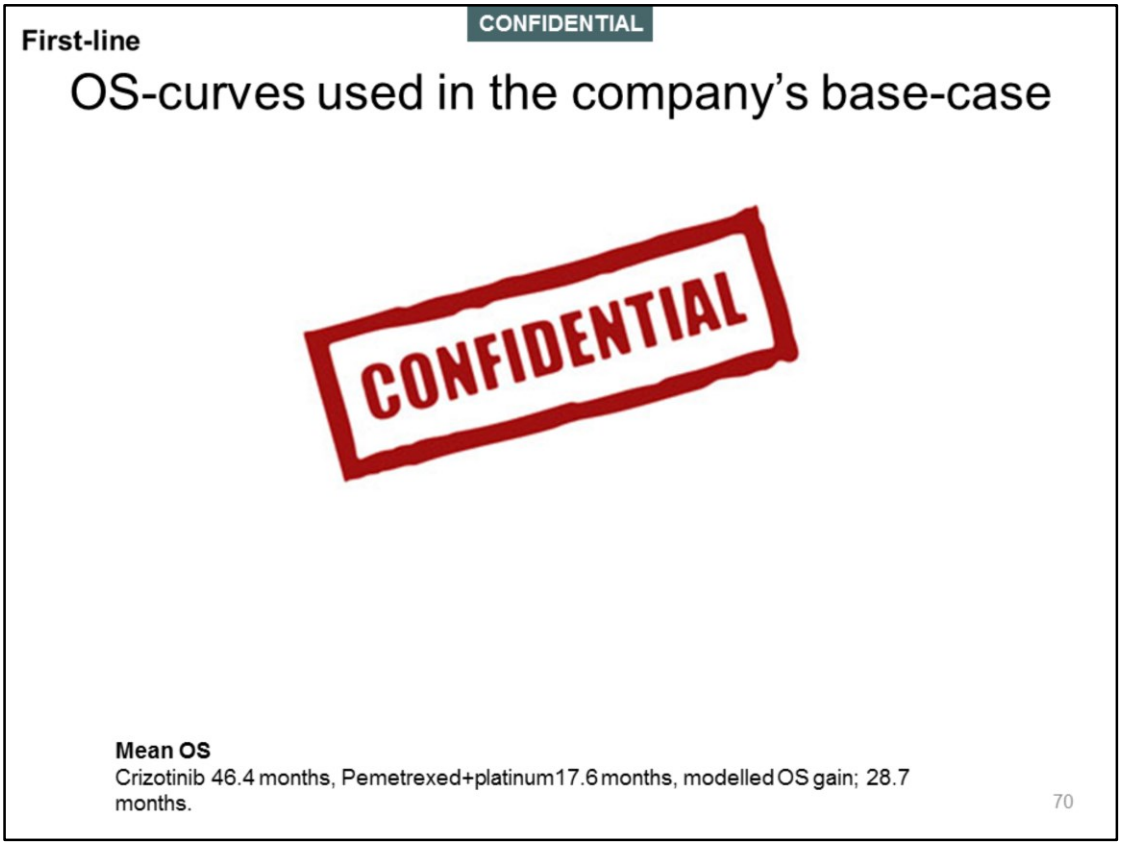
Source: Table 30 and 31 Company's submission page 102 and 103

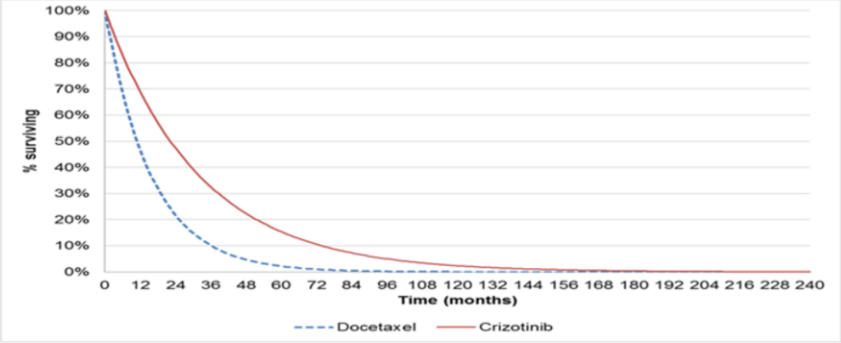


Source: Figure 14 Company's submission, page 105

Subsequent-line

Overall survival

- Data from PROFILE 1007
- Company used extrapolation accepted in TA422
  - Exponential curve fitted to OS data from docetaxel (comparator) arm
  - Assuming proportional hazard, HR of 0.49 applied to model OS for crizotinib arm



Mean OS

Crizotinib 33.0 months, docetaxel16.7 months, modelled OS gain; 16.3 months.

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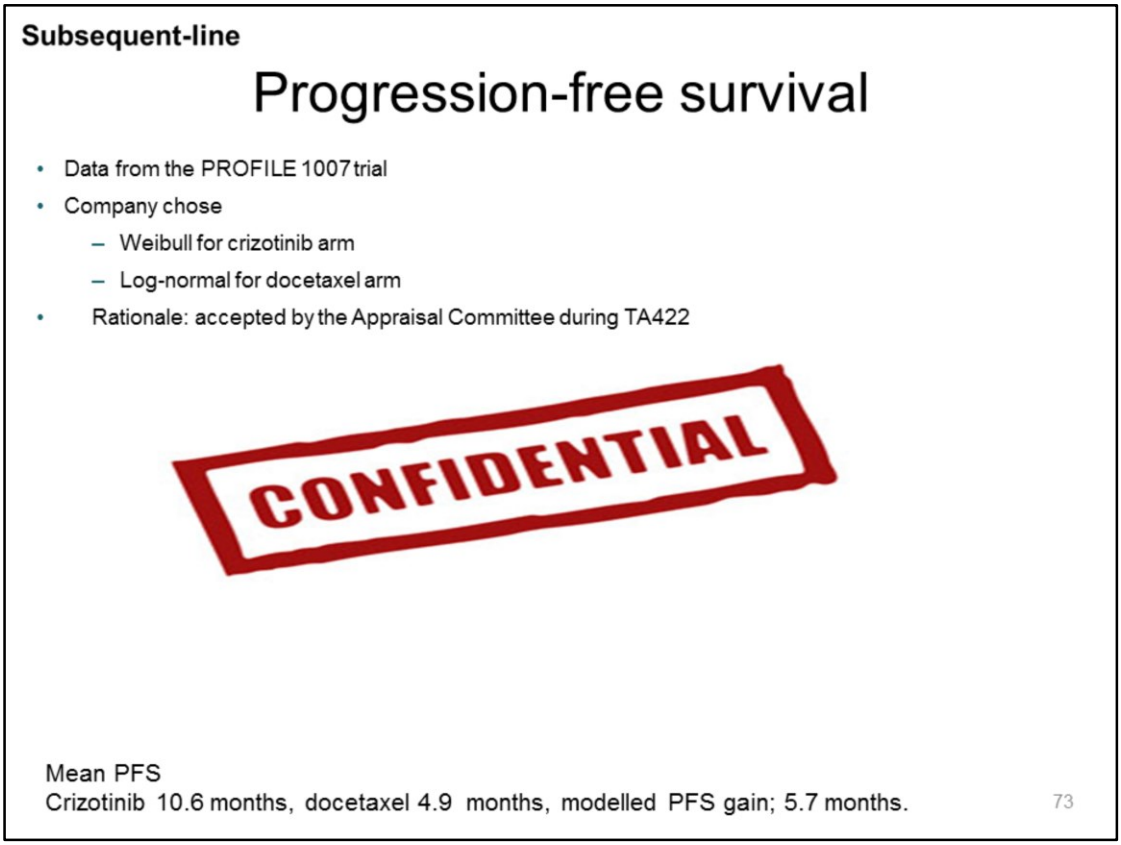
Source: Figure 15 Company's submission, page 106

Source: Figure 16. Company's addendum 2 (page 7) replacing Figure 16 of Company's submission page 106



Source: Figure 17, Company's submission (page 108)

First-line

Time on treatment

- Data from PROFILE 1014
- Company chose fully stratified curves, adjusted for the baseline characteristics
  - exponential for crizotinib
  - gompertz for pemetrexed plus platinum (up to a maximum 6 cycles)
- Rationale: accepted by the Appraisal Committee during TA406

Subsequent-line

- Data from PROFILE 1007
- Company chose fully stratified curves, adjusted for the baseline characteristics
  - Weibull for crizotinib
  - 3 cycles for docetaxel
- Rationale: accepted by the Appraisal Committee during TA422

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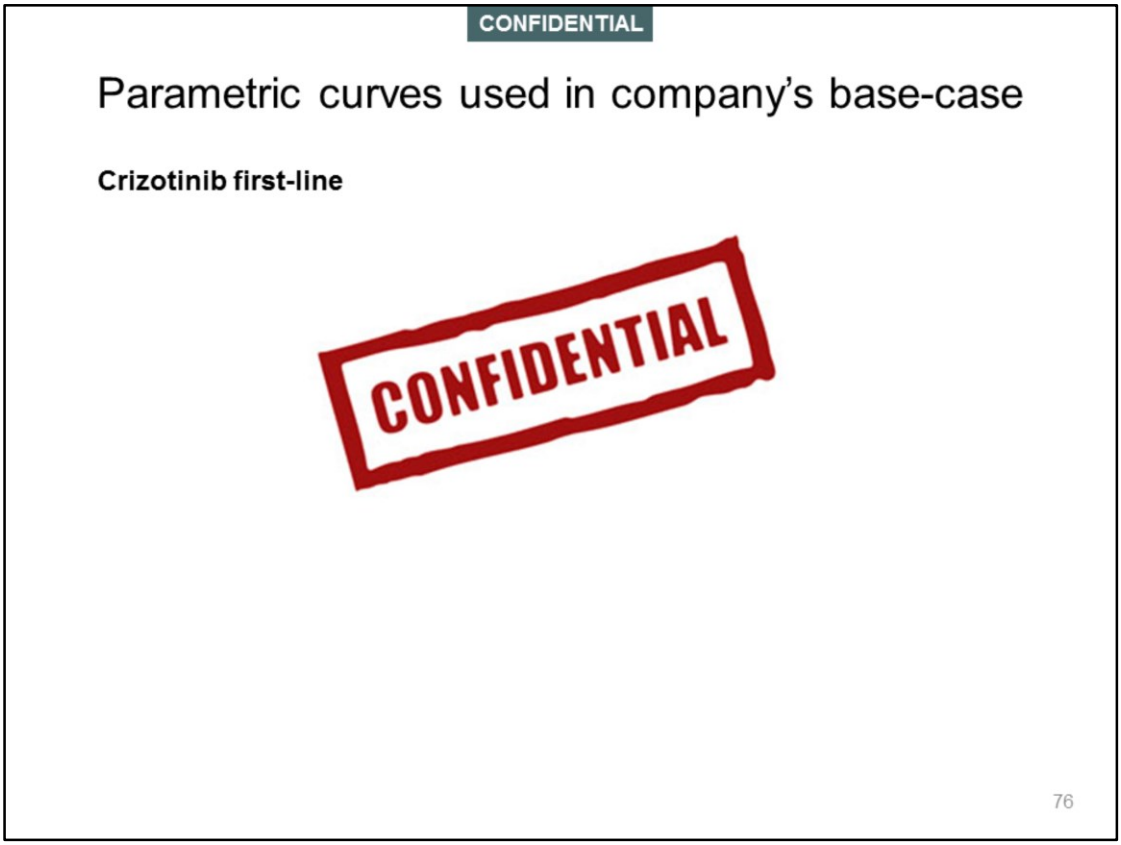
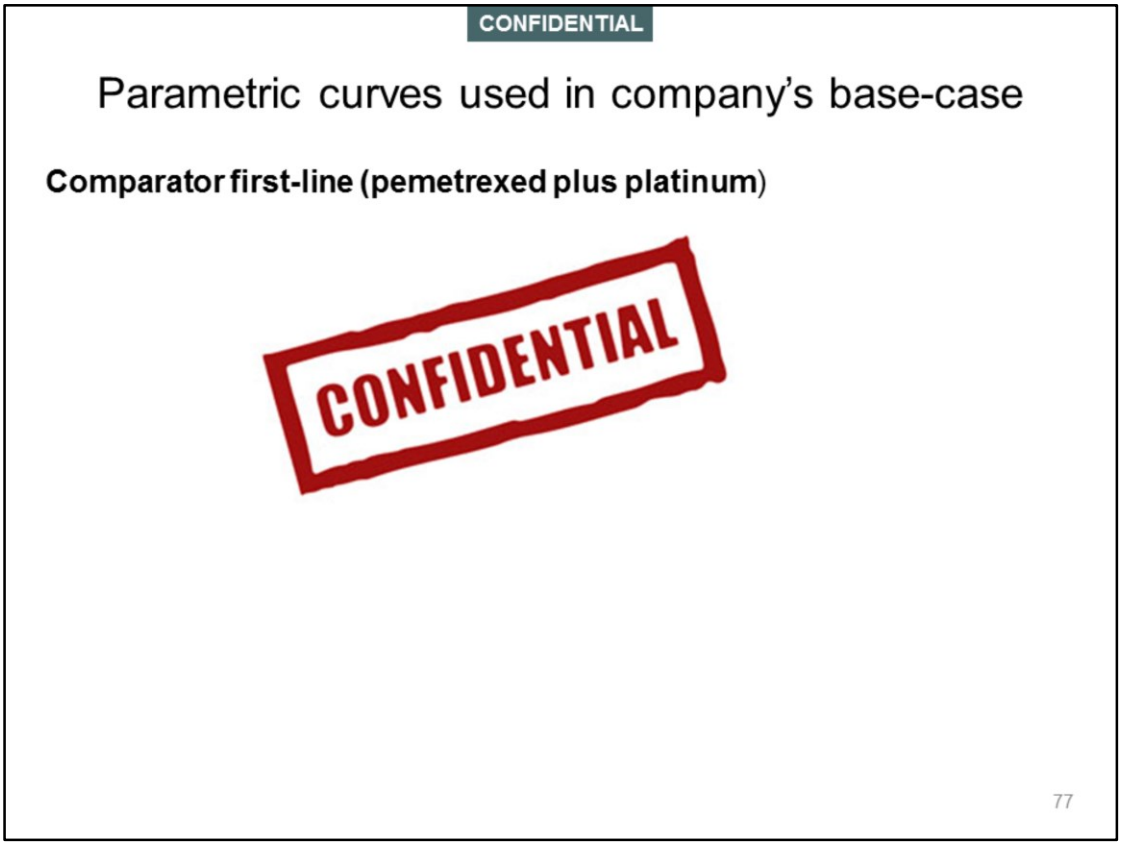
Summary of modelled effectiveness

		First-line (PROFILE 1014)	Subsequent-line (PROFILE 1007)
OS	Crizotinib	Exponential	Exponential (PH) adjusted from comparator HR=0.49 (CI=0.37 to 0.64)
	Comparator	Exponential	Exponential (PH)
PFS	Crizotinib	Stratified log-normal	Weibull
	Comparator	Stratified generalised gamma	Log-normal
TTD	Crizotinib	Stratified exponential	Weibull
	Comparator	Stratified gompertz	3 cycles only

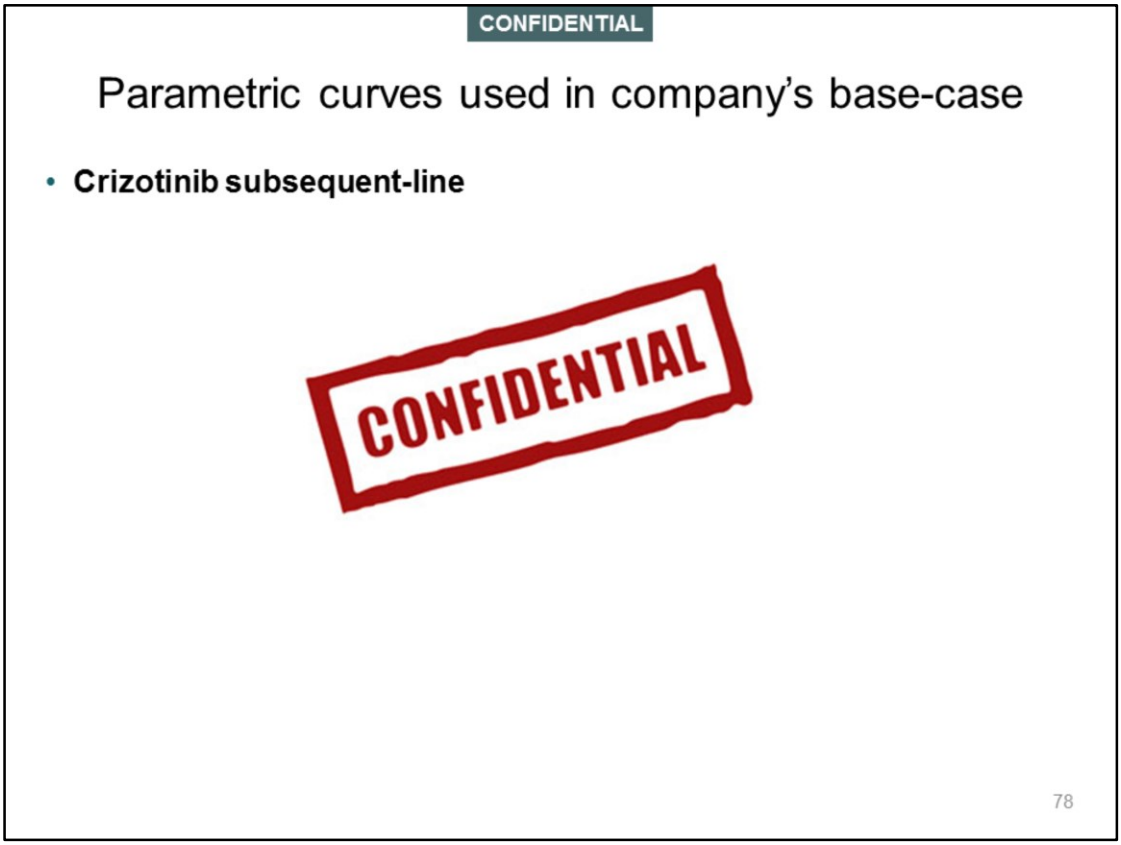
75



Source: Figure 18 Company's addendum 2 (page 8) replacing Figure 18 of Company's submission page 108



Source: Figure 19 of Company's submission page 109



Source: Figure 20 of Company's submission page 110

Parametric curve fitting for PROFILE 1001 scenario

- For the crizotinib treatment arm, standard parametric curve fitting was done for OS, PFS, and TTF, data from PROFILE 1001.
- For the comparator treatment arm, inverse of hazard ratios (from ALK-positive trials)
  - PROFILE 1014 for pemetrexed plus platinum (first-line)
  - PROFILE 1007 for docetaxel (subsequent-line)

  were applied to OS and PFS curves from PROFILE 1001
- No distinction was made between first and subsequent lines of treatment with crizotinib because of the small number of people receiving treatment as first line (n=7)

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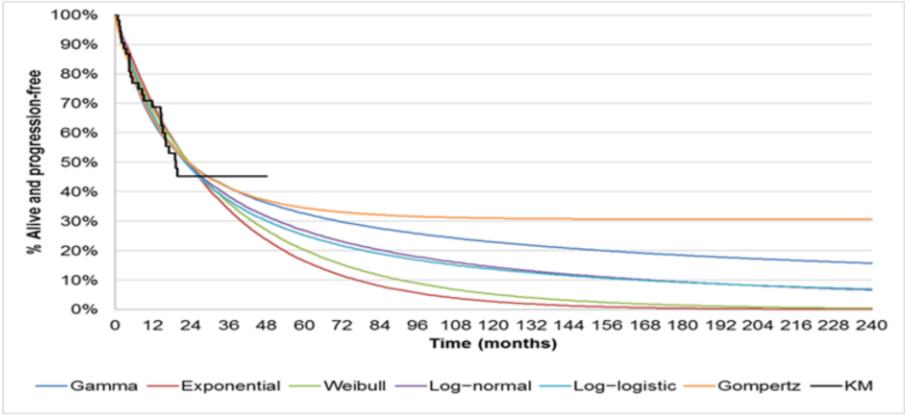
PROFILE 1001 scenario: Parametric curveS: PFS



Model	AIC	BIC
Log-normal	412.36	416.3
Gompertz	413.27	417.21
Generalised Gamma	413.51	419.42
Log-logistic	413.6	417.54
Exponential	**414**	**415.97**
Weibull	415.48	419.42

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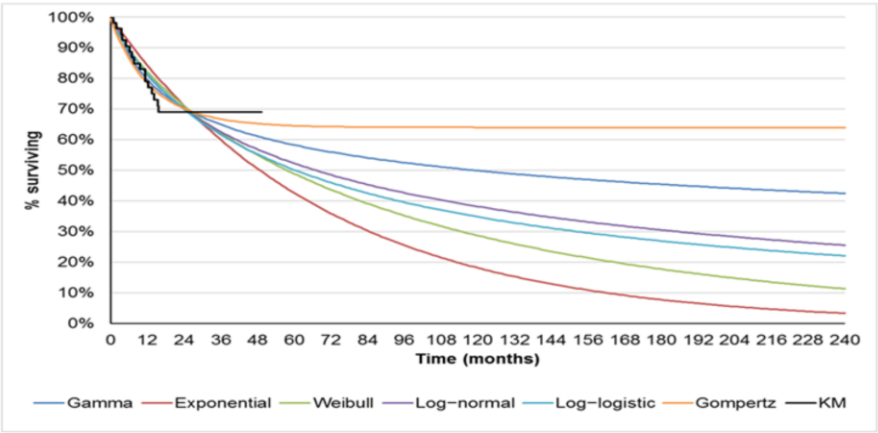
Source: Figure 26 and Table 35 of Company's submission (page 118)

PROFILE 1001 scenario: Parametric curves: OS



Model	AIC	BIC
Gompertz	276.54	280.48
Log-normal	278.01	281.95
Generalised Gamma	278.59	284.5
Log-logistic	279.34	283.28
Exponential	**279.41**	**281.38**
Weibull	280.42	284.36

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Source: Figure 24 and Table 32 of Company's submission (page 114 and 113)

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PROFILE 1001 scenario: Parametric curves: TTD

Model	AIC	BIC
Exponential	**464.71**	**466.68**
Log-normal	465.43	469.37
Log-logistic	465.89	469.83
Gompertz	466.03	469.97
Weibull	466.37	470.31
Generalised Gamma	467.39	473.3

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Source: Figure 30 and Table 38 of Company's submission (page 122)

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PROFILE 1001 scenario: Summary of modelled effectiveness

		First-line (PROFILE 1001)	Subsequent-line (PROFILE 1001)
OS	Crizotinib	Exponential (PH)	Same as first-line
	Comparator	Exponential (PH) adjusted from intervention HR=[redacted]	Exponential (PH) adjusted from intervention HR=2.61, CI=1.01 to 23.81
PFS	Crizotinib	Exponential (PH)	Same as first-line
	Comparator	Exponential (PH) adjusted from intervention HR=2.20 (CI=1.68 to 2.89)	Exponential (PH) adjusted from intervention HR=2.05 (CI=1.57 to 2.70)
TTD	Crizotinib	Exponential	Same as first-line
	Comparator	Stratified gompertz 6-cycles only	3 cycles only

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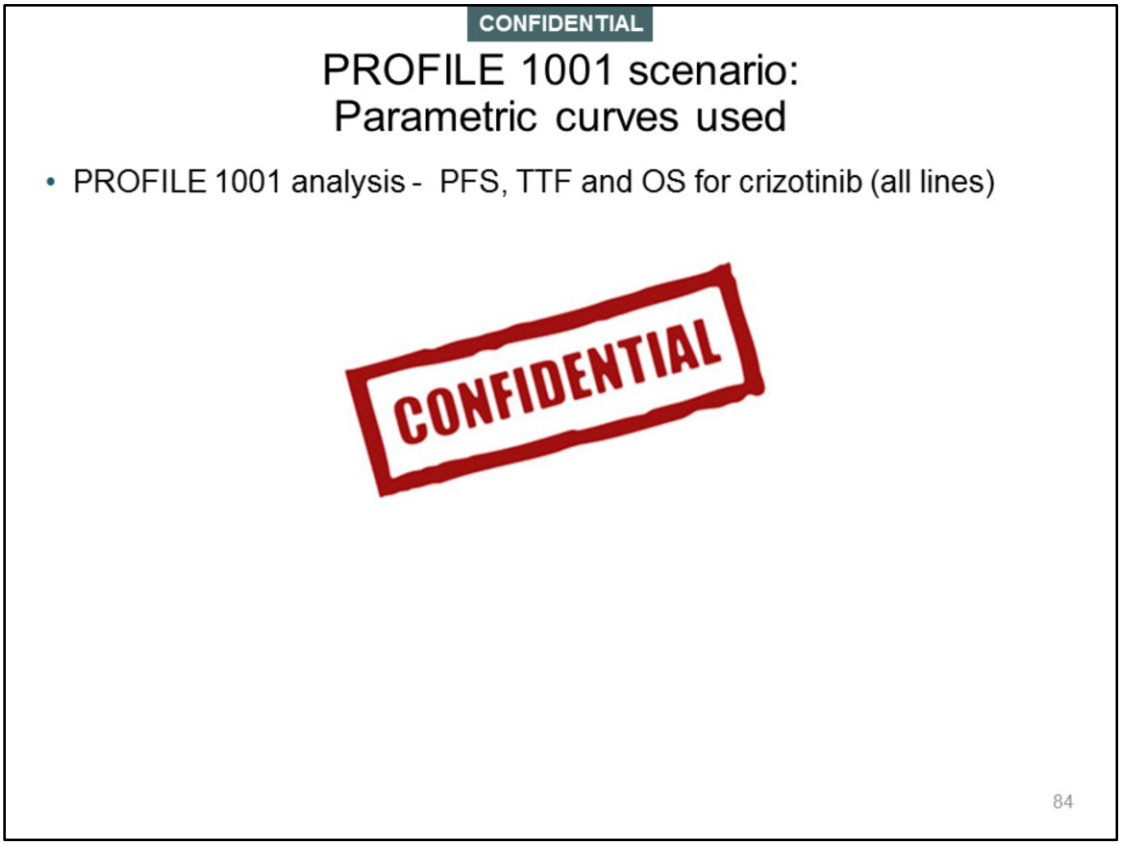

Source: Figure 31 of Company's submission (page 123)

Modelling of health-related quality of life

- HRQoL data were not collected in PROFILE 1001
- Company used utility value data from PROFILE 1014 and PROFILE 1007 assuming that HRQoL of ALK+ population could be used as proxy for HRQoL for the ROS1+ population
- Patients who continued having crizotinib beyond progression continued to have the 'treatment with crizotinib' utility value (0.81)
- Disutility as a result of adverse events were not modelled
  - Company stated 'utility estimates ….are taken directly from patients on treatment in the PROFILE 1014 and PROFILE 1007 trials, and hence this HRQoL reporting is expected to already reflect the negative changes in utility incurred through the adverse event profiles of the treatments'.

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Utility values (first-line)

State	Utility value: mean (SE)	95% CI	Source
Treatment with crizotinib	0.81 (0.01)	0.79 to 0.82	PROFILE 1014 (measured whilst on treatment)
Progression-free: Pemetrexed plus platinum therapy	0.72 (0.01)	0.70 to 0.74	PROFILE 1014
Progressed: second-line treatment with docetaxel monotherapy	0.66 (0.02)	0.58 to 0.74	PROFILE 1007
Progressed: third-line treatment with BSC	0.47 (0.05)	0.38 to 0.56	From literature Nafees et al. (2008) utility values for third-line treatment of NSCLC

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Source: Table 40 of Company's submission (page 128)

Utility values (subsequent-lines)

State	Utility value: mean (SE)	95% CI	Justification
Treatment with crizotinib	0.81 (0.01)	0.79 to 0.82	PROFILE 1007 (measured whilst on treatment)
Progression free on docetaxel	0.66 (0.02)	0.58 to 0.74	PROFILE 1007
Progressed – third line treatment with BSC	0.47 (0.05)	0.38 to 0.56	Nafees et al. (2008)

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Source: Table 40 of Company's submission (page 129)

Resource use and costs

Company included the following costs in the model

1. ROS1+ testing
2. Drug acquisition cost
3. Drug administration cost
4. Adverse event costs
5. Health state cost including monitoring costs
6. Palliative care cost

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Resource use and costs ROS1 testing

- Introduction of crizotinib to treat ROS1-positive advanced NSCLC would require additional resource for ROS1 testing
- Company envisaged
  - all patients with non-squamous NSCLC will be tested for ROS1 rearrangements
  - testing strategy was modelled as IHC (83% specificity and 100% sensitivity) followed by confirmatory FISH (diagnostic accuracy 100%)
  - cost assumed in the model for IHC £50 and for FISH £120
  - no impact of ROS1 testing on resource use except cost of the tests as NHS already has infrastructure to carry out testing
- Company modelled
  - upfront testing (with ALK and EGFR testing) in the base case and
  - sequential testing (after patients have been found to be for ALK and EGFR negative) in a scenario analysis

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Cost for ROS1 testing

Upfront ROS1 testing cost (base case)	
Test	**Cost**
IHC	Cost per IHC test: £50
FISH	Cost per FISH test: £120 Proportion of true-positive and false-positive patients from IHC: (1.69%+17%)= 18.7% Cost of FISH testing: £120*18.7% = £22.44
Total cost of testing	£50 + £22.44 = £72.44
Total cost per ROS1-positive patient diagnosed	ROS1 incidence in non-squamous patients: 1.69% £72.44 / 1.69% = **£4,287.92**
Scenario analysis – sequential testing	
IHC	Cost per IHC test: £50 Number of EGFR-negative and ALK-negative non-squamous NSCLC patients: (100% - 24.54% - 4.73%)= 70.73% Cost of IHC testing: £50*70.73% = £35.37
FISH	Cost per FISH test: £120 Number of true-positive and false-positive patients from IHC: (70.73%*17%)+1.69% = 13.72% Cost of FISH testing: £120*13.72% = £16.50
Total cost of testing	£35.37 + £16.50 = £51.84
Total cost per ROS1-positive patient diagnosed	£51.84 / 1.69% = **£3,068.08**

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Source: Tables 53 and 54 of Company's submission (page 143 and 144)

Drug acquisition cost

- Crizotinib costs in the first- and subsequent-line models calculated according to proportion of patients on treatment in each cycle according to TTD curve from relevant trials
- For pemetrexed + platinum in first-line model, costs are applied according to the proportion of patients on treatment in each cycle according to TTD data from the PROFILE 1014 trial
  - In the base case for concomitant company used cisplatin (54%) + carboplatin (46%)
  - investigated alternative proportions in a sensitivity analysis.
- For docetaxel costs in the subsequent-line model, company assumed a maximum of 3 cycles
  - based on a median PFS of 2.6 months PROFILE 1007 trial.
- Company assumed drug wastage for all treatments except for crizotinib
- Dosing for pemetrexed, cisplatin and docetaxel is based on body surface area
  - 1.73m^2 for first-line (TA406)
  - 1.80m^2 for subsequent-line (TA422)
- Dosing for carboplatin based on a target area under the concentration versus time curve (AUC in mg/mL/min)
  - Company assumed a target AUC for carboplatin of 5 mg/mL/min, which translates to 500 mg

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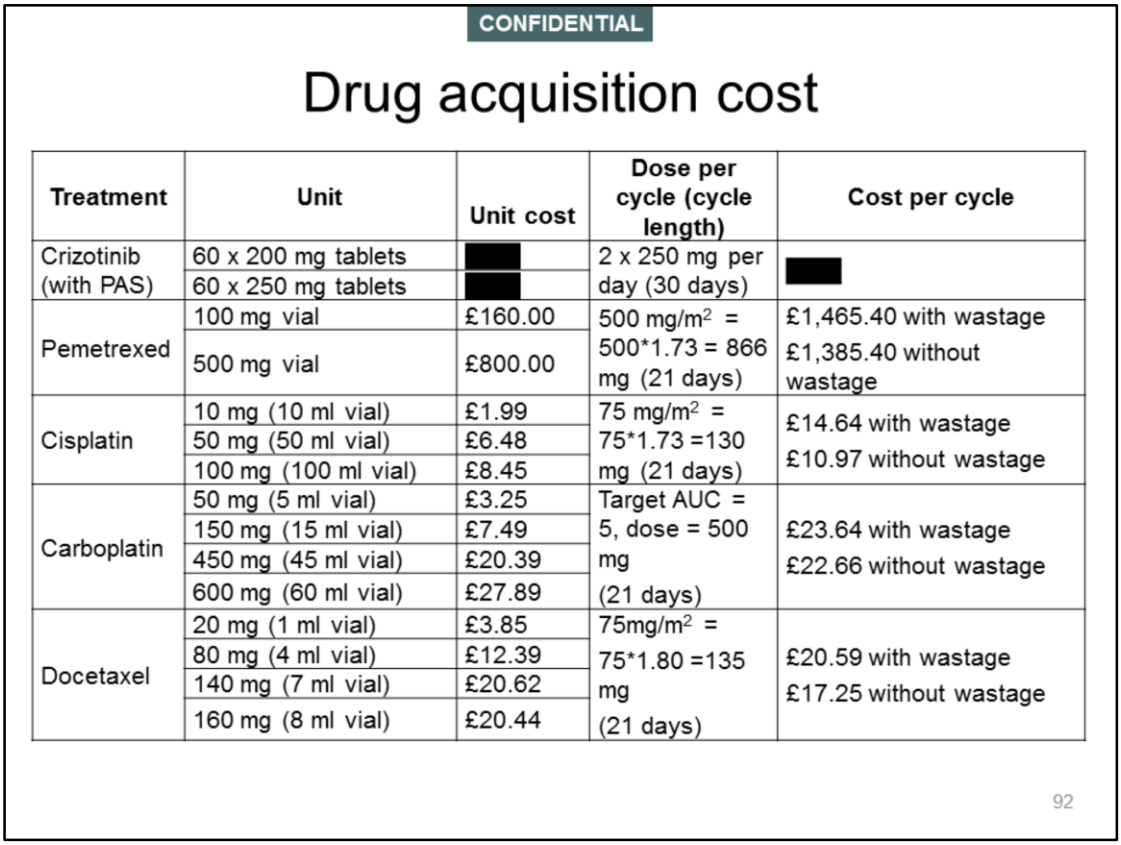

Treatment	Unit	Unit cost	Dose per cycle (cycle length)	Cost per cycle
Crizotinib (with PAS)	60 x 200 mg tablets	[redacted]	2 x 250 mg per day (30 days)	[redacted]
	60 x 250 mg tablets	[redacted]		
Pemetrexed	100 mg vial	£160.00	500 mg/m^2 = 500*1.73 = 866 mg (21 days)	£1,465.40 with wastage £1,385.40 without wastage
	500 mg vial	£800.00		
Cisplatin	10 mg (10 ml vial)	£1.99	75 mg/m^2 = 75*1.73 =130 mg (21 days)	£14.64 with wastage £10.97 without wastage
	50 mg (50 ml vial)	£6.48		
	100 mg (100 ml vial)	£8.45		
Carboplatin	50 mg (5 ml vial)	£3.25	Target AUC = 5, dose = 500 mg (21 days)	£23.64 with wastage £22.66 without wastage
	150 mg (15 ml vial)	£7.49		
	450 mg (45 ml vial)	£20.39		
	600 mg (60 ml vial)	£27.89		
Docetaxel	20 mg (1 ml vial)	£3.85	75mg/m^2 = 75*1.80 =135 mg (21 days)	£20.59 with wastage £17.25 without wastage
	80 mg (4 ml vial)	£12.39		
	140 mg (7 ml vial)	£20.62		
	160 mg (8 ml vial)	£20.44		

Source: Table 41 of Company's submission (page 130)

Drug administration cost

Cisplatin-containing regimens incurred a day case administration appointment, whereas carboplatin-containing regimens and docetaxel monotherapy were assumed to incur an outpatient administration appointment.

Treatment	Setting	Cost code	Description	Unit cost
Crizotinib	N/A	N/A	Dispensing cost (12 minutes pharmacist time)	£14.59
Pemetrexed plus cisplatin	Day case and regular day/night	SB14Z	Deliver Complex Chemotherapy, including Prolonged In fusional Treatment, at First Attendance	£406.63
Pemetrexed plus carboplatin	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Docetaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30

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Source: Table 42 of Company's submission (page 132)

Adverse event costs

- Company used treatment-related adverse events of Grade 3/4 occurring in ≥5% of patients
  - From PROFILE 1014 for first-line and
  - From PROFILE 1007 subsequent-line
  - From PROFILE 1001, for scenario analysis (hypophosphatemia was an additional Grade 3/4 adverse event that occurred in ≥5% of patients)

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Proportions of patients experiencing each adverse event

Adverse event	Crizotinib, First-line (PROFILE 1014)	Crizotinib, subsequent-line (PROFILE 1007)	Crizotinib, in PROFILE 1001 analyses (PROFILE 1001)	Pemetrexed plus platinum (PROFILE 1014)	Docetaxel monotherapy (PROFILE 1007)
Elevated transaminases	14.04%	15.70%	0.00%	2.37%	2.34%
Neutropenia	11.11%	13.37%	9.43%	15.38%	19.30%
Anaemia	0.00%	2.33%	0.00%	8.88%	5.26%
Leukopenia	1.75%	1.16%	0.00%	5.33%	4.68%
Thrombocytopenia	0.00%	0.00%	0.00%	6.51%	0.00%
Hypophosphatemia	0.00%	0.00%	13.21%	0.00%	0.00%
Pulmonary embolism	6.43%	5.23%	0.00%	6.51%	1.75%

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Source: Table 49 of Company's submission (page 141)

Cost of treating adverse events in company model

Adverse event	Resource required (hospital days)	Source	Unit cost	Total cost	Reference for unit cost (NHS reference costs 2015/16)
Anaemia	1.7	Consistent with TA296 (replaced by TA422) and TA406	£335.57 per day	£570.47	Iron Deficiency Anaemia with CC Score 0-1 SA04L
Thrombocytopenia	2.0		£303.52 per day	£607.04	Thrombocytopenia with CC Score 0-1 SA12K
Neutropenia	Managed by dose reduction (assumption)		-	-	-
Leukopenia			-	-	-
Elevated transaminases			-	-	-
Hypophosphatemia	1	Assumption	£287.19 per day	£287.19	Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N
Pulmonary embolism	1		£26.34 per day	£26.34	Weighted average of Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4 (YR23B) and Anticoagulant Services (Outpatient Attendances)

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Source: Table 50 of Company's submission (page 141)

Health state costs (1)

- Company assumed 2 separate monthly costs for
  - Patients in the progression free health state or the progressed disease health state whilst receiving second-line treatment (£185.53)
  - Patients in the progressed disease health state who were receiving third-line treatment with best supportive care (£181.65)

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Health state costs (2)

Progression free state or on-treatment progressed disease state		
Resources Required	**Frequency**	**Unit cost**
Outpatient Visit	0.75 visits per month	£151.12
GP visit	10% of patients per month	£27.00
Cancer nurse	20% of patients receive 1 per month	£69.20
Complete Blood Count	0.75 per month	£3.10
Biochemistry	0.75 per month	£1.18
CT scan	30% patients receive 0.75 per month	£132.19
Chest X-ray	0.75 per month	£30.26
Total cost per month (first- and second-line treatment)		**£185.53**

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Source: Table 47 of Company's submission (page 137)

Health state costs (3)

Patients in progressed disease health state receiving third-line treatment		
Resources Required	Frequency	Unit cost
Oncologist Visit	1 visit	£151.12
GP visits	28% patients (1 visit)	£27.00
Cancer nurse	10% patients (1 visit)	£69.20
Complete Blood Count	All patients, 1 per month	£3.10
Biochemistry	All patients, 1 per month	£1.18
CT scan	5% of patients, 0.75 per month	£132.19
X-ray	30% of patients, 0.75 per month	£30.26
Total cost per month, Progressed Disease		**£181.65**

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Source: Table 47 of Company's submission (page 137)

Cost of palliative care

- Company applied a one-off cost for palliative care before death
  - based on Georghiou and Bardsley (2014)
  - in line with previous NICE appraisal in untreated ALK-positive NSCLC, TA406

Cost	Unit cost	2015/16 Uplifted cost (PSSRU 2016)
District nurse	£278	£298
Nursing and residential care	£1,000	£1,106
Hospice care – inpatient	£550	£590
Hospice care – final 3 months of life	£4,500)	£4,830
Marie Curie nursing service	£550	£590
Total cost		**£7,415**

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Source: Table 48 of Company's submission (page 141)

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Company's result (deterministic)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line							
Pemetrexed+platinum	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]
Base case: subsequent-line							
Docetaxel	£11,076	1.39	0.71				
Crizotinib	[redacted]	2.75	1.63	[redacted]	1.36	0.93	[redacted]
Scenario analysis (PROFILE 1001): first-line							
Pemetrexed+platinum	£22,570	2.15	1.29				
Crizotinib	[redacted]	5.75	3.25	[redacted]	3.60	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line							
Docetaxel	£12,706	2.32	1.29				
Crizotinib	[redacted]	5.75	3.24	[redacted]	3.43	1.95	[redacted]

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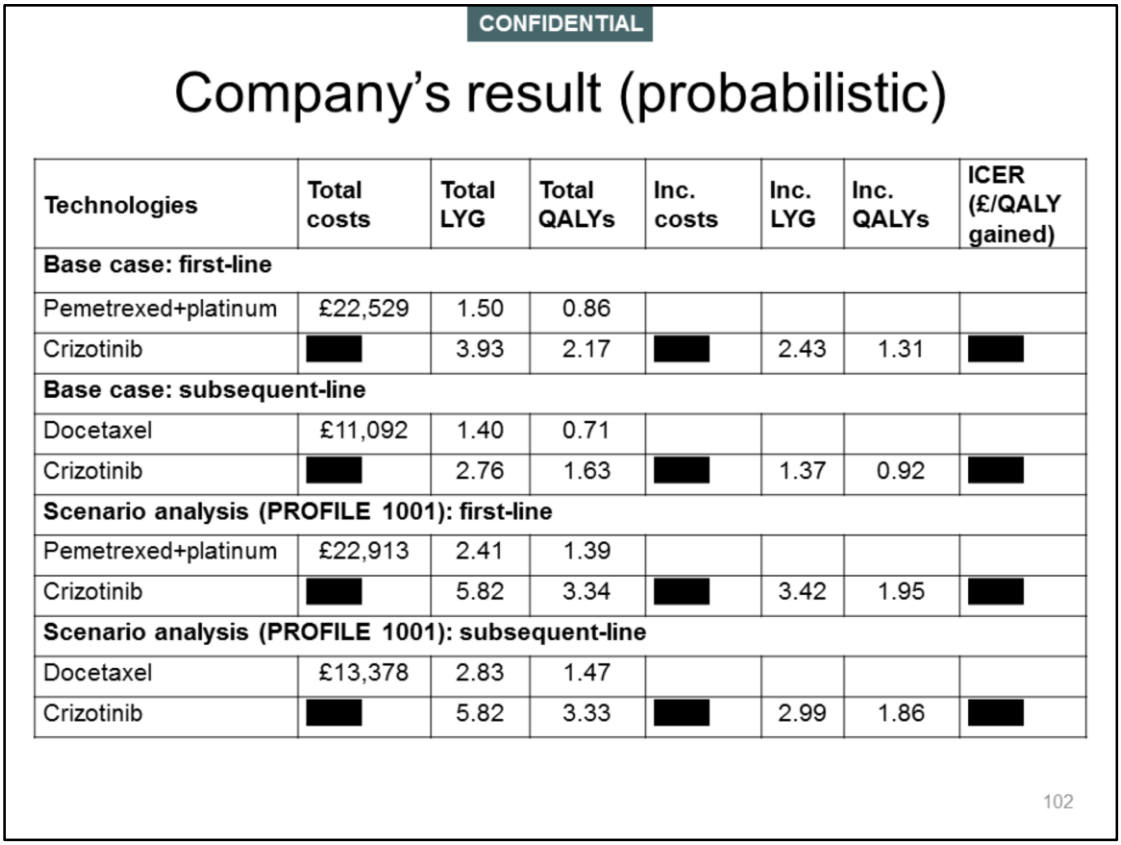
Source: Table 63 of Company's submission (page 158) and Table 62 of the Company's addendum 2 (page 18)



Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line							
Pemetrexed+platinum	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]
Base case: subsequent-line							
Docetaxel	£11,092	1.40	0.71				
Crizotinib	[redacted]	2.76	1.63	[redacted]	1.37	0.92	[redacted]
Scenario analysis (PROFILE 1001): first-line							
Pemetrexed+platinum	£22,913	2.41	1.39				
Crizotinib	[redacted]	5.82	3.34	[redacted]	3.42	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line							
Docetaxel	£13,378	2.83	1.47				
Crizotinib	[redacted]	5.82	3.33	[redacted]	2.99	1.86	[redacted]

Source: Table 68 of Company's submission (page 163) and Table 66 of the Company's addendum 2 (page 21)

Company's deterministic sensitivity analysis

- Company's deterministic sensitivity analysis showed the results were most sensitive to:
- For first-line, base case analysis
  - TTD and OS parametric model coefficients for crizotinib
  - utility value for BSC
- For subsequent-line, base case analysis
  - HR for OS
  - OS and PFS parametric curves for crizotinib
  - utility values for treatment with docetaxel and BSC
- For first-line and subsequent-line PROFILE 1001 analysis HR for OS
  - OS, PFS and TTD parametric curves for crizotinib
  - utility value for BSC.

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Company's scenario analysis (base-case)

Scenario	Scenario setting	First-line ICER	Subsequent-line ICER
	Base case	[redacted]	[redacted]
1	Time horizon 5 years	[redacted]	[redacted]
2	Time horizon 10 years	[redacted]	[redacted]
3	Time horizon 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	**Sequential testing for ROS1**	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	N/A
7	Crossover adjustment method: Log-rank	[redacted]	N/A
8	Weibull OS models	[redacted]	N/A
9	Gamma OS models	[redacted]	N/A
10	Log normal OS models	[redacted]	N/A
11	Log logistic OS models	[redacted]	N/A
12	Gompertz OS models	[redacted]	N/A
13	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

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Source: Table 71 Company's addendum 2 (page 24)

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Company's scenario analysis (PROFILE 1001 analysis)

S. No	Scenario	First-line ICER	Subsequent-line ICER
	PROFILE 1001	[redacted]	[redacted]
1	Time horizon 5 years	[redacted]	[redacted]
2	Time horizon 10 years	[redacted]	[redacted]
3	Time horizon 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	Sequential testing for ROS1	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	[redacted]
7	Maximum of 4 pemetrexed cycles	[redacted]	[redacted]
8	Include covariate for line of treatment for crizotinib	[redacted]	[redacted]
9	Weibull OS model	[redacted]	[redacted]
10	Weibull PFS model	[redacted]	[redacted]
11	Weibull TTF model	[redacted]	[redacted]
12	Weibull OS, PFS, TTF model	[redacted]	[redacted]
13	OS HR (1st line): RPSFTM Log-rank (new data cut)	[redacted]	N/A
14	OS HR (Subsequent-line): RPSFTM Wilcoxon	N/A	[redacted]
15	OS HR (Subsequent-line): RPSFTM Cox	N/A	[redacted]
16	PFS HR (Subsequent-line): crizotinib versus docetaxel	N/A	[redacted]
17	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

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Source: Table 73 of Company's submission (page 174)

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Probabilistic sensitivity analysis

- Company run 10,000 probabilistic iterations and total costs, and QALYs obtained from each simulation were recorded and averaged

Scenario	Probabilistic ICER	Probability of being cost effective at a cost-effectiveness threshold		
		£20K/QALY*	£30K/QALY*	£50K/QALY
Base-case				
First-line	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent-line	[redacted]	[redacted]	[redacted]	[redacted]
PROFILE 1001 scenario				
First-line	[redacted]	Not reported	Not reported	[redacted]
Subsequent-line	[redacted]	Not reported	Not reported	[redacted]

* Not reported in the submission, extracted from the model

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Source: Figures 35, 37, and 39 of Company's submission (page 162, 164 and 165) and Figure 33 of the Company's addendum 2 (page 22)

ERG's comments (1)

- The evidence underpinning the company's base case analyses is from a proxy population (ALK-positive advanced NSCLC)
- The ERG identified issues that prevented it from providing a detailed critique
  - The company used assumptions and modelling approaches from 3 previous NICE appraisals (TA406, TA422 and TA296) without providing sufficient justification
  - The ERG could not investigate the effects of key assumptions because of the lack of model functionality

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ERG's comments (2)

Post-progression survival

- Difference between overall survival gain and progression-free survival gain is improbably high

Health state	Crizotinib (months)	Pemetrexed + platinum (months)	Increment (months)	Increment
First-line				
Pre-progression	*16.8*	7.3	*9.5*	*33.3%*
Post-progression	*29.6*	10.4	*19.2*	*66.7%*
Total	*46.4*	17.7	*28.7*	100%
Subsequent-line				
Pre-progression	10.6	4.9	5.7	34.8%
Post-progression	22.5	11.8	10.6	65.2%
Total	33.0	16.7	16.3	100.0%

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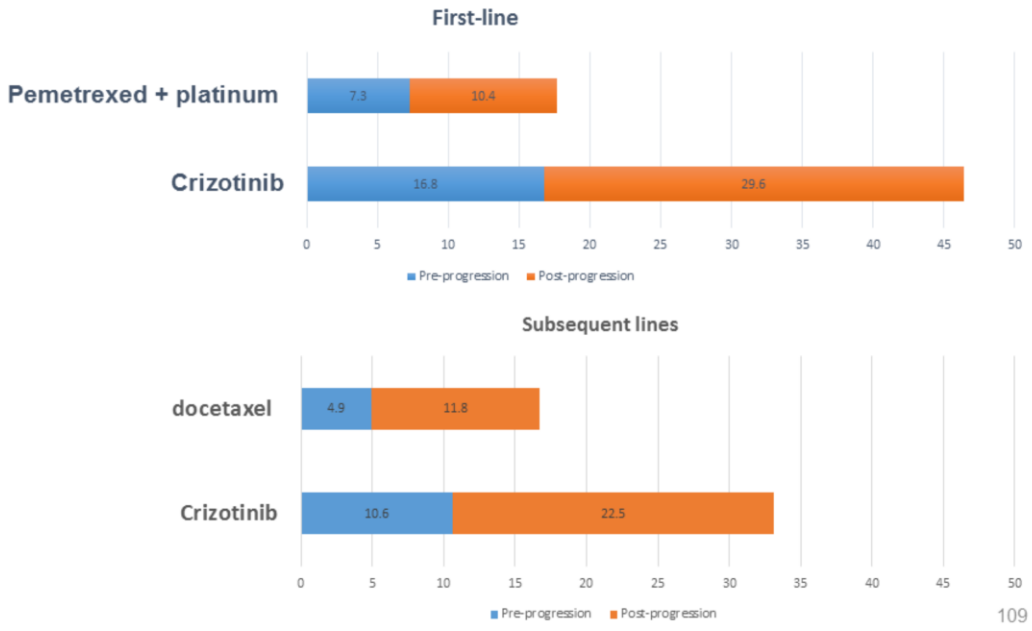
Source: ERG report table 37 and 38 (page 116-117) Note: for first-line, table has been updated following identification of an error in the company's original analysis regarding PFS modelling.

Modelled survival (months)



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ERG's comments (3)

PROFILE 1001 analysis

- Due to immature and heavily censored data, PROFILE 1001 analysis lacks face validity
  - modelling of PROFILE 1001 data resulted in very long survival projections
  - company estimated time-to-event curves for comparator by using inverse HRs from the PROFILE 1014 and PROFILE 1007 trials
  - These HRs based on RPSFTM crossover adjustments which resulted in implausible difference in overall survival

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ERG's comments (4)

Progression-free utility values: first-line treatment

- ERG agreed that the EQ-5D scores from PROFILE 1014 trial show greater HRQoL benefit with crizotinib than with pemetrexed + platinum
- However the ERG questioned the magnitude of that benefit noting
  - lack of long-term off-treatment EQ-5D data for pemetrexed + platinum treatment arm,
  - lack of a statistically significant difference between mean EQ-5D for those cycles where data have been recorded
  - open-label nature of the trial
- The ERG explored other scenarios
  - no HRQoL benefit with crizotinib
  - using a PFS utility value of 0.75 (preferred by committee during TA406) for treatment with pemetrexed + platinum.
- The ERG commented that utility values reflect PROFILE 1014 trial population, whereas, in the first-line base case model, the time-to-event estimates have been adjusted to reflect the population observed in clinical practice

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ERG's comments (5)

Cost of pulmonary embolism

- The ERG considered the company's estimated cost for pulmonary embolism (£26.34) to be underestimated
  - Hospital Episode Statistics report mean time in hospital for pulmonary embolism to be 6 days.
  - NICE guidance on treating thromboembolism indicates that patients should be initially treated for at least 5 days with a low molecular weight heparin (LMWH) and that a LMWH should be given for 6 months if a patient with active cancer develops a pulmonary embolism.

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ERG's comments (6)

Testing for ROS1 rearrangements

- The ERG questioned the company's approach that assumed upfront testing for subsequent-line model
  - Clinical advice to ERG: only a small percentage of patients who are eligible to receive crizotinib as a subsequent-line treatment would not have already been tested for ALK and EGFR mutations earlier in their treatment pathway.
  - In the subsequent-line model sequential testing (ROS1 testing in EGFR- and ALK-negative population) would be more appropriate
- The ERG noted that NHS laboratory services may offer a discount when testing for more than one mutation at the same time.
  - All Wales Genetic Laboratory list price for FISH analysis (ALK) is £120 and for EGFR is £175 when both test undertaken at the same time is price is £250, (15% discount)
  - Similar discount plausible for upfront cost of carrying testing for ROS1 alongside other tests

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ERG's exploratory analyses (1)

Citing the lack of transparency of data and model functionality issue, the ERG did not provide its preferred assumptions for the base-case

ERG explored alternative modelling approaches for time to event data and utility values

Overall survival: first-line treatment

- ERG explored 2 scenarios
  - PFS treatment effect is the same as the PPS treatment effect
    - Implemented using PFS HR to modelled crizotinib OS estimates
    - ERG noted that this analysis should be treated with caution as proportional hazard assumption did not hold for PFS in the PROFILE 1014
  - no benefit with crizotinib after progression
    - PPS is equal for both treatments and any gain in OS is attributable only to better survival before progression
    - implemented by adjusting the exponential OS curve for pemetrexed so that PPS is equal to PPS for treatment with crizotinib

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ERG's exploratory analyses (2)

Overall survival: subsequent-line treatment

- ERG questioned company's approach of applying PFS HR from PROFILE 1007 trial to the RPSFTM-adjusted docetaxel OS curve
  - 'applying a HR to OS data that has already been adjusted for crossover somewhat defeats the point of trying to find a method that avoids the pitfalls of the RPSFTM approach'
- ERG explored 2 OS scenarios
  - OS treatment effect=PFS HR and
  - OS treatment effect=no PPS gain

  based on an exponential curve for treatment with crizotinib calculated from unadjusted OS estimates from the PROFILE 1007 trial

  ERG commented that not adjusting for patients who receive further active treatment is an optimistic assumption for treatment with crizotinib

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ERG's exploratory analyses (3)

Progression-free utility values: first-line treatment

- The ERG explored the impact of assuming no difference in PFS utility values between the crizotinib treatment arm and the pemetrexed + platinum treatment arm
  - Using crizotinib utility value (0.81) for both treatments
  - Using pemetrexed utility value (0.72) for both treatments
- The ERG also used PFS utility value (0.75) for the pemetrexed utility value

ERG's Scenario

- ERG presented a series of ICERs combining aforementioned modelling approaches and utility values

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ERG's exploratory analyses (first-line)

ERG revisions	Incremental		ICER £/QALY
	Cost (£)	QALYs	
First-line base-case			
Company base case	[redacted]	1.28	[redacted]
OS treatment effect: use PFS HR from 1014	[redacted]	1.11	[redacted]
OS treatment effect: no PPS gain	[redacted]	0.56	[redacted]
PFS utility: crizotinib utility (0.81) for both	[redacted]	1.23	[redacted]
PFS utility: pemetrexed utility (0.72) for both	[redacted]	1.15	[redacted]
PFS utility: pemetrexed utility = 0.75	[redacted]	1.26	[redacted]

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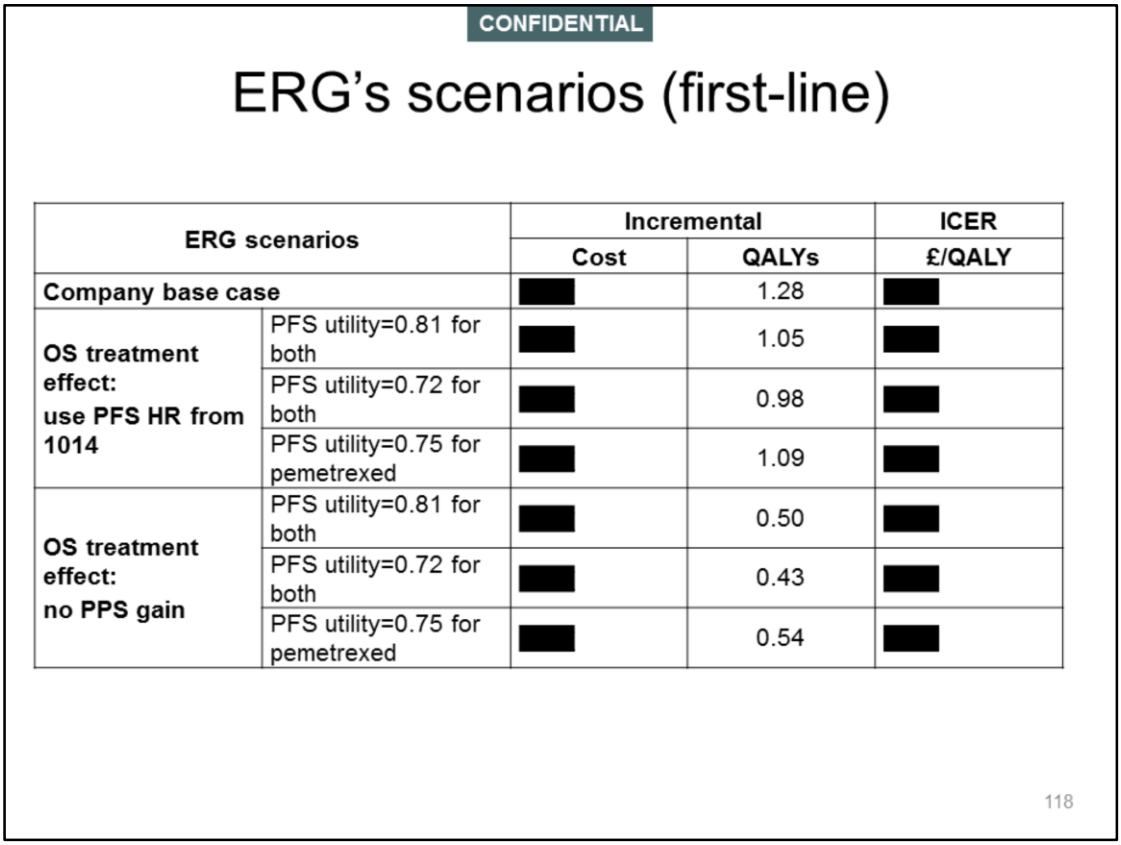
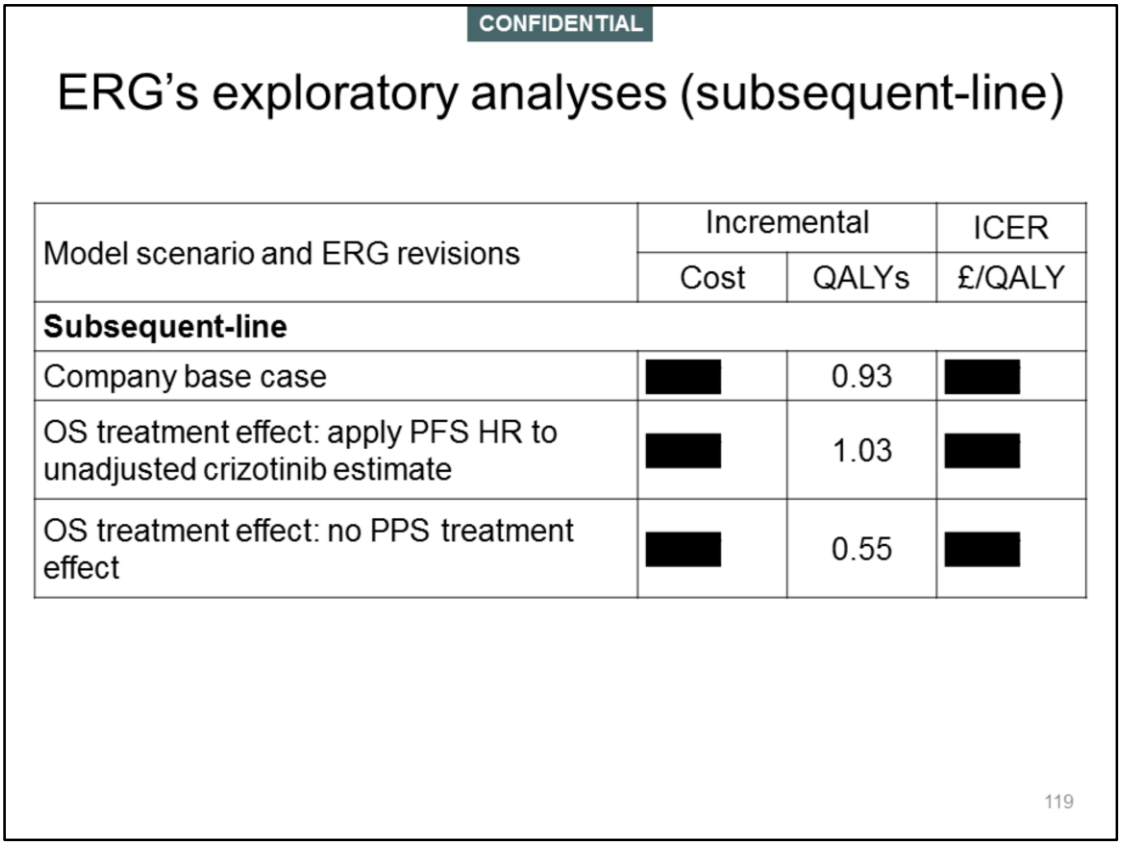
Source: Table 41 ERG updated ICER tables (page 2)



ERG scenarios		Incremental		ICER
		Cost	QALYs	£/QALY
Company base case		[redacted]	1.28	[redacted]
OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	1.05	[redacted]
	PFS utility=0.72 for both	[redacted]	0.98	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.09	[redacted]
OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	0.50	[redacted]
	PFS utility=0.72 for both	[redacted]	0.43	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	0.54	[redacted]

Source: Table 42 ERG updated ICER tables (page 3)



Model scenario and ERG revisions	Incremental		ICER
	Cost	QALYs	£/QALY
Subsequent-line			
Company base case	[redacted]	0.93	[redacted]
OS treatment effect: apply PFS HR to unadjusted crizotinib estimate	[redacted]	1.03	[redacted]
OS treatment effect: no PPS treatment effect	[redacted]	0.55	[redacted]

Source: Table 47 ERG updated ICER tables (page 3)

ERG's exploratory analyses: PROFILE 1001 analysis (1)

- ERG did not consider data from PROFILE 1001 to be robust enough to provide reliable estimates of time-to-event outcomes
- Comparative effectiveness of crizotinib and chemotherapy remained uncertain in ROS1-positive advanced NSCLC.
  - Treatment effect of pemetrexed + platinum, or docetaxel on ROS1-positive advanced NSCL remains unknown
- To improve the face validity of the results, the ERG explored
  - different assumptions of **treatment effect** applied to the company's modelling of OS data of crizotinib
  - different modelling approaches for OS, PFS and TTD.

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ERG's exploratory analyses: PROFILE 1001 analysis (2)

Different treatment effect

- First line: company used RPSFTM (Wilcoxon)-adjusted hazard ratio from PROFILE 1014 to estimate the treatment effect for OS for the ROS1-positive advanced NSCLC population in the first-line setting.
  - The ERG applied PFS hazard ratio from PROFILE 1014 and assumed equal PPS for each treatment.
- Subsequent line: Company used the PFS hazard ratio from PROFILE 1007 in its PROFILE 1001 scenario for subsequent-line treatment.
  - The ERG explored the effect of assuming equal PPS for docetaxel and crizotinib.

Different modelling approaches for time to event data

- ERG explored the impact of remodelling OS, PFS and TTD from PROFILE 1001 by using 'all-lines' Kaplan-Meier data directly as far as possible and then appending an exponential tail to project out to the time horizon

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ERG's exploratory analyses: PROFILE 1001 analysis (3)

ERG exploratory analyses	Incremental		ICER
	Cost	QALYs	£/QALY
First-line			
Company PROFILE 1001 scenario	[redacted]	1.95	[redacted]
OS treatment effect: use PFS HR from 1014	[redacted]	1.71	[redacted]
OS treatment effect: no PPS gain	[redacted]	1.13	[redacted]
Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	1.43	[redacted]
PFS utility: crizotinib utility (0.81) for both	[redacted]	1.84	[redacted]
PFS utility: pemetrexed utility (0.72) for both	[redacted]	1.70	[redacted]
PFS utility: pemetrexed utility = 0.75	[redacted]	1.91	[redacted]

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Source: Table 45 ERG report (page 136)

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ERG's exploratory scenarios: PROFILE 1001 (first-line) (4)

Model scenarios		Incremental		ICER
		Cost	QALYs	£/QALY
Company PROFILE 1001 scenario		[redacted]	1.95	[redacted]
OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	1.59	[redacted]
	PFS utility=0.72 for both	[redacted]	1.46	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.67	[redacted]
OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	1.02	[redacted]
	PFS utility=0.72 for both	[redacted]	0.89	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.09	[redacted]
Remodel crizotinib time-to-event: K-M data+ exponential	PFS utility=0.81 for both	[redacted]	1.33	[redacted]
	PFS utility=0.72 for both	[redacted]	1.18	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.40	[redacted]

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Source: Table 46 ERG report (page 137)

ERG's exploratory analyses: PROFILE 1001 (subsequent-lines) (5)

ERG exploratory analyses	Incremental		ICER
	Cost	QALYs	£/QALY
Subsequent-line			
Company PROFILE 1001 scenario	[redacted]	1.95	[redacted]
OS treatment effect: no PPS gain	[redacted]	1.21	[redacted]
Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	1.45	[redacted]

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Source: Table 47 ERG updated ICER tables (page 4)

End-of-life

1. **Short life expectancy (less than 24 months)**

- The company expected life expectancy to be less than 24 months
  - no conclusive evidence that ROS1-positivity is a better prognostic factor for survival, compared to unselected NSCLC.
  - opinion from 12 UK clinical experts, supports similar PFS in chemotherapy-treated ROS1-positive patients than chemotherapy-treated ALK-positive patients.
  - limited data on OS for ROS1-positive advanced NSCLC patients
  - Estimated median OS in ALK-positive range from 6 to 22 months, with median OS in the chemotherapy arm of PROFILE 1007 reaching 21.9 months at the final analysis.

ERG commented that evidence for life expectancy in the ROS1-positive advanced NSCLC population is uncertain

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End-of-life

- Evidence of extension to life (at least an additional 3 months)
  - in PROFILE 1001, median PFS was 19.3 months,
  - Ii a previous appraisal (TA422) of it was acknowledged that PFS is a conservative indicator of OS
  - Crizotinib demonstrated clear benefits in terms of tumour response in PROFILE 1001,
  - In both first-line and subsequent-line settings, NICE has accepted an extension of life of more than 3 months in ALK-positive NSCLC patients receiving crizotinib
  - The model predicts an extension to life associated with crizotinib in ROS1-positive patients of 2.39 years compared to pemetrexed plus platinum therapy and 1.36 years compared to docetaxel therapy

ERG noted that given the lack of a comparator to crizotinib in the PROFILE 1001 study, the duration of extension to life in the ROS1-positive advanced NSCLC population is uncertain.

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Equality issues

- Company commented that if there are regional variations in the access to ROS1 testing, this could lead to inequitable access.
- Company noted the upfront testing strategy of all non-squamous NSCLC as proposed by the company would reduce the inequality associated with access of targeted therapy to ROS1-positive patients.
- Company considered sequential testing strategy may increase inequities, as ROS1-positive patients would experience a delay in access to targeted therapy, compared to EGFR-positive and ALK-positive patients.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

September 2017

File name	Version	Contains confidential information	Date
NICE Crizotinib ROS1 Document B	**FINAL**	**Yes**	**12th September 2017**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and [redacted] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [redacted] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the full marketing authorisation for crizotinib in ROS1-positive advanced non-small cell lung cancer (NSCLC). Pemetrexed plus cisplatin/carboplatin and docetaxel have been considered as relevant comparators in this submission.

Data for crizotinib in ROS1-positive advanced NSCLC are available in both first- and subsequent-lines from the phase I pivotal trial PROFILE 1001, providing evidence for the whole indication of crizotinib for the treatment of ROS1-positive advanced NSCLC. However, due to the single-arm trial design, it was not possible to collect comparative data from standard of care medicines used in clinical practice. A systematic literature review (SLR) of studies in ROS1-positive advanced NSCLC failed to identify comparative data; the paucity of which highlights the need to consider viable alternative approaches to address the issue. One such approach is to use the comparator data from randomised controlled trials (RCTs) of patients with anaplastic lymphoma kinase (ALK) gene-rearrangements as a proxy for the efficacy and safety of crizotinib in the ROS1-positive NSCLC population. This is believed to be plausible, firstly, because ROS1 and ALK receptor tyrosine kinases (RTKs) are both part of the insulin-receptor family and consequently share close structural homology between the adenosine triphosphate (ATP)-binding kinase domains, to which crizotinib binds with high affinity in both ROS1 and ALK RTKs. Secondly, the clinical behaviour of ROS1- and ALK-positive NSCLC are similar to each other, but distinct from an unselected population of patients with NSCLC, despite ROS1- and ALK-positive NSCLC appearing to be mutually exclusive.[1, 2] The clinical similarities between ROS1- and ALK-positive NSCLC, and the generalisability of ALK data to the ROS1-positive population, is supported and validated by 12 clinical experts in the United Kingdom (UK).[3]

The choice of comparators in the current submission was based on clinical guidelines, the National Institute for Health and Care Excellence (NICE) guidance and UK expert opinion,[4-6] as well as the availability of efficacy data from the studies including patients with ROS1-positive advanced NSCLC or proxy data from the studies including patients with ALK-positive advanced NSCLC.[5, 7, 8] The comparators have been chosen to reflect UK clinical practice and additionally to minimise the uncertainty in the analysis, given the paucity of data from the clinical studies which specifically included patients with ROS1-positive advanced NSCLC. The comparators included in this submission are pemetrexed plus platinum therapy in the first-line, and docetaxel monotherapy in the subsequent-line. These comparators were accepted by the committees in the appraisals of crizotinib in untreated and previously treated ALK-positive NSCLC.[5, 8] The use of data from the ALK-population in the economic analysis was chosen in order to minimise the uncertainty from the limited data available in ROS1-positive NSCLC. Data from ROS1-positive NSCLC is presented as a scenario economic analysis.

No data that specifically addresses the clinical outcomes for ROS1-positive advanced NSCLC and that could be used to form a reliable comparison are available for the other comparators listed in the final scope. These therapies (first-line docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with platinum drug; first-line pemetrexed maintenance treatment; first-line single-agent chemotherapy; subsequent-line docetaxel with nintedanib; and subsequent-line

best supportive care [BSC]) are therefore excluded from consideration in this submission. For the rationale for their exclusion, please refer to Table 1.

A summary of the decision problem for crizotinib in ROS1-positive advanced NSCLC is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with ROS1-positive advanced non-small cell lung cancer	Adults with ROS1-positive advanced NSCLC	N/A
Intervention	Crizotinib	Crizotinib 250 mg	N/A
Comparator(s)	Untreated disease: • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment • Single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based therapy After previous chemotherapy treatments: • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care	• Pemetrexed in combination with platinum • Docetaxel monotherapy	• Biological and clinical similarities between the ROS1 and ALK oncogenes, as well as similarities in patient characteristics of ROS1- and ALK-positive NSCLC patients, mean that it is possible to use ALK data as a proxy for ROS1 data. The generalisability of ALK data to ROS1-patients is validated and supported by 12 UK leading clinical experts[3] • No comparators have sufficient data in the ROS1-positive population, but due to the similarities between ROS1 and ALK, pemetrexed plus cisplatin/carboplatin and docetaxel are included as comparators for crizotinib in this submission, using data from the ALK-positive NSCLC population, including in the economic analysis to avoid the uncertainty associated with the data from the small number of ROS1-positive patients • Clinical expert opinion suggests that it is uncommon for docetaxel, paclitaxel or vinorelbine with platinum-based chemotherapy to be used in non-squamous patients in the first-line setting. These are instead therapies more commonly used to treat squamous NSCLC. Therefore, these

			comparators are not included in this submission • Similarly, only a small proportion of patients (~15%) of patients with advanced NSCLC would be eligible for pemetrexed maintenance and therefore this therapy was not included in the submission. Furthermore, there is insufficient evidence on the efficacy of pemetrexed maintenance in ROS1-positive NSCLC patients, and the data available from the ALK-population is from a mixed chemotherapy comparator (pemetrexed plus platinum followed by pemetrexed maintenance) • Only data in unselected NSCLC are available for first-line docetaxel, gemcitabine, paclitaxel and vinorelbine; first-line single agent chemotherapy with a third-generation drug; subsequent-line docetaxel with nintedanib; and subsequent-line BSC. Because ROS1-positive NSCLC is fundamentally different to unselected NSCLC, it is not possible to use these data to inform a reliable comparison, and therefore these therapies are not included in this submission
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	As per final scope	N/A

Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The availability of any patient access schemes for the intervention or comparator technologies will be taken into account • The use of crizotinib is conditional on ROS1-positive status. The economic modelling should include the costs associated with diagnostic testing for ROS1 status in people with advanced non-small-cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals	As per final scope	N/A
Special considerations including issues related to equity or equality	N/A	If regional variations in the access to ROS1-testing exists, this could lead to inequitable access	• The European licence for crizotinib required an accurate and validated test for ROS1-positivity • Diagnostic testing is not currently established in England and Wales for ROS1 • Upfront testing would reduce the potential inequality associated with access to ROS1-positive targeted therapy with crizotinib

Abbreviations: ALK, anaplastic lymphoma kinase; BSC, best supportive care; NICE, National Institute for Health and Care Excellence; N/A, not applicable; NSCLC, non-small cell lung cancer; UK, United Kingdom.

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with crizotinib for ROS1-positive advanced NSCLC is presented in Table 2. The summary of product characteristics (SmPC) and European public assessment report (EPAR) for crizotinib in this indication are presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Crizotinib (Xalkori®)
Mechanism of action	Crizotinib is a first-in-class, orally available, small-molecule, RTK inhibitor with selective, dose-dependent activity against ROS1 RTK and its oncogenic variants (e.g. ROS1 fusion proteins and selected ROS1 mutant variants).[7] Crizotinib is also an inhibitor of the ALK RTK and its oncogenic variants (i.e. ALK fusion events and selected ALK mutations), HGFR (c-MET) and RON RTKs[7]
Marketing authorisation/CE mark status	Crizotinib received a positive opinion from the CHMP on 21st July 2016 for the treatment of adults with ROS1-positive advanced NSCLC, and received EU marketing authorisation for this indication on 25th August 2016. Due to the rarity of the condition, the evidence base for crizotinib in ROS1-positive NSCLC was unavoidably limited. Despite this, the EMA were satisfied by the available evidence to approve crizotinib in the ROS1 population
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Crizotinib monotherapy has the following indications in the UK: • *XALKORI is indicated for the treatment of adults with ROS1-positive advanced NSCLC*.[7] This licensed indication represents the indication detailed in this submission. EU marketing authorisation was granted on 25th August 2016 for access in all lines • *XALKORI is indicated for the first-line treatment of adults with ALK-positive advanced NSCLC*.[9] EU marketing authorisation was granted on 24th November 2015 for first-line patients • *XALKORI is indicated for the treatment of adults with previously treated ALK-positive advanced NSCLC*.[10] EU marketing authorisation was granted on 23rd October 2012 for patients previously treated for advanced NSCLC Crizotinib has the following contraindications: • Severe hepatic impairment • Hypersensitivity to crizotinib or excipients listed in the SmPC[10]
Method of administration and dosage	Oral 250 mg twice daily (a total of 500 mg daily)
Additional tests or investigations	An accurate and validated assay for ROS1 is necessary for the selection of ROS1-positive patients for treatment with crizotinib[10]
List price and average cost of a course of treatment	**List price**: £4,689.00 for 1 pack 60 x 200 mg or 60 x 250 mg capsules **Average cost of a course of treatment**:

	• Based on an average course of treatment of [redacted] packs of crizotinib in the first-line setting, the average cost of a course of treatment is expected to be [redacted] at list price and [redacted] with PAS • Based on an average course of treatment of [redacted] packs of crizotinib in the subsequent-lines setting, the average cost of a course of treatment is expected to be [redacted] at list price and [redacted] with PAS
Patient access scheme (if applicable)	A simple confidential discount patient access scheme was agreed with the Department of Health for crizotinib in first-line ALK-positive NSCLC, and this scheme is to be applied to all future indications (including ROS1). This simple discount is a confidential [redacted] reduction in list price

Abbreviations: ALK, anaplastic lymphoma kinase; CHMP, Committee for Human Medicinal Products; EMA, European Medicines Agency; EU, European Union; HGFR, hepatocyte growth factor receptor; NSCLC, non-small cell lung cancer; PAS, patient access scheme; RON, Recepteur d'Origine Nantais; RTK, receptor tyrosine kinase; SmPC, Summary of Product Characteristics; UK, United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

Overview of the disease

- As a broad category, lung cancer is the third most common cancer in the UK, with NSCLC accounting for 88% of lung cancer cases; the majority of patients (75.3%) are diagnosed at an advanced stage of disease
- NSCLC can be stratified by genotype and histology and these stratifications are important in terms of outcomes and treatment options; ROS1-positive advanced NSCLC accounts for around 1.7% of non-squamous NSCLC, meaning it is very rare
- Currently there is no licensed targeted treatment option for patients with ROS1-positive advanced NSCLC available in the UK
- ROS1-positive advanced NSCLC and ALK-positive advanced NSCLC are very similar in terms of the structure of their RTKs and also in their clinical behaviour, including response to crizotinib. Their kinase domains share 77% amino acid identity within the ATP-binding site and crizotinib binds with a high affinity to both, which is consistent with this homology, and patient characteristics in these two subpopulations are similar (tend to be non-smokers and younger than unselected NSCLC and the histology is predominantly adenocarcinoma)
- Based on the similarities between ROS1- and ALK-positive NSCLC, the generalisability of data from ALK-positive patients to the ROS1-positive patients has been recognised by the European Medicines Agency (EMA) in their approval of crizotinib and is supported by 12 UK leading clinical experts from a recent UK advisory board
- NSCLC associated with ROS1 and ALK gene-rearrangements are fundamentally different from unselected NSCLC including unselected adenocarcinoma of the lung, as disease progression in ALK-positive and ROS1-positive NSCLC patients is dependent on the activated ALK or ROS1 RTK. Crizotinib specifically targets the RTKs from the ROS1 and ALK gene-rearrangements
- There is limited data available for the life expectancy of ROS1-positive NSCLC patients on current standard of care (chemotherapy). As ROS1-positivity is not expected to be a favourable prognostic factor, data from ALK-positive NSCLC populations can be used to estimate the life expectancy of patients with ROS1-positive NSCLC. Therefore, using ALK data, the life expectancy of patients with ROS1-positive NSCLC is estimated to be between 6–22 months on chemotherapy

Clinical pathway of care

- Currently patients with ROS1-positive advanced NSCLC do not have access to a targeted therapy
- Diagnostic testing for ROS1-positivity is not currently established in England and Wales, although centres are starting to define their own testing strategies
- Therefore, ROS1-positive NSCLC patients are currently treated using therapies available for unselected NSCLC patients

- Current standard of care for fit ROS1-positive patients includes first-line pemetrexed plus platinum therapy, and subsequent-line docetaxel monotherapy
- Pemetrexed maintenance is used in a small proportion of fit patients
- Docetaxel plus nintedanib is recommended by NICE for patients with advanced lung adenocarcinoma and BSC is an option for those patients unfit for systemic therapy

Proposed position of crizotinib

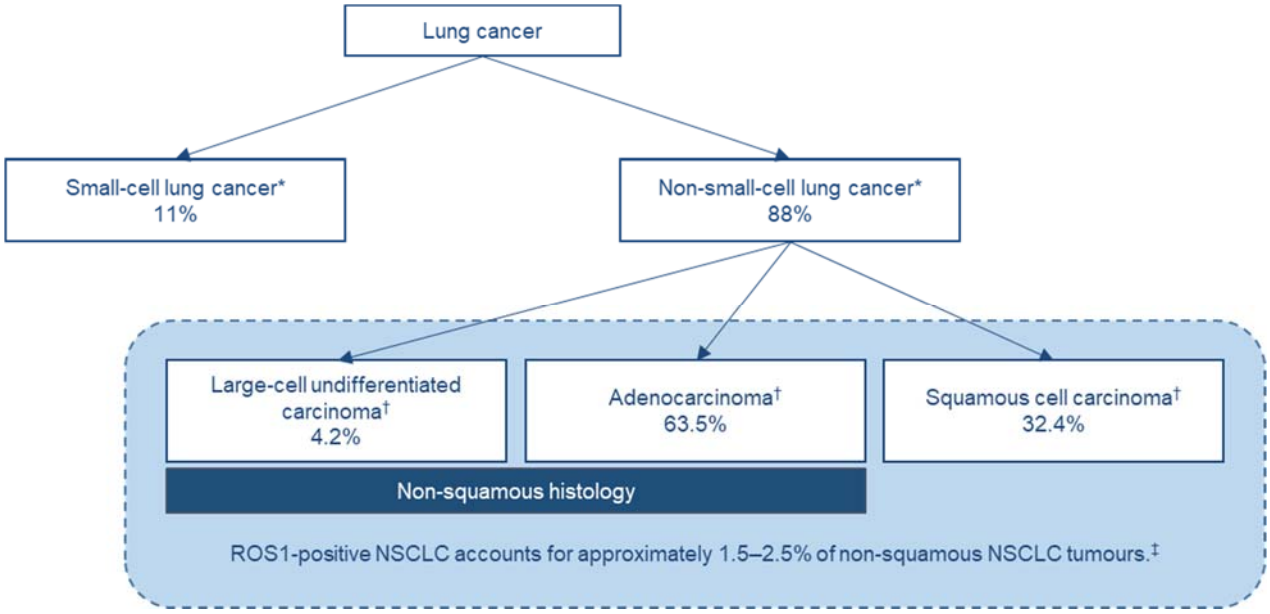
- As in the ALK-positive NSCLC population, crizotinib is appropriate for use in the first-line setting in ROS1 patients because this will provide crizotinib to patients who are most likely to respond to targeted inhibition with the greatest clinical benefit early on in the treatment pathway
- Access to crizotinib in the subsequent-line setting will ensure that patients who have progressed following chemotherapy and patients who received chemotherapy prior to their ROS1 diagnosis have access to a targeted therapy

B.1.3.1 Overview of the disease

Lung cancer

Lung cancer can be categorised into two major types: small-cell lung cancer (SCLC) and NSCLC.[11] NSCLC accounts for the majority (88% in England and Wales)[11] of lung cancer cases and can be sub-typed further into three histological types: adenocarcinoma (63.5% of NSCLC), large-cell undifferentiated carcinoma (4.2% of NSCLC) and squamous cell carcinoma (32.4% of NSCLC) (see Figure 1).[12] Both adenocarcinoma and large-cell undifferentiated carcinoma are classified as non-squamous histological sub-types of NSCLC.

Figure 1: Lung cancer and histological subtypes



All percentages presented are a proportion of total lung cancer.
Abbreviations: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

Sources:
* The proportion of patients with SCLC and NSCLC correspond to those reported in the National Lung Cancer Audit Report (2016) for England and Wales.[11] The sum of percentages does not equal 100% due to the exclusion of carcinoid with accounts for the remaining 1% of all lung cancer
† The proportion of lung tumours of each histology sub-type are derived from the Clinical Lung Cancer Genomics Project (2013).[12] Within this project, a number of tumours were given a classification of 'other', which may account for the lower than expected proportion of large-cell undifferentiated carcinoma observed in this study
‡ The proportion of non-squamous NSCLC tumours estimated to be ROS1-positive is taken from published ROS1 incidence studies; the incidence rate reported was converted, when necessary, to the incidence rate in non-squamous NSCLC [1, 13-15]

As a broad category, lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases.[16] Importantly, NSCLC can be stratified by histology and genotype, where clinical evidence supports consideration of different treatment pathways for distinct subtypes of lung cancer. ROS1-positive advanced NSCLC accounts for approximately 1.1–1.8% of non-squamous NSCLC,[1, 13, 14] meaning it is very rare and found almost exclusively in non-squamous tumours,[1, 13, 14] and is associated with patients of younger age and non-smoker status.[1, 17, 18] Of the published studies reporting the ROS1 incidence rate, the Scheffler *et al.* (2015) study was considered to be most representative of the ROS1 incidence in the UK, as the study sample was large and from Europe.[14] The ROS1 incidence reported by Scheffler *et al.* (2015) was 1.8% of adenocarcinoma patients.[14]

According to the National Lung Cancer Audit Report (2016), 38,232 cases of lung cancer were reported in England and Wales in 2015.[11] The outcomes for patients with lung cancer are largely dependent on many factors, including the stage of presentation of the disease.[19] Lung cancer is often diagnosed at an advanced stage due to the low index of suspicion surrounding the symptoms or the presence of symptoms only at an advanced stage of the disease.[20] In England, 75.3% of lung cancer cases are diagnosed at an advanced stage of disease (21.4% and 53.9% for stages III and IV, respectively).[21] Due to late diagnosis, the prognosis for patients diagnosed with lung cancer is often poor.[22]

Patients diagnosed with advanced NSCLC are clinically and radiologically followed-up until they experience disease progression. Progressive disease is defined radiologically using the Response Evaluation Criteria In Solid Tumours (RECIST) guidelines.[23, 24] RECIST is a validated tool used for defining radiological progression within clinical trial settings and is also applied in clinical practice. Radiological progression, however, does not necessarily translate to symptomatic progression. The current version of the guidelines is version 1.1, which replaced version 1.0.[24] Differences are identified in Table 3.

Once the lung cancer has progressed after first-line treatment, patients who are considered fit enough for follow-on therapy can receive a subsequent-line treatment with the aim of regaining control of the disease. At some point, however, patients will experience disease progression again. Disease progression has negative implications for both quality of life and overall survival.[25, 26]

Table 3: RECIST definitions of tumour response

Tumour response	RECIST v1.0 Definition	RECIST v1.1 Definition
Complete response	Disappearance of all target lesions	• Disappearance of all target lesions • Any pathological lymph nodes (whether target or non-target)

		must have reduction in short axis to <10 mm
Partial response	At least a 30% decrease in the sum of the longest diameters of target lesions compared with baseline	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive disease	At least a 20% increase in the sum of the longest diameter of target lesions compared with the smallest sum of longest diameter recorded since treatment started (best response) or the appearance of one or more new lesions	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
Stable disease	Neither progressive disease or partial response	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters whilst on study

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumours.
Source: RECIST v1.0: Nishino *et al.* (2010)[24]; RECIST v1.1: Eisenhauer *et al.* (2009)[23]

ROS1-status and molecular sub-types of NSCLC

It has been recognised that there are different molecular subtypes of lung cancer, and that there is a shift towards practising precision medicine with the availability of targeted therapies which can treat specific molecular subtypes of cancer. Targeted therapies are now the standard of care for patients with epidermal growth factor receptor (EGFR)-mutant or ALK-positive advanced NSCLC. ROS1-positive advanced NSCLC is considered to represent another group of patients who would benefit from a targeted treatment option.

Based on published studies, ROS1-positive advanced NSCLC is estimated to occur in 1.1–1.8% of NSCLC patients and to be found almost exclusively in non-squamous tumours.[1, 13, 14] This incidence is considerably lower than tumours harbouring ALK, EGFR or Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations, which account for between 3.4%, 15.3% and 32.6% of NSCLC, respectively.[12] This suggests that ROS1-positive NSCLC is rare in England and Wales. ROS1-translocations are usually mutually exclusive to other oncogenic drivers.[1, 2]

ROS1 was initially identified as an oncogenic product of an avian sarcoma ribonucleic acid (RNA) tumour virus.[27-29] It has since been identified as a key oncogenic driver in a number of other cancers, including NSCLC in 2007.[30] In lung cancer, there is no single most common fusion partner with ROS1, with several being described.[31] Different fusion partners are not thought to impact on the efficacy of crizotinib, as the ROS1 tyrosine kinase protein (and binding site for crizotinib) is consistent.[32] Inhibition of ROS1 is associated with anti-tumour activity in preclinical models, as demonstrated in both *in vitro* phenotypic assays and *in vivo* transgenic mouse and xenograft models.[7] As in ALK, crizotinib, via inhibition of ROS1, has demonstrated dose-dependent inhibition of cell proliferation and induced apoptosis in cell-based assays, as well as dose-dependent tumour regression in *in vivo* xenograft models.[5, 7]

The clinical and pathologic features of ROS1-positive tumours have been characterised, with ROS1-positivity showing associations with non-smoker status and a younger age of diagnosis.[7] In addition, ROS1-translocations are almost exclusively detected in non-squamous tumour types, and predominantly in adenocarcinoma tumour types.[7] NSCLC associated with an underlying ROS1 gene-rearrangement is, however, fundamentally different from unselected NSCLC and unselected adenocarcinoma, as disease progression in ROS1-positive NSCLC patients is dependent on the activated ROS1 RTK.[15, 30] Similarly, the clinical benefit of specific targeted therapies, such as crizotinib, is dependent on the role of the activated ROS1 RTK in driving cancer progression.[15, 30]

Similarities between ROS1 and ALK

The ROS1 oncogene encodes an orphan RTK related to ALK.[33] In both ROS1-positive and ALK-positive NSCLC the genetic translocation events lead to gene fusions that result in deregulated expression of the respective kinase domain, ALK or ROS1, with constitutive activation of the kinase activity.[15, 18, 30, 34] This oncogene activation event means that ROS1-positive and ALK-positive NSCLC are fundamentally different from unselected NSCLC and unselected adenocarcinoma, as disease progression is dependent on these activated RTKs.[15, 30] The kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites, and crizotinib binds with high affinity to both ALK and ROS1, as expected based on their homology.[35] This was recognised by the European Medicines Agency (EMA) as supporting the biology of ALK and ROS1 fusions in NSCLC in many ways being analogous.[7]

As with ALK-positive NSCLC patients, ROS1-positive NSCLC patients are usually non-smokers or light smokers, predominantly have histologic features of adenocarcinoma and younger in age.[1, 17] A small proportion of patients in both the ROS1-positive and ALK-positive NSCLC populations have demonstrated sensitivity to pemetrexed-based chemotherapy, providing further evidence to support the similarities between these two populations.[18] These similarities were supported and validated by leading UK clinical experts.[3]

Given the similarities between ROS1-positive and ALK-positive NSCLC patients, data from RCTs of crizotinib in ALK-positive patients are deemed relevant to the clinical efficacy and safety of crizotinib in ROS1-positive patients. PROFILE 1007 provided evidence for the approval of crizotinib for previously treated ALK-positive advanced NSCLC by the EMA and NICE,[8, 36] and PROFILE 1014 provided data on the activity of crizotinib in the approval of crizotinib for first-line ALK-positive advanced NSCLC.[5, 37] As such, the data from PROFILE 1007 and 1014 in ALK-positive advanced NSCLC has been deemed suitable by clinical experts as an appropriate proxy for ROS1 and will be used where data for crizotinib versus a comparator in ROS1-positive advanced NSCLC are limited.[3]

There are substantial similarities in the patient characteristics of the pivotal ROS1 trial PROFILE 1001, and ALK trials PROFILE 1007 and PROFILE 1014, with comparable median age and smoking status across all three trials (see Section B.2.3.2). The majority of patients were classed as having adenocarcinoma histology across the ROS1 and ALK populations (94.0–96.2%). These similarities support the use of data from ALK-positive RCTs (PROFILE 1007 and PROFILE 1014) as a proxy to inform the current submission, given the lack of data available in ROS1-positive NSCLC due to the ultra-orphan nature of this disease. The EMA also concluded in their authorisation of crizotinib that:

"Based on the pre-clinical and anti-tumour similarities between ALK-positive and ROS1-positive NSCLC the EMA concluded there was no concern regarding the efficacy of crizotinib in the first-line treatment of patients with ROS1-positive NSCLC." [7]

In line with this, the efficacy and safety data from ALK-positive NSCLC patients are important evidence sources to support the appraisal of ROS1-positive NSCLC patients.[7]

Life expectancy – lung cancer and NSCLC

Current prognosis for patients with lung cancer is poor, with five-year survival rates in England and Wales estimated to be around 10%.[38] This five-year survival rate is considerably worse than other common cancers such as breast (87%) and prostate cancer (85%).[39] A poorer prognosis for patients with lung cancer is believed to be associated the with high proportion of patients presenting at an advanced stage of disease (73.5% diagnosed at stage III or IV) and the concurrent difficulty in treating patients with advanced or metastatic disease.[21] The outlook for patients with advanced-stage lung cancer in England and Wales is markedly worse than for those patients with early-stage disease for whom surgery is a curative treatment option (see Table 4).

Table 4: One-year and five-year survival rates for lung cancer patients by stage

Stage at diagnosis	One-year survival rate (males)	One-year survival rate (females)	Five-year survival rate (males and females)
I	81%	85%	35%
II	66%	69%	21%
III	42%	46%	6%
IV	15%	19%	Unavailable[a]
Stage not known	23%	28%	6%
All stages	45%[b]	50%[b]	10%

[a]Five-year survival rates for patients diagnosed with stage IV lung cancer could not be calculated due to so few patients surviving more than two years. [b]Average of stages I–IV and stage not known.
Source: Cancer Research UK – one year and five year survival rates[40, 41]

Life expectancy of ROS1-positive advanced NSCLC patients treated with chemotherapy

ROS1-positive advanced NSCLC is an ultra-orphan indication and therefore there are limited data for the life expectancy of ROS1-positive NSCLC patients treated with chemotherapy. Several studies were identified in the clinical SLR, where patients who were identified as ROS1-positive were treated with chemotherapy. However, few studies reported overall survival (OS), and in those which did (see Appendix D), the study sizes were extremely small, with studies reporting patient numbers between one and ten.[42, 43] Therefore, these studies do not provide reliable estimates of OS for ROS1-positive advanced NSCLC patients.

Due to the uncertainty in the data available from patients with ROS1-positive advanced NSCLC and due to the similarities between ROS1-positive and ALK-positive NSCLC as described above, it was deemed appropriate to use data from patients with ALK-positive NSCLC as a proxy for the life expectancy of ROS1-positive NSCLC patients treated with current standard of care.

As with ALK-positive NSCLC, ROS1-positive NSCLC is overall not considered to be a favourable prognostic factor.[7, 44-46] Estimates of OS for ALK-positive advanced NSCLC patients treated with chemotherapy are presented in Table 5. The median OS for ALK-positive NSCLC patients is expected to be between 6 and 22 months.[46, 47] In a previous NICE appraisal of crizotinib, the committee accepted that the estimated life expectancy for ALK-positive NSCLC patients on current platinum-based chemotherapy is less than 24 months, and therefore these patients were considered to be at end-of-life.[48] Clinical experts predict that overall, ROS1-positive advanced NSCLC patients will act similarly to other non-squamous NSCLC patients in terms of clinical outcomes, and in particular they will be comparable to overall ALK-positive patients, due to the similar patient characteristics and homology discussed above.

In line with estimates from studies assessing OS in ALK-positive NSCLC and based on support from 12 UK leading clinical experts,[3] patients with ROS1-positive advanced NSCLC receiving chemotherapy should be considered to be at end-of-life, with a life-expectancy of less than 24 months, as is required to qualify for NICE's end-of-life criteria (see Section B.2.13.2).[49]

Table 5: Estimates of overall survival in patients with ALK-positive NSCLC receiving chemotherapy

Source	Description	Median OS, months
Shaw *et al.* (2011)[46]	Retrospective analysis of ALK-positive advanced NSCLC patients enrolled in the phase I clinical trial with crizotinib. ALK-positive patients included those who had received crizotinib treatment (n=82) and those who were crizotinib-naïve but had received any other treatment, including erlotinib (n=36) Median OS was reported for crizotinib-naïve patients who had received multiple, previous lines of therapy (range 1–4), most of whom had received pemetrexed and/or platinum-based therapy: ALK-positive, crizotinib-naïve, all lines (n=36) ALK-positive, crizotinib-naïve, second-line (n=23)	 20 (95% CI: 13–26) 6 (95% CI: 4–17)
UK clinical expert opinion from first-line ALK NICE submission[5]	Estimated life expectancy of patients with ALK-positive advanced NSCLC treated with first-line chemotherapy	~15
Shaw *et al.* (2016)[47]	Final analysis of OS from the phase III PROFILE 1007 trial of crizotinib vs. chemotherapy in previously treated advanced ALK-positive NSCLC: ALK-positive NSCLC patients who received crizotinib (n=172), or chemotherapy (n=171) ALK-positive, chemotherapy	 21.9 (95% CI: 16.8–26.0)

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; UK, United Kingdom.

B.1.3.2 Clinical pathway of care

NICE lung cancer clinical guideline [CG 121]

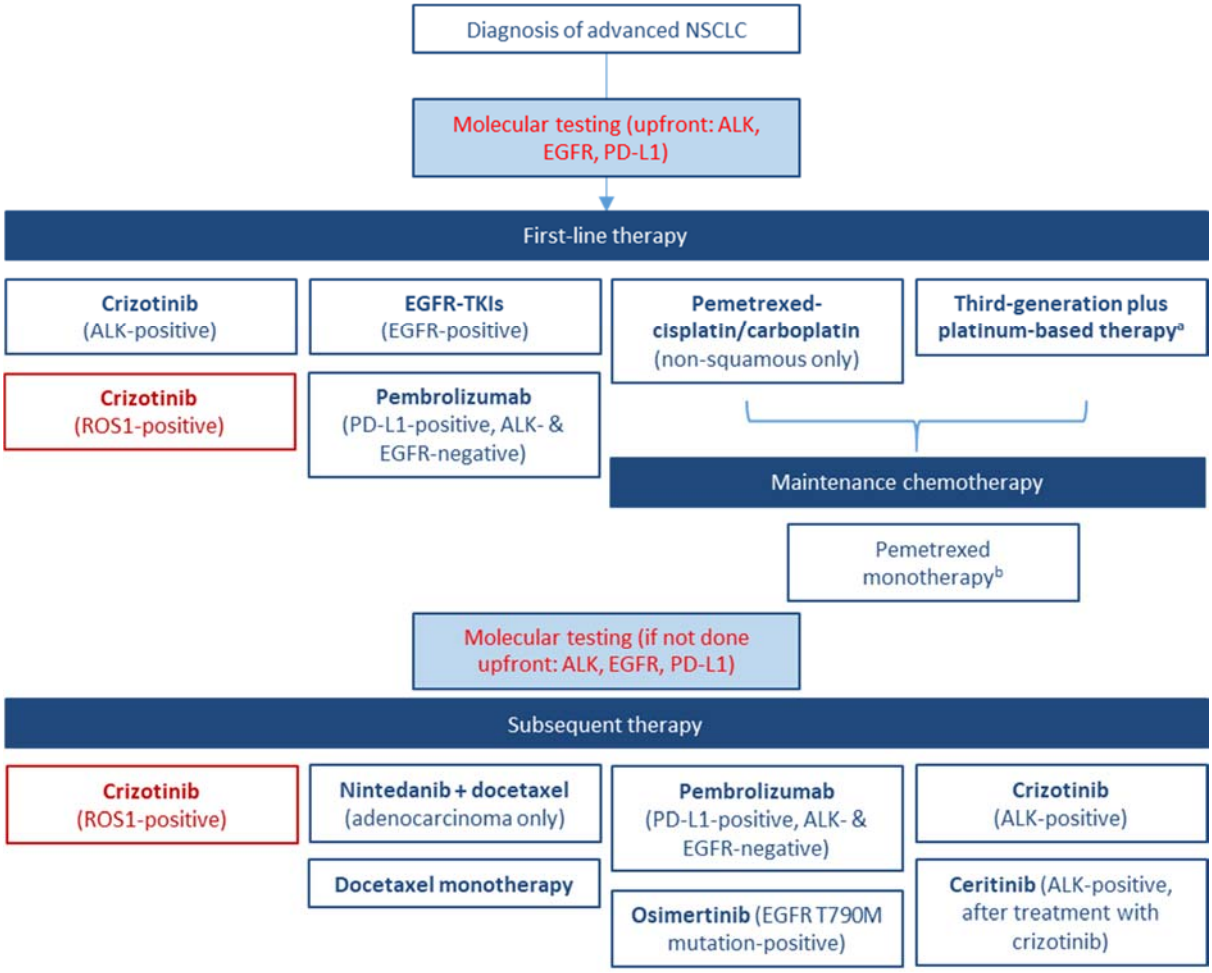
Chemotherapy for NSCLC

According to the current NICE clinical guideline for lung cancer [CG121], first-line chemotherapy is considered for NSCLC patients with inoperable stage III or IV disease and a good performance status (WHO score: 0 or 1, or Karnofsky score: 80–100).[4] Chemotherapy should be a combination of a single third-generation drug plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience.[4] Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug.[4] Docetaxel monotherapy may be offered as a second-line therapy to patients with locally advanced or metastatic NSCLC who have relapsed after prior chemotherapy treatment.[4] These recommendations were issued in 2005, prior to the positive guidance of pemetrexed in combination with cisplatin for the first-line treatment of non-squamous, advanced NSCLC, and subsequent-line treatment options, and do not make any distinction between histology-types, as recommendations for targeted therapies were also given after 2005.[4-6, 8, 50-56]

The clinical pathway for patients with advanced NSCLC, based on existing NICE clinical guidelines, is presented in Figure 2.

As shown in Figure 2, there are no currently licenced targeted therapies available for the treatment of patients with identified ROS1-positive advanced NSCLC. Consequently, ROS1 testing is not yet part of routine clinical practice. Crizotinib is being positioned as an alternative to non-targeted therapies for the treatment of ROS1-positive advanced NSCLC as per the licensed indication. Crizotinib would therefore replace non-targeted therapies in the first-line and subsequent-lines for patients with ROS1-positive advanced NSCLC, in line with past recommendations for crizotinib for patients with ALK-positive NSCLC.[5, 8]

Figure 2: Clinical pathway for patients with advanced NSCLC based on existing NICE clinical guidelines



Red boxes: Proposed use of crizotinib for ROS1-positive advance NSCLC, and of ROS1 testing if positive recommendation is given

[a]If patients cannot tolerate a platinum combination, single-agent chemotherapy with a third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) is recommended by NICE clinical guidelines for lung cancer [CG121]. [b]Pemetrexed maintenance therapy is only recommended after first-line treatment with platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel [TA190], and is not recommended following first-line treatment with pemetrexed-cisplatin [TA402].

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-L1, programmed-death ligand 1; TKI, tyrosine kinase inhibitor.

Sources: based on NICE clinical guidelines: lung cancer [CG121][4]; NICE pathway for the treatment of NSCLC[57]; and NICE guidance from the following technology appraisals: TA310, TA258 and TA192 for the EGFR-TKIs: afatinib, erlotinib and gefitinib, respectively[55, 56, 58]; TA395, TA422 and TA406 for the ALK-TKIs: crizotinib first-line and subsequent-line, and ceritinib, respectively[5, 8, 50]; TA181 for pemetrexed-cisplatin[6]; TA190 for pemetrexed maintenance therapy following induction therapy with platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel[51]; TA402 for pemetrexed maintenance therapy following induction therapy with pemetrexed-cisplatin[59]; TA428 and TA447 for pembrolizumab first- and subsequent-line therapy, respectively[52, 60]; TA347 for nintedanib for previously treated advanced disease[53]; TA416 for osimertinib therapy[54].

Positioning of crizotinib relative to the current treatment pathway

Crizotinib is being positioned as an alternative to non-targeted therapies for the first-line and subsequent-line treatment of ROS1-positive advanced NSCLC, as per the licensed indication (see Figure 2). This is consistent with the final scope issued by NICE for this appraisal.

Crizotinib would replace non-targeted therapies for ROS1-positive patients in all lines of treatment, in line with past recommendations for crizotinib in ALK-positive NSCLC.[5, 8]. Crizotinib is appropriate for use in the first-line setting because this will provide crizotinib to patients who are most likely to respond to targeted ROS1 inhibition with the greatest clinical benefit early in the treatment pathway. Access to crizotinib in the first-line setting would ensure that patients identified as being ROS1-positive can benefit from a targeted agent at an earlier stage of their disease. Furthermore, this would delay the use of poorly tolerated and potentially ineffective chemotherapy, thus improving outcomes for patients earlier in the treatment pathway. Access to crizotinib in the subsequent-line setting will ensure that patients who have not responded to chemotherapy, or where testing for ROS1-positivity may have been delayed, have access to a targeted therapy. ROS1 diagnostic testing is not yet widely established practice in England and Wales, and is not routinely conducted, given that there is no currently reimbursed ROS1-positive targeted medicine. Many laboratories are, however, developing a testing strategy for ROS1 which they would introduce if crizotinib is approved. Patients with advanced non-squamous NSCLC should be tested upfront for ROS1-positivity, alongside EGFR and ALK testing.[61] This upfront testing strategy minimises tissue wastage and importantly avoids delays in access to therapy.[61] Although less preferred, sequential testing is another possible strategy, whereby advanced non-squamous NSCLC patients with confirmed EGFR-negativity and ALK-negativity are selected for testing,[62] given that oncogenic drivers are thought to be mutually exclusive.[1, 2]

Clinical experts currently recommend the primary testing strategy of immunohistochemistry (IHC) screening followed by confirmatory fluorescence *in* situ hybridisation (FISH) for mainstream testing of ROS1 at the point of drug reimbursement. It is acknowledged that next-generation sequencing (NGS) will be an option in the future when this type of diagnostic test is more routinely available as part of a validated panel of tests.[63]

When crizotinib is first introduced, it is anticipated that more previously-treated ROS1-positive advanced NSCLC patients will receive crizotinib, particularly if access to diagnostic testing causes delays in diagnosis of ROS1-positivity. With time, however, ROS1-positive NSCLC patients anticipated to be treated with crizotinib are expected to become predominately treatment-naïve, as ROS1-positive patients will be diagnosed at an earlier stage in the treatment pathway before they have received a non-targeted therapy.

Comparators

As described in Section B.1.3.1, ROS1-positive NSCLC is predominantly associated with tumours of adenocarcinoma histology, and the presentation of a ROS1-positive patient with squamous cell carcinoma in the UK is thought to be extremely rare. This has been taken into account when determining the comparators relevant in this submission. The comparators listed in the final scope from NICE are discussed below.

Pemetrexed plus platinum-based therapy

Based on feedback from UK clinical experts, patients with ROS1-positive advanced NSCLC who are fit enough to be considered for systemic therapy would usually be treated with pemetrexed plus platinum-based chemotherapy in the first line. Pemetrexed in combination with cisplatin, specifically, is recommended by NICE in TA181 for the treatment of non-squamous, advanced NSCLC.[6] As such, pemetrexed plus platinum was chosen as the primary comparator for the assessment of crizotinib for untreated ALK-positive NSCLC, and evaluated using comparative data from the pivotal PROFILE 1014 trial.[5] In ROS1-positive NSCLC, there is limited data

available on the efficacy of pemetrexed plus platinum. Given the efficacy of crizotinib in ROS1 patients as demonstrated in the phase I single-arm PROFILE 1001 trial, clinical experts consider it unethical to conduct further comparative trials due to the lack of clinical equipoise. Nevertheless, due to the similarities between ROS1-positive and ALK-positive NSCLC (see Section B.1.3.1), it was possible to use data from the pivotal PROFILE 1014 trial in ALK-positive NSCLC patients as proxy evidence in this submission to compare the efficacy of crizotinib versus pemetrexed plus platinum-based therapy in ROS1-positive advanced NSCLC. This use of a proxy population is unavoidable because of the limited pemetrexed plus platinum data available in ROS1-positive NSCLC, due to the phase I trial design and the ultra-orphan disease nature of ROS1-positive NSCLC.

In clinical practice in the UK, it is estimated that about 54% of patients receive pemetrexed plus cisplatin.[11] The choice of pemetrexed plus platinum-based therapy (cisplatin or carboplatin) as a comparator is in line with final scope issued by NICE for this appraisal.

Clinical experts have suggested that approximately 15% of patients with advanced NSCLC would be eligible for pemetrexed maintenance after platinum doublet first-line chemotherapy, based on fitness. In the real world, only the fittest patients, (Eastern Cooperative Oncology Group [ECOG] performance status 0–1) who achieve disease control with four cycles of induction therapy would be considered for treatment with pemetrexed maintenance, as per NICE recommendation.[59] Given the small proportion of patients who receive maintenance therapy, this was not considered as a comparator in this submission. The exclusion of this comparator is in line with the final NICE scope for crizotinib for untreated ALK-positive NSCLC.[5] Furthermore, there is insufficient evidence on the efficacy of pemetrexed maintenance in ROS1-positive NSCLC patients, and the data available from the ALK-population is from a mixed chemotherapy comparator (pemetrexed plus platinum followed by pemetrexed maintenance).[64]

Docetaxel

Patients who are ROS1-positive may be treated with docetaxel as a subsequent-line therapy. NICE guidelines state that docetaxel monotherapy can be used in the second-line if a patient has relapsed after previous chemotherapy (CG121).[4] Docetaxel monotherapy is thus considered to represent one option for standard of care in the subsequent-line setting for ROS1-positive patients in the UK. The choice of docetaxel monotherapy as a comparator is in line with the final scope issued by NICE for this appraisal. In the absence of sufficient efficacy data on docetaxel in ROS1-positive advanced NSCLC, data from ALK-positive advanced NSCLC has been used as a proxy due to the similarities between the ROS1- and ALK-positive NSCLC (see Section B.1.3.1). Efficacy data from the pivotal PROFILE 1007 trial which was used as evidence for the recommendation of crizotinib for previously treated ALK-positive NSCLC by NICE, was used as a proxy.[8] This use of a proxy population is unavoidable due to the lack of efficacy data of docetaxel from ROS1-positive NSCLC patients, as the condition is so rare.

Nintedanib with docetaxel

Data for nintedanib with docetaxel was only available from the broader unselected NSCLC population, with subgroup analysis for patients with adenocarcinoma, and not from the ROS1-positive NSCLC population.[65] As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC or unselected adenocarcinoma,[15, 30] the efficacy data from the unselected NSCLC population (including unselected adenocarcinoma) is not deemed applicable to the ROS1-positive NSCLC population. No data in the proxy ALK-

positive population exists for nintedanib with docetaxel. Given that there are no data to form a reliable comparison to this therapy, nintedanib with docetaxel was not included in the decision problem addressed in this submission.

Third-generation (first-line docetaxel, gemcitabine, paclitaxel or vinorelbine)

Following consultation with UK clinical experts, it was noted that first-line docetaxel, paclitaxel or vinorelbine are rarely used in non-squamous patients in the first-line setting. These are instead comparators more commonly used to treat squamous patients. It is also understood that gemcitabine is not commonly used in non-squamous patients, however may be an alternative therapy offered to a small number of non-squamous patients who are not be able tolerate pemetrexed-platinum doublet therapy This approach was also used for the NICE appraisal of crizotinib for untreated ALK-positive NSCLC (TA406).[5] Additionally, data for single-agent chemotherapy are only available in the unselected NSCLC population and not from the ROS1-positive NSCLC population. As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC, efficacy data for first-line docetaxel, gemcitabine, paclitaxel or vinorelbine in unselected NSCLC is not deemed applicable in the ROS1-positive NSCLC population. Therefore, there are no data to form a reliable comparison to first-line docetaxel, gemcitabine, paclitaxel or vinorelbine, and as such it has not been addressed in the decision problem.

Best supportive care

Data for BSC as a subsequent-line option in patients who have received upfront chemotherapy are only available in the unselected NSCLC population and not from the ROS1-positive advanced NSCLC population. As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC, efficacy data for BSC in unselected NSCLC is not deemed applicable in the ROS1-positive NSCLC population. Therefore, there are no data to form a reliable comparison to BSC, and as such it has not been addressed in this decision problem. This aligns with comments from the Evidence Review Group (ERG) from the ALK subsequent-line NICE appraisal,[48] where the mixed treatment comparison to BSC was criticised for lacking robustness due to key differences between the selected and unselected patient populations. Furthermore, ROS1-positive patients are typically young and otherwise fit enough for chemotherapy, and as such BSC is likely to be used in a smaller proportion of ROS1-positive NSCLC patients compared to unselected NSCLC patients.

B.1.4 Equality considerations

The European licence for crizotinib requires that an accurate and validated test for ROS1-positivity is performed for the selection of patients who would be able to receive treatment with crizotinib. If there are regional variations in the access to ROS1 testing, this could lead to inequitable access.

Previously, a potential inequality in the consideration for the treatment of ALK-positive NSCLC was raised in the appraisal of crizotinib as a subsequent-line therapy, where it was stated that *"…testing could be restricted to patients with a diagnosis of adenocarcinoma*."[8] The upfront testing strategy described in Section B.1.3.2 would reduce the corresponding inequality associated with access to ROS1-positive NSCLC therapy, since all non-squamous NSCLC patients considered for biological therapy would be tested, as per clinical guidelines.[66] The sequential testing strategy is potentially associated with further inequities as ROS1-positive

patients would experience a delay in access to targeted therapy, compared to EGFR-positive and ALK-positive patients. The upfront testing strategy of all advanced non-squamous NSCLC patients is preferred,[61] and as such has been used as the base case strategy in the economic analyses. The sequential testing strategy was considered in a scenario analysis.

It is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary of Clinical Evidence

Clinical evidence base for crizotinib

- A SLR was conducted to identify relevant clinical data on crizotinib for the treatment of ROS1-positive advanced NSCLC, from both RCTs and non-RCTs
- PROFILE 1001 was identified as the pivotal single-arm phase I clinical trial in ROS1-positive patients which provides evidence for crizotinib treatment in the population of interest
- Given the efficacy of crizotinib in ROS1-positive patients demonstrated in PROFILE 1001, clinical experts consider it unethical to conduct further comparative trials due to the lack of clinical equipoise
- Data from the pivotal trials for ALK in first- and subsequent-line advanced NSCLC (PROFILE 1014 and PROFILE 1007) are used as supportive evidence for crizotinib in ROS1-positive NSCLC, because of the lack of comparative data in ROS1 and the similarities between ROS1 and ALK NSCLC
- Other trials identified in the SLR provided limited clinical data on crizotinib and chemotherapy for the treatment of ROS1-positive advanced NSCLC

PROFILE 1001, PROFILE 1007 and PROFILE 1014 trial methodology

- PROFILE 1001 is an international, multicentre, single-arm, phase I clinical trial, which included an initial dose-escalation phase, followed by an expansion phase in ROS1-positive advanced NSCLC patients (n=53)
- PROFILE 1007 is a multi-centre, randomised, open-label, phase III efficacy and safety study of crizotinib versus chemotherapy (docetaxel or pemetrexed) in patients with previously treated NSCLC whose tumours harbour ALK translocations
- PROFILE 1014 is a multicentre, randomised, open-label, phase III trial comparing crizotinib with pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin), in previously untreated adult patients with confirmed ALK-positive, non-squamous, advanced NSCLC

Clinical efficacy results from PROFILE 1001, PROFILE 1007 and PROFILE 1014

- PROFILE 1001 reported a high objective response rate, with the majority of patients achieving a complete or partial response to crizotinib (69.8%; 95% CI: 55.7–81.7)
- The objective response rate reported in first- and subsequent-line ALK-positive NSCLC patients from PROFILE 1014 and PROFILE 1007 was comparable to that observed in PROFILE 1001 (74.4% and 65.3%, respectively)
- Median progression-free survival was 19.3 months (95% CI: 14.8–NR) in PROFILE 1001 at the time of data cut-off (30th November 2014), at which time 25 patients (47.2%) remained on treatment and 28 patients (52.8%) had discontinued treatment
- Compared to chemotherapy (pemetrexed plus platinum in the first-line and pemetrexed/docetaxel in the subsequent-line), median PFS significantly improved in

patients treated with crizotinib in PROFILE 1014 and PROFILE 1007 (increase versus chemotherapy of 3.9 in first-line and 3.7 months in subsequent-line)

- A median time to tumour progression of 19.8 months (95% CI: 15.2–NR) was reported in PROFILE 1001. Of the 53 ROS1-positive NSCLC patients, 43.4% had objective progression and the remaining (56.6%) were censored, including 39.6% who were still in follow-up for progression at the data cut-off date (30th November 2014)
- Median OS was not reached in PROFILE 1001 at the data cut-off date (30th November 2014). The probability of survival at 12 months was 79.0% (95% CI: 65.3–87.8)
- Median OS was reached in PROFILE 1007, where there was a statistically significant increase in OS for crizotinib versus chemotherapy (crossover adjusted HR: 0.383 (95% CI: 0.283–0.518). In [redacted])
- Crizotinib has demonstrated that it provides similar efficacy gains in both ROS1-positive and ALK-positive NSCLC populations, and this alongside the similarities in patient characteristics and the homology of their kinase domains supports the use of ALK as a proxy where limited data in ROS1 patients are available
- Health-related quality-of-life benefits of crizotinib have also been demonstrated in ALK-positive NSCLC patients from PROFILE 1014 and PROFILE 1007

Supportive evidence from other studies

- The EUCROSS study was in a European ROS1-positive NSCLC population, and therefore provides supportive evidence to PROFILE 1001. The ORR ([redacted]) and PFS [redacted]) from EUCROSS was comparable with PROFILE 1001
- A recently audit of ROS1 patients from the [redacted] UK, also provide supportive data, including data on the median PFS in ROS1 patients treated with crizotinib in the first-line and subsequent-line settings ([redacted] months) and by pemetrexed plus platinum and maintenance pemetrexed in the first-line setting ([redacted] months)
- The outcome from the other studies identified in the SLR were also associated with large amounts of uncertainty as the study populations were either small, or the study design was retrospective. In addition, several of these studies were not generalisable to the UK population and none provided comparative evidence due to single-arm study design. Therefore, these studies were not included in the clinical analysis for this submission

B.2.1 Identification and selection of relevant studies

A SLR was conducted to identify relevant clinical evidence on the efficacy and safety of crizotinib for the treatment of ROS1-positive advanced NSCLC. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

From the SLR, 28 publications on 14 unique studies were identified. Of these, 22 publications and 10 unique studies were found that included crizotinib specifically as an intervention. One full publication and nine abstracts or poster publications of the phase I study PROFILE 1001 were identified in the review (see Appendix D). The other 12 publications on nine unique studies which included crizotinib are summarised in Appendix D. The remaining six publications on four unique studies did not include crizotinib as an intervention and instead considered other comparators. These are also summarised in Appendix D. None of the identified studies were RCTs.

In the absence of any RCTs in ROS1-positive patients, the ROS1-positive registration trial, PROFILE 1001 (NCT00585195), a single-arm phase I clinical trial, was used as the main source of clinical effectiveness data for this submission in place of RCT data. PROFILE 1001 was also used as the main source of clinical evidence for the regulatory approval of crizotinib in Europe for the treatment of ROS1-positive advanced/metastatic NSCLC.[7] Evidence from the ROS1-positive cohort of the PROFILE 1001 study was considered to be sufficient by the EMA for regulatory approval given that ROS1-positive NSCLC is a rare genetic subgroup which shares structural similarities and clinical behaviour with ALK-positive NSCLC (see Section B.1.3.1).[1, 7, 15, 17, 30] Given the efficacy of crizotinib in ROS1 patients as demonstrated in the phase I single-arm PROFILE 1001 trial, clinical experts consider it unethical to conduct further comparative trials due to the lack of clinical equipoise. This trial has been validated by clinicians as generalisable to the UK population.[3]

In addition to data from PROFILE 1001, data from two phase III RCTs for crizotinib in first- and subsequent-line ALK-positive NSCLC (PROFILE 1014 and PROFILE 1007, respectively) have been included in this submission to provide evidence of crizotinib versus chemotherapy. Due to the ultra-orphan nature of ROS1-positive NSCLC, there are limited data available for therapies other than crizotinib in ROS1-positive NSCLC. Based on the similarities between ALK-positive and ROS1-positive NSCLC (see Section B.1.3.1), data from PROFILE 1007 and PROFILE 1014 were used as proxy to support the data available from the relatively small number of ROS1-positive NSCLC patients in PROFILE 1001. PROFILE 1014 provides evidence for crizotinib versus pemetrexed plus platinum in first-line ALK-positive advanced NSCLC, and PROFILE 1007 provides evidence for crizotinib versus pemetrexed/docetaxel in subsequent-line ALK-positive NSCLC.[8, 36] This data was used to provide evidence for crizotinib versus pemetrexed in the first-line setting and for crizotinib versus docetaxel in the subsequent-line setting for the base case of the economic analysis.

The recently completed EUCROSS study was considered to provide additional supportive clinical evidence, as the patients in the EUCROSS study were from Europe, and therefore generalisable to the UK.[67] Because of the lack of Kaplan-Meier curves for the progression-free survival (PFS) and OS from the EUCROSS study at the time of the economic analysis, evidence from the EUCROSS study could not be incorporated in the economic analysis. However, the objective response rate (ORR) and PFS from EUCROSS, reported as part of the preliminary results, provide supportive evidence in the clinical analysis of this submission.

A summary of the clinical effectiveness data used in the economic model from PROFILE 1001, PROFILE 1007 and PROFILE 1014 is presented in Table 6. A summary of the other studies identified by the SLR, but that were not used in the economic model, is presented in Table 7; their clinical effectiveness evidence presented in Appendix D. These studies were not suitable for use in the economic analysis as they did not provide comparative evidence for crizotinib versus

pemetrexed or docetaxel. Furthermore, these trials only included a small number of patients, and patient population were not generalisable to the UK in most of these studies.

Table 6: Clinical effectiveness evidence for studies used in the economic model

Study	**NCT00585195** **(PROFILE 1001)**					**NCT00932893** **(PROFILE 1007)**					**NCT01154140** **(PROFILE 1014)**				
Study design	Multicentre, open-label, single-arm, phase I study. Initial dose-escalation phase followed by an expansion phase to establish RP2D in molecularly defined cohorts of patients (ALK, ROS and MET enriched populations)[68]					Multicentre, double-blind, phase III randomised, placebo-controlled clinical trial Patients in the chemotherapy group who had disease progression defined using RECIST could cross over to crizotinib treatment as part of a separate study					Multicentre, open-label, phase III randomised controlled trial Patients in the chemotherapy group who had disease progression defined using RECIST v1.1, as verified by IRR, could cross over to crizotinib treatment if the safety criteria were met				
Population	Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic NSCLC that was positive for an ROS1 rearrangement (Three patients were included in the trial who were ALK-negative and retrospectively determined to be ROS1-positive)					Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic NSCLC that was positive for an ALK rearrangement, who had progressive disease only after one prior (platinum-based) chemotherapy regimen					Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic non-squamous NSCLC that was positive for an ALK rearrangement, who had not received previous treatment for advanced disease				
Intervention(s)	Crizotinib 250 mg twice daily					Crizotinib 250 mg twice daily					Crizotinib 250 mg twice daily				
Comparator(s)	N/A					Docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2 BSA					• Pemetrexed, 500 mg/m^2 BSA, plus platinum-based therapy; *i.v.*, administered every 3 weeks for a maximum of 6 cycles • Platinum-based therapy consisted of either cisplatin, 75 mg/m^2 BSA, or carboplatin, target AUC of 5–6 mg/mL/min				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X	Yes	X	**Indicate if trial used in the economic model**	Yes	X	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No		No			No		No			No	

Rationale for use/non-use in the model	PROFILE 1001 is the pivotal trial for crizotinib in ROS1-positive NSCLC. It therefore provides the most detail on patients with ROS1-positive NSCLC which can be used in the model, including IPD and transition probabilities. However, due to the uncertainties in indirectly comparing this data to pemetrexed and docetaxel, this data will be used as a scenario analysis in the model	PROFILE 1007 provides supportive comparative evidence for subsequent-line crizotinib versus chemotherapy, which can be applied in the economic model due to the homology between ROS1 and ALK, and the similar patient characteristics between both subtypes. This will be used as the base case in the economic model	PROFILE 1014 provides supportive comparative evidence for first-line crizotinib versus chemotherapy, which can be applied in the economic model due to the homology between ROS1 and ALK, and the similar patient characteristics between both subtypes. This will be used as the base case in the economic model
Reported outcomes specified in the decision problem	Primary outcome: • ORR defined as the percentage of patients with confirmed CR or PR according to RECIST (v1.0 for ROS1-positive cohort [n=50]; v1.1 for ALK-negative cohort [n=3]) Secondary outcomes: • **OS** • **PFS** • **Safety**	Primary outcome: • **PFS** defined as the time from randomisation to RECIST (v1.0) Secondary outcomes: • ORR • **OS** • **Safety** • **EQ-5D**	Primary outcome: • **PFS** defined as the time from randomisation to RECIST (v1.1)-defined progression (as assessed by IRR) or death Secondary outcomes: • ORR • **OS** • **Safety** • **EQ-5D**
All other reported outcomes	• DR • DCR • TTR • TTP • **TTF**	• DR • DCR • TTD in either cough, dyspnoea and pain • **TTF** • EORTC QLQ-C30 • EORTC QLQ-LC13	• BOR • TTR • DR • DCR • TTP • IC-TTP • EC-TTP • **TTF** • EORTC QLQ-C30 • EORTC QLQ-LC13 • TTD in either cough, dyspnoea and pain in chest symptoms, as assessed using EORTC QLQ-LC13

Abbreviations: ALK, anaplastic lymphoma kinase; AUC, area under the concentration-time curve; BOR, best overall response; BSA, body surface area; CR, complete response; DCR, disease control rate; DR, duration of response; EC, extracranial; EORTC QLQ(-C30 and -LC13), European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (-Core 30 and -Lung Cancer 13; EQ-5D, EurQoL-5 Dimensions; HRQoL, health-related quality of life; IC, intracranial; IPD, individual patient data; IRR, independent radiology review; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended Phase 2 dose; TTD, time to deterioration; TTF, time to treatment failure; TTP, time to progression; TTR, time to tumour response.
Source: PROFILE 1001[7, 69]; PROFILE 1007[70, 71]; PROFILE 1014[72, 73]

Table 7: Clinical effectiveness evidence from other studies identified in the clinical SLR

Study ID	Study design	Population	Intervention and comparator	Justification for exclusion from economic model
NCT02034981 (AcSé)[74]	Phase II single-arm study	Adults with advanced disease harbouring a genomic alteration in a crizotinib target (ALK, MET or ROS1). Patients could not be eligible for any other trial targeting the same genomic alteration	Crizotinib 250 mg twice daily continuously over 28 day cycles (n=37)	Overall study population was small (N=37), and the trial was single-arm
NCT02183870 (EUCROSS)[75]	Phase II single-arm study	Patients >18 years old with ECOG performance status 0–2 and advanced ROS1-positive lung adenocarcinomas (n=30 response evaluable patients; however, safety population included 4 additional patients who received treatment despite being ineligible)	Crizotinib 250 mg twice daily for 28-day cycles until disease progression or intolerance (n=30)	This is an ongoing study (see Section B.2.11). Overall study population is small and the trial was single-arm. Baseline characteristics and KM plots of OS were not available at the time of the economic analysis
EUROS1[2]	Retrospective study	Patients (n=32) with FISH-confirmed ROS1-positive NSCLC treated with crizotinib, though 1 patient was subsequently found to be ROS1-negative through NGS	Crizotinib 250 mg twice daily (n=32) In addition, 26 patients had received pemetrexed (alone or in combination with platinum, and either before or after crizotinib); some outcomes	Overall study population was small and the study was a retrospective analysis

		Patients were excluded from final analysis if they had died before first tumour assessment or if they were retrospectively determined to be ROS1-negative	therefore reported for pemetrexed-based chemotherapy	
NCT02499614 (METROS)[76]	Phase II, two-arm, non-comparative study	Patients with locally advanced or metastatic NSCLC, pre-treated with at least one previous chemotherapy line, with MET amplification, MET exon 14 mutation or ROS1 rearrangement	Crizotinib 250 mg twice daily until disease progression, unacceptable toxicity or patient refusal (n=24)	Overall study population was small and the trial was single arm This is an ongoing study, please see Section B.2.11 for further details
NCT01945021 (OX-ONC)[77]	Phase II single-arm study	East Asian patients (n=127) with ROS1-positive, ALK-negative locally advanced or metastatic NSCLC with ≤3 lines of prior chemotherapy	Crizotinib; dose and dosing frequency NR (n=127)	Patients were of East-Asian origin, and therefore not representative of the general UK population. This was a single-arm study This is an ongoing study, please see Section B.2.11 for further details
Bennati 2015[78]	Retrospective study	Adult patients with NSCLC: ROS1-positive status (n=11)	All patients had received both pemetrexed and crizotinib (n=11) Dose and dosing frequency: NR	Retrospective study with an extremely small study population, and no dose and frequency of crizotinib treatment was given
Lu 2017[79]	Retrospective study	Chinese ROS1-positive NSCLC patients treated with crizotinib	Crizotinib (n=36) Dose and dosing frequency: NR	This retrospective study included a Chinese population only and was not representative of the UK population, with no dose and frequency of crizotinib treatment provided

Oz 2015[80]	Regional analysis of data from PROFILE 1001 expansion cohort	Turkish ROS1-positive patients with advanced NSCLC, negative for EGFR mutation and ALK rearrangement (n=5).	Crizotinib 250 mg twice daily continuously over 28 day cycles (n=5)	Data are from a regional analysis of patients from PROFILE 1001, therefore these patients have already been accounted for in PROFILE 1001; inclusion of these data would lead to double counting. Overall study population was extremely small
Zhang 2016[81]	Retrospective study	Chinese ROS1-positive NSCLC patients receiving crizotinib (n=15), pemetrexed-based chemotherapy (n=49) or non-pemetrexed-based chemotherapy (n=44) at any treatment-line	Crizotinib (n=15) or pemetrexed (n=49); dose and dosing frequency NR	This retrospective study included a Chinese population only and is not representative of the UK population
Chen 2016[82]	Retrospective study	Advanced lung adenocarcinoma patients who had received pemetrexed-based regimens at any treatment line	Pemetrexed administered at a dose of 500 mg/m^2 every 3 weeks Pemetrexed administered as monotherapy (n=7; 36.8%) or as platinum/pemetrexed combination therapy (n=12; 63.2%)[a]	Study population for pemetrexed plus platinum subgroup (n=12) was extremely small, and the overall study did not include patients treated with crizotinib
Drilon 2016[42]	Retrospective study	Advanced (stage IIIB/IV) NSCLC with documented evidence of a recurrent gene rearrangement involving RET, ROS1, ALK or a mutation in KRAS, and treatment with pemetrexed for advanced disease (n=10 for ROS1-positive patients)	Pemetrexed; dose and dosing frequency NR (n=10)	Overall study population was extremely small, with the dose and frequency of pemetrexed not provided, and the study did not include patients treated with crizotinib

Liang 2016[43]	Retrospective study	Patients with metastatic, non-squamous NSCLC who received pemetrexed for ≥12 months either as maintenance treatment after first-line platinum-based chemotherapy or as a subsequent-line treatment ROS1-positive patients: n=5	Pemetrexed; dose and dosing frequency NR (n=5)	Overall study population was extremely small, with no dose or frequency given for pemetrexed, did not include patients treated with crizotinib, and the number of events was low
Song 2016[83]	Retrospective study	ROS1-positive NSCLC patients, any treatment-line (n=34)	Pemetrexed; dose and dosing frequency NR (n=34)	Overall study population was small, with no dose or frequency given for pemetrexed, and did not include patients treated with crizotinib

[a]Data from Table 3 in the Chen et al. 2016 publication; note that Table 2 in Chen *et al.* (2016) reports eight ROS1-positive patients as receiving pemetrexed monotherapy and 11 patients as receiving platinum/pemetrexed combination therapy.
Abbreviations: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridisation; KM, Kaplan-Meier; KRAS, Kirsten rat sarcoma; NGS, next generation sequencing; NR, not reported; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Summary of PROFILE 1001 methodology

PROFILE 1001 (NCT00585195) was a multicentre, open-label, single-arm, phase I clinical trial which was originally designed to include an initial dose-escalation phase in ALK-positive NSCLC patients, followed by an expansion phase to establish the recommended phase II dose (RP2D). The protocol was amended to include an expansion RP2D cohort of ROS1-positive NSCLC patients; it is data from this subset of PROFILE 1001 patients that informs this submission. A summary of the PROFILE 1001 methodology and trial design is presented in Table 8. Items 3 to 6b of the CONSORT checklist are provided within this table.

PROFILE 1007 and 1014 are both pivotal phase III RCTs for ALK-positive NSCLC, which are used in this submission to provide supportive evidence for crizotinib in ROS1-positive NSCLC, and provide the base case for the economic analysis of crizotinib versus chemotherapy in ALK-positive NSCLC as a proxy for ROS1-positive NSCLC. The use of proxy data is due to the limited and uncertain comparator data in the ROS1 population. The summary of the methodology for PROFILE 1007 is located in Appendix L, whereas the summary for PROFILE 1014 is presented in the manufacturer's submission to NICE for first-line crizotinib.[84]

Table 8: Summary of PROFILE 1001 methodology

Trial number (acronym)	**NCT00585195 (PROFILE 1001)**
Location	International: Eight locations across USA, Australia and South Korea
Trial design	Multicentre, open-label, single-arm, phase I study. Initial dose-escalation phase followed by an expansion phase to establish RP2D in molecularly defined cohorts of patients (ALK, ROS and MET enriched populations)[68] Eligibility for ROS1 expansion phase: • Age ≥18 years • Locally advanced or metastatic, histologically confirmed NSCLC positive for rearrangements in the ROS1 gene with disease that was measurable by RECIST v1.0 (or by RECIST v1.1 for the three ALK-negative patients who were retrospectively determined to be ROS1-positive) • ECOG PS of 0 or 1. Patients with ECOG PS of 2 could be allowed to enrol into the study upon agreement between the investigator and sponsor Treatment: • Crizotinib was administered orally at the RP2D dose of 250 mg twice daily in continuous 28-day cycles (or 21-day cycles for the three ALK-negative patients who were retrospectively determined to be ROS1-positive), until the occurrence of RECIST-defined disease progression or clinical deterioration • Patients with RECIST-defined disease progression or clinical deterioration could continue on crizotinib treatment at the investigator's discretion and with the approval from the Sponsor[68] Patient cohort: • 53 patients were enrolled in the trial, comprising of 50 patients who were ROS1-positive, and three additional patients who were from the ALK-negative cohort of PROFILE 1001, and then retrospectively determined to be ROS1-positive[69] ROS1 testing: • Patients underwent diagnostic testing for ROS1 translocation. Of the 53 patients included in the ROS1 cohort: 26 patients were tested using FISH by

	a Massachusetts General Hospital laboratory-developed test; 25 patients were tested by FISH using local tests; two patients were tested using the PCR technique. Tissue samples from 36 patients were retrospectively tested for ALK rearrangement
Duration of study	Between October 2010 and September 2013, a total of 53 patients had received crizotinib. Treatment was continued until RECIST-defined disease progression or clinical deterioration, unacceptable toxicity effects, study withdrawal, or death At the time of the data cut-off date (30th November 2014) for the primary analysis, the median duration of follow-up for overall survival was 25.4 months Data cut-off date for the ALK-negative patients who were retrospectively defined to be ROS1-positive (n=3) was 24th June 2014
Method of randomisation	Not applicable as this was a single-arm study
Method of blinding	Open-label for patients and study investigators due to being a single-arm study An IRR was carried out in the ROS1-positive cohort (n=50). The assessors carrying out the IRR were blinded to outside radiology reports and investigator assessments IRR was not performed for tumour scans from the three ALK-negative NSCLC patients who were retrospectively found to be ROS1-positive due to differences in RECIST versions used and treatment cycle lengths
Trial drugs and method of administration	ROS1-positive NSCLC cohort (n=50): • Crizotinib 250 mg twice daily, orally continuously in 28 day cycles ALK-negative NSCLC patients (n=3), retrospectively found to be ROS1-positive: • Crizotinib 250 mg twice daily, orally continuously in 21 day cycles
Permitted and disallowed concomitant medication	Permitted concomitant medication[69]: • Medications intended for supportive care (i.e. antiemetics, analgesics and megestrol acetate for anorexia) • Haematopoietic growth factors, at the discretion of the treating physician • Anti-inflammatory medications or narcotic analgesics • Packed red blood cell and platelet transfusions, as clinically indicated • Appropriate hormone replacement therapy, as clinically indicated, in the absence of PD or unacceptable treatment-associated toxicity • Bisphosphonate therapy for metastatic bone disease • Low-dose acetaminophen (maximum total daily dose of 2 g) • Disallowed concomitant medication[69]: • Any other anticancer therapies • Cytochrome P450 3A inhibitors and inducers (except for topical use of inhibitors) • Bradycardic agents, medicinal products known to prolong the QT interval, and/or antiarrhythmics were to be avoided in patients receiving crizotinib • Non-prescription drugs (except vitamins) or herbal supplements Concomitant radiotherapy and surgery[69]: • Palliative radiotherapy to specific sites of disease was permitted if considered medically necessary by the treating physician. Radiotherapy was performed at least one day before or one day after chemotherapy and during an interruption in crizotinib treatment (stopped one day before and resumed one day after) • In the event that elective surgery was necessary during study participation, treatment with crizotinib was to be avoided 48 hours before surgery and

	resumed no sooner than 48 hours after surgery
Primary outcomes (including scoring methods and timings of assessments)	ORR was defined as the percentage of patients with confirmed CR or PR according to RECIST (v1.0 for ROS1-positive cohort [n=50]; v1.1 for ALK-negative cohort [n=3]) Tumour assessments were performed every eight weeks in the ROS1-positive cohort, and every six weeks in the ALK-negative cohort until RECIST-defined disease progression. Once a patient had completed 15 cycles, tumour assessments reduced to every 16 weeks in the ROS1-positive cohort or every 12 weeks in the ALK-negative cohort, until after 24 cycles in the ROS1-positive cohort or 35 cycles in the ALK-negative cohort. After 24 cycles, tumour assessment was performed every 24 weeks
Secondary outcomes (including scoring methods and timings of assessments)	Secondary outcomes included: • DCR at Weeks 8 and 16 • DR • TTR • PFS • TTP • TTF • OS
Pre-specified subgroup analyses	ORR by baseline characteristics
Duration of follow-up	**Survival:** After discontinuation of study treatment, follow-up survival data was collected at least every three months for a minimum of one year after the final dose **Safety:** Patients were to be followed for AEs until at least 28 days after the last dose of study treatment[68]

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; CR, complete response; DCR, disease control rate; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence *in situ* hybridisation; IRR, incidence response ratio; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended Phase II dose; TTF, time to treatment failure; TTP, time to progression; TTR, time to tumour response; USA, United States of America.
Source: EPAR Xalkori/crizotinib 21st July 2016[7], unless stated otherwise

Eligibility criteria for PROFILE 1001, PROFILE 1007 and PROFILE 1014

Patients were considered for enrolment if they had histologically or cytologically confirmed locally advanced or metastatic NSCLC that was positive for a ROS1 translocation. The full eligibility criteria for PROFILE 1001 is presented in Appendix M. The full eligibility criteria for PROFILE 1007 is presented in Appendix L and for PROFILE 1014 is available in the crizotinib first-line manufacturer's submission to NICE.[84]

Description of outcomes reported in PROFILE 1001, PROFILE 1007 and PROFILE 1014

The definitions and methods of assessment of the primary and secondary outcomes reported in PROFILE 1001 are provided in Table 9. The primary and secondary outcomes reported in PROFILE 1007 is located in Appendix L, whereas the summary for PROFILE 1014 is presented in the manufacturer's submission to NICE for first-line crizotinib.[84] ORR was the primary outcome of PROFILE 1001. Anti-tumour activity, measured as reduction in lesion size, is an indicator of a drug's effectiveness, and a high ORR demonstrates that a high proportion of patients have responded to treatment. In addition, a greater and more durable tumour response to treatment is believed to be associated with improvements in patient health-related quality of life (HRQoL).[85, 86] ORR was a secondary outcome in PROFILE 1007 and PROFILE 1014.[71, 73]

- PFS was a secondary outcome of PROFILE 1001. Prolonged PFS is considered to be of considerable benefit to patients, with disease progression having been shown to be associated with worsening HRQoL.[87] This was the primary outcome in PROFILE 1007 and PROFILE 1014.[71, 73]
- OS was also a secondary outcome of PROFILE 1001. Extension of life is a key goal of therapy for patients with advanced NSCLC who otherwise have a short life expectancy. As described in Section B.1.3.1, patients with ROS1-positive advanced NSCLC are expected to have a life expectancy of less than 24 months with current standard of care. OS was also a secondary outcome in PROFILE 1007 and PROFILE 1014.[71, 73]

Table 9: Description of outcomes reported in PROFILE 1001

Outcome	Description
Primary outcome	
Objective response rate (ORR)	Percentage of patients with confirmed CR or PR according to RECIST v1.0 (ROS1-positive cohort) or RECIST v1.1 (ALK-positive cohort), relative to the RE population The analysis of ORR, including censoring of data, is described fully in Section B.2.6.1
Secondary efficacy outcomes	
Progression-free survival (PFS)	Time from date of first dose to the date of the first documentation of objective tumour progression or death on-study due to any cause, whichever occurred first
Time to response (TTR)	Time from date of first dose to first documentation of CR or PR that was confirmed
Duration of response (DR)	Time from first documentation of CR or PR that was confirmed, to first documentation of objective tumour progression or death on-study due to any cause, whichever occurred first
Disease control rate (DCR)	Percentage of patients with a confirmed CR, PR or SD according to RECIST v1.0 (ROS1-positive cohort) or RECIST v1.1 (ALK-positive cohort) based on the response at Week 8 and Week 16, relative to the RE population
Time to progression (TTP)	Time from the date of first dose to the date of the first documentation of objective tumour progression
Time to treatment failure (TTF)	Time from the date of first dose to time of last dose
Overall survival (OS)	Time from date of first dose to date of death from any cause
Safety	
Safety[69]	• Included the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory parameters • AEs were classified and graded according to the CTCAE v3.0 • Only events that occurred during the period from the first dose of study treatment until 28 days after the last dose of study treatment, were included in the analysis Duration of follow-up: • Patients were to be followed for adverse events until at least 28 days after the last dose of study treatment

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; CR, complete response; CTCAE, Common Terminology Criteria for AEs; DCR, disease control rate; DR, disease response; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response; RE, response evaluable; RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation; TTF, time to treatment failure; TTR, time to tumour response; TTP, time to tumour progression.
Source: EPAR Xalkori/crizotinib 21st July 2016[7], unless otherwise stated

B.2.3.2 Comparative summary of the methodology of the clinical effectiveness trials

A comparative summary of the methodology of PROFILE 1001, PROFILE 1007 and PROFILE 1014 is presented in Table 10. Further information on the methodology of PROFILE 1007 is available in Shaw *et al.* (2013)[71] and for PROFILE 1014 is presented in the manufacturer's submission to NICE.[84]

Table 10: Comparative summary of the methodology used in the PROFILE trials

Trial number (acronym)	PROFILE 1001	PROFILE 1007	PROFILE 1014
Location	International: Eight locations across USA, Australia and South Korea	International sites in North America, Australia, Brazil, China, Japan, Korea, Taiwan, Hong Kong and Europe (nine study sites were located in the UK)[88]	International: 251 locations across USA, Canada, Mexico, Australia, Asia, Europe (nine study sites were located in the UK), South America and South Africa.[89]
Trial design	Multicentre, open-label, single-arm, phase I study. Initial dose-escalation phase followed by an expansion phase to establish RP2D in molecularly defined cohorts of patients (ALK, ROS and MET enriched populations)[68]	Multicentre, open-label, phase III, randomised, placebo-controlled clinical trial Patients in the chemotherapy group who had disease progression defined using RECIST could cross over to crizotinib treatment as part of a separate study	Multicentre, open-label, phase III randomised controlled trial Patients in the chemotherapy group who had disease progression defined using RECIST v1.1, as verified by IRR, could cross over to crizotinib treatment if the safety criteria were met
Eligibility criteria for patients	Eligibility for ROS1 expansion phase: • Age ≥18 years • Locally advanced or metastatic, histologically confirmed NSCLC positive for rearrangements in the ROS1 gene with disease that was measurable by RECIST v1.0 (or by RECIST v1.1 for the 3 ALK-negative patients who were retrospectively determined to be ROS1-positive) • ECOG PS of 0 or 1. Patients with ECOG PS of 2 could be allowed to enrol into the study upon agreement between the investigator and Sponsor	Inclusion criteria: • Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic • Positive for translocation or inversion events involving the ALK gene locus • Patients must have had progressive disease after only one prior (platinum-based) chemotherapy regimen, which may have included maintenance therapy. Patients must have been considered appropriate candidates for additional chemotherapy with either single-agent pemetrexed or single-agent docetaxel • Patients with brain metastases were eligible if appropriately treated and neurologically stable for at least 2 weeks and were not taking any medications contraindicated in the Exclusion Criteria • Any prior chemotherapy or major surgeries must have been completed at	Inclusion criteria: • Aged ≥18 years old • Histologically or cytologically confirmed locally advanced, recurrent or metastatic, non-squamous NSCLC • Positive for ALK rearrangement, confirmed with the use of a Vysis ALK Break Apart FISH Probe Kit (Abbot Molecular) • Received no previous systemic treatment for advanced disease • Measurable disease as assessed according to the RECIST v1.1 • ECOG PS of 0, 1 or 2 • Adequate hepatic, renal and bone marrow function • Patients with treated brain metastases were eligible if the metastases were neurologically stable for at least 2 weeks before enrolment and the patient had no ongoing requirement for corticosteroids

		least 4 weeks prior to initiation of study medication. Any prior radiation or minor surgeries/ procedures must have been completed at least 2 weeks prior to the initiation of study medication. Any acute toxicity must have recovered to ≤ Grade 1 (except alopecia) • Tumours must have been measurable as per RECIST (v1.0) • Female or male, 18 years of age or older • ECOG PS 0-2. • Adequate organ function A full list of inclusion and exclusion criterion is presented in the NICE submission for crizotinib in first-line ALK-positive NSCLC[90]	• Written informed consent provided A full list of inclusion and exclusion criterion is presented in the NICE submission for crizotinib in first-line ALK-positive NSCLC[84]
Settings and locations where data were collected	Clinical trial setting	Clinical trial setting – the investigator was responsible for the collection and reporting of safety and concomitant medication[70] A self-administered questionnaire to obtain the EORTC-QLQ-C30 and QLQ-LC13, EQ-5D and [redacted] outcomes were filled in by the patients at the clinic prior to any study of medical procedures[70]	Clinical trial setting – the investigator had ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data (and any other data collection forms)[72] Self-administered questionnaires to obtain patient-reported outcomes were completed on-site prior to testing, treatment, or discussion with the physician or site personnel. [redacted]
Trial drugs	Intervention: crizotinib 250 mg twice daily (n=53)	Intervention: crizotinib 250 mg twice daily (n=173) Comparator: docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2 BSA (total chemotherapy n=174)	Intervention: crizotinib 250 mg twice daily (n=172) Comparator: • pemetrexed, 500 mg/m^2 BSA, plus platinum-based therapy; *i.v.*, administered every 3 weeks for a

			maximum of 6 cycles (n=171) • platinum-based therapy consisted of either cisplatin, 75 mg/m^2 BSA, or carboplatin, target AUC of 5–6 mg/mL/min
Permitted and disallowed concomitant medication	Permitted concomitant medication[69]: • Medications intended for supportive care (i.e. antiemetics, analgesics and megestrol acetate for anorexia) • Haematopoietic growth factors, at the discretion of the treating physician • Anti-inflammatory medications or narcotic analgesics • Packed red blood cell and platelet transfusions, as clinically indicated • Appropriate hormone replacement therapy, as clinically indicated, in the absence of PD or unacceptable treatment-associated toxicity • Bisphosphonate therapy for metastatic bone disease • Low-dose acetaminophen (maximum total daily dose of 2 g) • Disallowed concomitant medication[69]: • Any other anticancer therapies • Cytochrome P450 3A inhibitors and inducers (except for topical use of inhibitors) • Bradycardic agents, medicinal products known to prolong the QT interval, and/or antiarrhythmics were to be avoided in patients receiving crizotinib • Non-prescription drugs (except vitamins) or herbal supplements Concomitant radiotherapy and surgery[69]: • Palliative radiotherapy to specific sites of disease was permitted if considered	Permitted concomitant medication[70]: • Medications intended for supportive care (i.e. antiemetics and analgesics) • Haematopoietic growth factors, at the discretion of the treating physician • Anti-inflammatory medications (except as noted below for pemetrexed) or narcotic analgesics • Appropriate hormone replacement therapy, as clinically indicated, in the absence of PD or unacceptable treatment-associated toxicity • Bisphosphonate therapy for metastatic bone disease Disallowed concomitant medication[70]: • Any other anticancer therapies • NSAIDs with long half-lives in patients receiving pemetrexed • Cytochrome P450 3A inhibitors and inducers • Any medications formulated with polysorbate 80. Concomitant radiotherapy and surgery:[70,72] • Palliative radiotherapy to specific sites of disease was permitted if considered medically necessary by the treating physician. Radiotherapy was performed at least one day before or one day after chemotherapy and during an interruption in crizotinib treatment (stopped 1 day before and resumed 1 day after) • In the event that elective surgery was	Patients in the chemotherapy group were required to take folic acid (350–1000 µg orally daily) and Vitamin B_{12} (1000 µg, injected intramuscularly every 9 weeks). In order to keep treatment conditions similar, patients receiving crizotinib were also required to take folic acid and Vitamin B_{12}.[72] Permitted concomitant medication:[72] • Medications intended for supportive care (i.e. antiemetics and analgesics) • Haematopoietic growth factors, at the discretion of the treating physician • Anti-inflammatory medications (except as noted below for pemetrexed) or narcotic analgesics • Packed red blood cell and platelet transfusions, as clinically indicated • Appropriate hormone replacement therapy, as clinically indicated, in the absence of PD or unacceptable treatment-associated toxicity • Bisphosphonate therapy for metastatic bone disease • Low-dose acetaminophen (maximum total daily dose of 2 g) Disallowed concomitant medication:[72] • Any other anticancer therapies • NSAIDs with long half-lives in patients receiving pemetrexed • Cytochrome P450 3A inhibitors and inducers • Bradycardic agents, medicinal products known to prolong the QT interval,

	medically necessary by the treating physician. Radiotherapy was performed at least one day before or one day after chemotherapy and during an interruption in crizotinib treatment (stopped one day before and resumed one day after). In the event that elective surgery was necessary during study participation, treatment with crizotinib was to be avoided 48 hours before surgery and resumed no sooner than 48 hours after surgery	necessary during study participation, treatment with either crizotinib or chemotherapy was to be avoided 1 week before surgery and resumed no sooner than 1 week after surgery	and/or anti-arrhythmics were to be avoided in patients receiving crizotinib Concomitant radiotherapy and surgery:[72] • Palliative radiotherapy to specific sites of disease was permitted if considered medically necessary by the treating physician. Radiotherapy was performed at least one day before or one day after chemotherapy and during an interruption in crizotinib treatment (stopped 1 day before and resumed 1 day after) • In the event that elective surgery was necessary during study participation, treatment with either crizotinib or chemotherapy was to be avoided 48 hours before surgery and resumed no sooner than 48 hours after surgery
Primary outcomes	ORR defined as the percentage of patients with confirmed CR or PR according to RECIST (v1.0 for ROS1-positive cohort [n=50]; v1.1 for ALK-negative cohort [n=3])	PFS defined as the time from randomisation to RECIST (v1.0)	PFS defined as the time from randomisation to RECIST (v1.1)-defined progression (as assessed by IRR) or death
Other outcomes used in the economic model/specified in the scope	• OS • PFS • TTF • Safety	• OS • TTF • Safety • EQ-5D	• OS • TTF • Safety • EQ-5D
Pre-planned subgroups	ORR by baseline characteristics		• PFS by stratification factors/baseline characteristics • IC-TTP and EC-TTP by treatment group and baseline brain metastases

Abbreviations: ALK, anaplastic lymphoma kinase; AUC, area under the concentration-time curve; BSA, body surface area; CR, complete response; EC, extracranial; ECOG PS, Eastern Cooperative Oncology Group performance status; EQ-5D, EurQoL-5 Dimensions; FISH, fluorescence in situ hybridisation;; IC, intracranial; IRR, independent radiology review; i.v, intravenous; NSAID, non-steroidal anti-inflammatory drug; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PRO, patient-reported outcome; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended Phase 2 dose; TTF, time to treatment failure; TTP, time to progression; UK, United Kingdom; USA, United States of America; VSAQ, Vendor Security Assessment Questionnaire.
Source: PROFILE 1001[7, 69]; PROFILE 1007[70, 71]; PROFILE 1014[72, 73]

B.2.3.3 Patient characteristics

The baselines characteristics of ROS1-positive NSCLC patients from PROFILE 1001 are presented in Table 11, alongside the baseline characteristics of ALK-positive NSCLC patients from PROFILE 1007 and PROFILE 1014. The majority of patients enrolled in PROFILE 1001 were relatively young, with a mean age of 54.1 years (SD: 13.44), had never smoked (75.5%), and had adenocarcinoma as the underlying histopathology (96.2%). These baseline characteristics of the ROS1-positive cohort are similar to those of ALK-positive patients observed in PROFILE 1007 and PROFILE 1014, and provide supporting evidence for the use of ALK-positive NSCLC data as a proxy.[7, 71, 73, 91, 92]

PROFILE 1001 enrolled both treatment naïve and pre-treated patients with advanced ROS1-positive NSCLC. Seven patients had never received systemic advanced/metastatic treatments, and were therefore receiving crizotinib as a first-line therapy.

Table 11: Patient characteristics from PROFILE 1001, 1007 and 1014

	PROFILE 1001	PROFILE 1007		PROFILE 1014	
	ROS1 SA population	ALK ITT population		ALK ITT population	
	Crizotinib (N=53)	Crizotinib (N=173)	Chemotherapy (N=174)	Crizotinib (N=172)	Chemotherapy (N=171)
Age (years): Median, (Min, Max)	55 (25–81)	51 (22–81)	49 (24–85)	52.0 (22–76)	54 (19–78)
Category (years) – no. (%)					
<65	38 (71.7)	146 (84.4)	[redacted]	[redacted]	[redacted]
≥65	15 (28.3)	27 (15.6)	[redacted]	[redacted]	[redacted]
Sex – no. (%)					
Male	23 (43.4)	75 (43.4)	78 (44.8)	68 (39.5)	63 (36.8)
Female	30 (56.6)	98 (56.6)	96 (55.2)	104 (60.5)	108 (63.2)
Race – no. (%)					
White	30 (56.6)	90 (52.0)	91 (52.3)	91 (52.9)	85 (49.7)
Black	2 (3.8)	2 (1.2)	3 (1.7)	[redacted]	[redacted]
Asian	21 (39.6)	79 (45.7)	78 (44.8)	77 (44.8)	80 (46.8)
Other	NR	2 (1.2)	2 (1.2)	4 (2.3)	2 (1.2)
Weight (kg)					
Mean (SD)	71.9 (16.0)	65.3 (17.3)	[redacted]	[redacted]	[redacted]
Median (range)	70.0 (48.0-106.3)	62.0 (35.2-160.0)	[redacted]	[redacted]	62.5 (35.8–151.6)[a]
ECOG Performance Status					
0	23 (43.4)	72 (41.6)	65 (37.4)	[redacted]	[redacted]
1	29 (54.7)	84 (48.6)	95 (54.6)	[redacted]	[redacted]

	PROFILE 1001	PROFILE 1007		PROFILE 1014	
	ROS1 SA population	ALK ITT population		ALK ITT population	
	Crizotinib (N=53)	Crizotinib (N=173)	Chemotherapy (N=174)	Crizotinib (N=172)	Chemotherapy (N=171)
2	1 (1.9)	16 (9.2)	14 (8.0)	9 (5.2)	[redacted]
Smoking status – no. (%)					
Never smoker	40 (75.5)	108 (62.4)	111 (63.8%)	106 (61.6)	112 (65.5)
Ex-smoker	13 (24.5)	59 (34.1)	54 (31.0%)	56 (32.6)	54 (31.6)
Current smoker	NR	5 (2.9)	9 (5.2%)	10 (5.8)	5 (2.9)
Histological classification – no. (%)					
Adenocarcinoma	51 (96.2)	163 (94.2)	160 (92.0%)	158 (91.9)	159 (93.0)
Non-adenocarcinoma	2 (3.8)	9 (5.2)	14 (8.0)	14 (8.1)	12 (7.0)
Prior surgeries – no. (%)	53 (100)	NR		NR	NR
Prior radiation therapies – no. (%)					
No	34 (64.2)	[redacted]	[redacted]	[redacted]	[redacted]
Yes	19 (35.8)	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior systemic therapy regimens:					
0	7 (13.2)	[redacted]	[redacted]	172 (100)	171 (100)
1	20 (37.7)	[redacted]	[redacted]	0	0
2	13 (24.5)	[redacted]	[redacted]	0	0
3	3 (5.7)	[redacted]	[redacted]	0	0
>3	10 (18.9)	[redacted]	0	0	0
Not reported	0	[redacted]	0	0	0
Extent of disease[c]- no. (%)					
Locally advanced	NR	7 (4.0)	8 (4.6%)	4 (2.3)	3 (2)
Metastatic	NR	165 (95.4)	166 (95.4%)	168 (97.7)	168 (98.2)
Brain metastases present – no. (%)	NR	60 (35)		45 (26.2)	47 (27.5)

	PROFILE 1001	PROFILE 1007		PROFILE 1014	
	ROS1 SA population	ALK ITT population		ALK ITT population	
	Crizotinib (N=53)	Crizotinib (N=173)	Chemotherapy (N=174)	Crizotinib (N=172)	Chemotherapy (N=171)
Time since first diagnosis median (months)	NR	[redacted]	[redacted]	1.2 (0–114.0)	1.2 (0–93.6)

[a]One person's weight incorrectly reported as 151.6kg instead of 151.6 pounds. [b]Two patients in the crizotinib group did not report their prior radiation therapy status. [c]Data missing for 4 patients in the crizotinib arm in PROFILE 1007

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; N/A, not applicable; NR, not reported; SA, safety analysis population; SD, standard deviation.

Source: PROFILE 1001[7, 69]; PROFILE 1007[70, 71]; PROFILE 1014.[72, 73]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A total of 53 patients were enrolled in PROFILE 1001. The trial populations used in the analysis of outcomes are presented in Table 12. The trial populations used in the analysis of outcomes for PROFILE 1007 are presented in Appendix L and for PROFILE 1014 are presented in the manufacturer's submission to NICE for first-line crizotinib.[84]

Table 12: Trial populations used in the analysis of PROFILE 1001

Analysis	Trial population
Response analysis (ORR, DR, TTR, DCR)	**RE population (n=53)** – all patients in the SA population who had an adequate baseline disease assessment. Patients also needed to meet one of the two following criteria: 1. Had at least one post-baseline disease assessment at least six weeks from first dose of crizotinib. or 2. Withdrew from the study or experienced progressive disease/death at any time on study.
Safety analysis (PFS, TTP, TTF, OS, safety, patient characteristics)	**SA population (n=53)** – included all enrolled patients who received at least one dose of crizotinib.

Abbreviations: DR, disease response; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RE, response evaluable; SA, safety analysis; TTF, time to treatment failure; TTP, time to tumour progression; TTR, time to tumour response.

Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Interim analyses and patient stopping guidelines

For PROFILE 1001, [redacted][69]

In PROFILE 1001, treatment was continued until the occurrence of RECIST-defined disease progression or clinical deterioration. Patients with RECIST-defined disease progression or clinical deterioration could continue on crizotinib treatment at the investigator's discretion and with the approval from the Sponsor.[68]

For PROFILE 1007, details of any interim analysis is located in the clinical study report (CSR), and for PROFILE 1014 is presented in the manufacturer's submission to NICE for first-line crizotinib.[84]

Methods for additional analyses: subgroup analyses

All subgroup analyses were pre-specified in the Statistical Analysis Plan (see Table 8) for PROFILE 1001.

For PROFILE 1007, details of any subgroup analyses is located in the CSR, and for PROFILE 1014 is presented in the manufacturer's submission to NICE for first-line crizotinib.[84]

Analysis population

A response evaluable (RE) population was used in the primary analysis of ORR in PROFILE 1001, as described in Table 12. The point estimate of the ORR was provided along with the corresponding 95% CI's using the exact method based on the F-distribution.[69]

For PROFILE 1007, details of the analysis population is located in Appendix L, and for PROFILE 1014 is presented in the manufacturer's submission to NICE for first-line crizotinib.[84]

Statistical tests

The primary endpoint in PROFILE 1001 was ORR. A summary of the statistical tests used in the primary analysis of PROFILE 1001 is presented in Table 13 alongside sample size calculations and methods for handling missing data.

The data cut-off date for PROFILE 1001 was 30th November 2014. All analyses and data summaries included all data pertaining to visits or assessments performed up to and including this data cut-off date. OS data was immature at this latest data cut-off date.

For PROFILE 1007, details of the statistical tests is located in Appendix L, and for PROFILE 1014 is presented in the manufacturer's submission to NICE for first-line crizotinib.[84]

Table 13: Statistical tests for the primary analysis of PROFILE 1001

Trial number (acronym)	NCT00585195 (PROFILE 1001)
Hypothesis objective	Exploratory The primary endpoint was ORR **Null hypothesis (H_0):** ORR is less than or equal to 0.10 **Alternative hypothesis (H_A):** ORR is greater than 0.10, at an assumed target rate of 0.30
Statistical tests	The point estimates of the rates of ORR and DCR were provided alongside corresponding exact 2-sided 95% CIs using the exact method based on the F-distribution Continuous endpoints were assessed using descriptive statistics (mean, standard deviation, median, minimum and maximum values) Time-to-event data (DR, PFS, TTP and OS) were analysed using the Kaplan-Meier method with 2-sided 95% CIs using the Brookmeyer-Crowley method[68]
Sample size, power calculation	It was estimated that a sample size of 30 patients would mean that the study would have at least an 85% power to test the null hypothesis, with a one-sided single state design at 0.05 significance level, that the ORR is greater than 0.10. The alternative target rate was assumed to be 0.30 The sample size was then increased to 50 patients to provide a more robust estimation of efficacy
Data management, patient withdrawals	Patients could withdraw from the study at any time at their own request, or they could be withdrawn for non-compliance to the study protocol[7] For the analysis of PFS and TTP, data was censored on first dose if patients: • Had inadequate baseline assessments • Lacked an evaluation of tumour response after the date of the first dose • Had their first on-study tumour assessment after 16 weeks (or 14 weeks for the ALK-negative cohort) For patients who had at least one on-study disease assessment, PFS, DR and TTP data were censored on the date of the last evaluable tumour assessment documenting absence of progressive disease for patients who: • Were alive, on-study and progression-free at data cut-off • Had PD >35 days after treatment end date or died >16 weeks after last on-study tumour assessment (>14 weeks for ALK-negative cohort) • Had PD after ≥2 consecutively missed tumour assessments • Had new anti-cancer treatment prior to PD • Withdrew consent for follow-up • Were lost to follow-up • Were off-treatment prior to progression • Were in follow-up for progression For the analysis of OS, data was censored at the date of first dose if patients did not have any data beyond this first dose. Data was also censored at the time of

	data cut-off, and the last date a patient was known to be alive and included patients who: • Remained in follow-up • Withdrew consent for follow-up (also censored on date consent was withdrawn) • Were lost to follow-up • Completed the required 1-year follow-up

Abbreviations: CI, confidence interval; DCR, disease control rate; DR, disease response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; TTP, time to tumour progression.
Source: EPAR Xalkori/crizotinib 21st July 2016[7], unless otherwise stated

B.2.4.1 Potential biases in the evidence

PROFILE 1001 was a single arm, non-comparative study and therefore the discussion of bias is not relevant here. UK clinical experts confirmed that the baseline characteristics in PROFILE 1001 are representative of patients encountered in UK clinical practice,[3] and as such selection bias is unlikely to be a concern.

PROFILE 1007 and 1014 were of open-label design due to the different routes of administration for each treatment; crizotinib is an oral therapy whilst chemotherapy is administered intravenously. Open-label study designs are at risk of ascertainment bias because study patients and investigators have knowledge of the treatment received. In PROFILE 1007 and 1014, this source of bias was mitigated by the use of an independent radiologic review (IRR) group who were blinded to the treatment group to assess tumour response and disease progression.

Another potential source of bias arises from the fact that patients in the chemotherapy arms in both PROFILE 1007 and 1014 were permitted to cross over to crizotinib after disease progression. This has the potential to contaminate OS estimates for the chemotherapy arm and hence introduce bias in the OS results. This bias was mitigated by analyses using several validated methodologies to adjust for crossover bias.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The study design of PROFILE 1001 was assessed using the Downs and Black checklist, which has been recommended as being suitable for use in systematic reviews that include non-randomised studies.[93-95]

The results from the quality assessment can be found in Appendix D. PROFILE 1001 has a single-arm study design and therefore there was a lack of randomisation and blinding. To mitigate detection bias, the assessments of tumour response and disease progression were made by IRR. In all other respects, the study was deemed to be of reasonable high quality given the small size of the ROS1-positive NSCLC population.

PROFILE 1001 was used as the main source of clinical evidence for the regulatory approval of crizotinib in Europe for the treatment of ROS1-positive advanced/metastatic NSCLC.[7] Evidence from the ROS1-positive cohort of the PROFILE 1001 study was considered to be sufficient by the EMA for regulatory approval given that ROS1-positive NSCLC is a rare genetic subgroup which shares similarities in terms of the amino acid sequence of the RTK, patient response to crizotinib,

and patient clinical characteristics with the ALK-positive genetic subgroup of NSCLC patients.[1, 7, 15, 17, 30]

Quality assessments for the crizotinib in ALK-positive NSCLC (PROFILE 1007 and PROFILE 1014) are also presented in Appendix D. Both studies are high-quality RCTs.

The study designs of all the non-RCTs identified in the clinical SLR which were not PROFILE 1001 were also assessed using the Downs and Black checklist. The results of the quality appraisal of these studies are provided in Appendix D. As may be expected from non-RCT trials, none of the trials scored highly in terms of internal validity mostly due to lack of blinding of participants and assessors. However, in other aspects of the assessment, the studies were deemed to be of reasonably high quality, such as clear reporting of patient characteristics and study outcomes. Outcome measures and statistical tests used in the studies were also valid and reliable, and outcomes were adjusted for differences in the length of follow-up.

B.2.6 Clinical effectiveness results of the relevant trials

Summary of PROFILE 1001 clinical efficacy results

- The primary endpoint, ORR, derived by investigator assessment, was 69.8% (95% CI: 55.7–81.7) in the cohort including patients with ROS1-positive advanced NSCLC from PROFILE 1001 (N=53).
- Crizotinib was associated with an ORR of 85.7%; 95% CI: 42.1–99.6) in six out of the seven patients who had not received prior treatment.
- Objective response to crizotinib was rapid, with a median TTR of 7.9 weeks (95% CI: 4.3–32.0), which coincided with the first scan patients received whilst on-treatment.
- Median OS had not been reached at data cut-off (30th November 2014); probability of survival at 12 months was 79.0% (95% CI: 65.3–87.8), suggesting prolonged clinical benefit for patients receiving crizotinib.

Summary of PROFILE 1007 and 1014 clinical efficacy results

- The primary endpoint, PFS, was significantly prolonged compared to chemotherapy in PROFILE 1007 and PROFILE 1014, with increases of 3.7 and 3.8 months, respectively.
- The ORR reported for patients receiving crizotinib in PROFILE 1007 and PROFILE 1014 was comparable to that observed in PROFILE 1001 (65.3% and 74.4%, respectively)
- Median OS was reached in PROFILE 1007. In PROFILE 1007, there was an increase in OS for crizotinib versus chemotherapy (crossover adjusted HR: 0.383 [95% CI: 0.283–0.518). In PROFILE 1014 the crossover adjusted HR for crizotinib versus chemotherapy was [redacted]
- HRQoL outcomes from PROFILE 1007 show the absolute EQ-5D index scores to be [redacted] Furthermore, a mixed-model analysis of PROFILE 1014 data found the overall EQ-5D index score to be [redacted]

A summary of the key clinical effectiveness results reported in PROFILE 1001 is presented in Table 14. As discussed in Section B.2.2, no comparative RCT data is available for ROS1-positive patients due to the phase I trial design of PROFILE 1001 for this ultra-orphan indication, and due to the lack of clinical equipoise to conduct further comparative trials. Based on the similarities in ROS1-positive and ALK-positive NSCLC (see Section B.1.3.1), data from the RCTs of crizotinib

in ALK-positive patients (PROFILE 1007 and PROFILE 1014) provide relevant comparative evidence for the clinical efficacy and safety of crizotinib versus chemotherapy and can be used as a proxy for ROS1-positive NSCLC.[3]

A summary of the key clinical effectiveness results reported in PROFILE 1007 and PROFILE 1014 are presented in Table 15, alongside the results from PROFILE 1001. Median PFS in patients treated with crizotinib was higher in PROFILE 1001 (first-line and subsequent-line patients) compared to PROFILE 1007 (subsequent-line patients) and PROFILE 1014 (first-line patients). In PROFILE 1007 and PROFILE 1014, the PFS in patients treated with crizotinib was higher than in patients treated with chemotherapy. Median ORR was comparable across all three trials for crizotinib-treated patients.

Table 14: Overview of clinical efficacy results from PROFILE 1001

Outcome	**PROFILE 1001 (N=53)**
	Crizotinib (N=53)
Objective response rate (ORR) (based on derived tumour assessment)	
ORR, (%) (95% CI)	37 (69.8) [55.7–81.7]
Complete response, (%)	5 (9.4)
Partial response, (%)	32 (60.4)
SD, (≥6 weeks)	11 (20.8)
PD	3 (5.7)
Early death	1 (1.9)
Indeterminate	1 (1.9)
ORR (based on IRR)	
ORR, (%) (95% CI)	33 (66.0) [51.2–78.8]
Complete response, (%)	1 (2.0)
Partial response, (%)	32 (64.0)
SD, (≥6 weeks)	12 (24.0)
PD	4 (8.0)
Early death	1 (2.0)
Indeterminate	0 (0.0)
Disease control rate (DCR)	
DCR, at Week 8, (%) (95% CI)	46 (86.8) [74.7–94.5]
DCR, at Week 16, (%) (95% CI)	42 (79.2) [65.9–89.2]
Duration of response (DR) – months (n=37, objective responders only)	
Median, (range)	NR (15.2–NR)
Time to tumour response (TTR) – weeks (n=37, objective responders only)	
Median, (range)	7.9 (4.3–32.0)
Progression free survival (PFS)	
Patients with event, (%)	26 (49.1)
Median, (range)	19.3 months (14.8–NR)

Time to tumour progression (TTP)	
Patients with event, (%)	23 (43.4)
Median, (95% CI)	19.8 months (15.2–NR)
Time to treatment failure (TTF)	
Median, (95% CI)	23.2 months (15.0–NR)
Overall survival (OS) - months	
Median	NR
Hazard ratio, (95% CI, p-value)	NA
Probability of survival at 6 months,[a] (95% CI)	90.6% (78.8–96.0)
Probability of survival at 12 months,[a] (95% CI)	79.0% (65.3–87.8)
Median duration of follow up, (95% CI)	25.4 months (22.5–28.5)

[a]Probability was determined by Kaplan-Meier estimate
Abbreviations: CI, confidence intervals; DCR, disease control rate; DR, duration of response; IRR, independent radiology review; NR, not reported; ORR, objective response rate; OS, overall survival; PD, progressed disease; PFS, progression free survival; SD, stable disease.
Source: EPAR Xalkori/crizotinib 21st July 2016[7], unless stated otherwise

Table 15: Overview of key clinical efficacy results from PROFILE 1001, 1007 and 1014

Outcome	PROFILE 1001 (N=53)	PROFILE 1007 (N=347)	PROFILE 1014 (N=343)
Median progression-free survival (PFS)			
Crizotinib, months (95% CI)	19.3 (14.8–NR)	7.7 (6.0–8.8)	10.9 (8.3–13.9)
Chemotherapy	NA	3.0 (2.6–4.3)	7.0 (6.8–8.2)
HR, (95% CI; p-value)	NA	0.487 (0.371–0.638; p<0.0001)	0.45 (0.35–0.60; p<0.001)[a]
% of patients who crossed-over			
Crizotinib	NA	65/173 (37.6%)	33/172 (19.2%)
Chemotherapy	NA	154/174 (88.5%)	144/171 (84.2%)
Tumour response, overall response rate (ORR)[b]			
Crizotinib, no. of patients (%) [95% CI][c]	37 (69.8) [55.7–81.7]	112 (65.3) [57.7–72.4]	128 (74.4) [67.2–80.8)
Chemotherapy	NA	34 (19.5) [13.9–26.2]	77 (45) [37–53]
Median overall survival (OS)			
Crizotinib, months	NR	21.7 (18.9–30.5)	[redacted]
Chemotherapy	NA	21.9 (16.8–26.0)	[redacted]
HR, (95% CI, p-value)	NA	Unadjusted: 0.854 (0.66–1.10; p=0.11)	Unadjusted: [redacted]
		Crossover adjusted: 0.383 (0.283–0.518)	Crossover adjusted: [redacted] See Table 33 and Section B.3.3.4 for details

[a]For between-group comparisons (crizotinib vs. chemotherapy), two-sided log-rank test stratified according to baseline stratification factors were used; stratified Cox regression models were applied to estimate HRs. [b]Tumour response was assessed using RECIST (v1.0 for ROS1 patients in PROFILE 1001, v1.1 for PROFILE 1007, 1014 and three patients from ALK-negative cohort respectively determined to be ROS1-positve in PROFILE 1001) and were confirmed by IRR. [c]P<0.001 for between-group comparison.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria on Solid Tumours.
Source: PROFILE 1001: EPAR Xalkori/crizotinib 21st July 2016[7]; PROFILE 1007: Shaw et al. 2013[71], CSR[70]; Shaw et al. 2016[47]; PROFILE 1014: Solomon et al. 2014[73], CSR[72], updated CSR[96], Mok et al. 2017[97]

B.2.6.1 Objective response rate

Objective response rate (ORR) was high with crizotinib in ROS1-positive NSCLC

The ORR based on derived-tumour assessment was high for the ROS1-positive cohort (n=53) in PROFILE 1001, with the majority of patients (69.8%; 95% CI: 55.7–81.7) achieving either a partial (60.4%) or complete (9.4%) response with crizotinib. The individual patient responses to crizotinib treatment in terms of percentage decrease or increase in tumour size from baseline are shown in Figure 3.

The ORR based on derived-tumour assessment in PROFILE 1001 was consistent with the ORR based on IRR in the ROS1-positive cohort (n=50) in PROFILE 1001, (ORR n=33, [66.0%], complete response n=1 [2.0%], partial response n=32, [64.0%]), and the total event agreement rate between the derived tumour assessment and IRR was 82.0%, suggesting detection bias to be negligible.

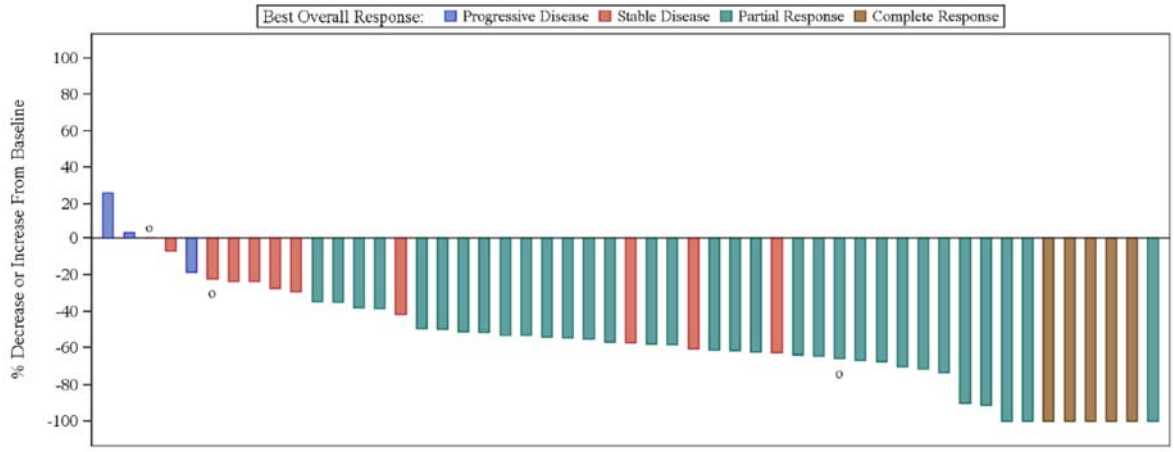
Most patients had previously received systemic therapy for ROS1-positive NSCLC (n=46; 86.8%) in PROFILE 1001. Of the seven treatment-naïve patients, six achieved an objective response (85.7% [95% CI: 42.1–99.6]) compared to 31 out of 46 patients (67.4% [95% CI: 52.0–80.5]) in patients who have received one or more prior therapies in the advanced setting, supporting the use of crizotinib in all lines of therapy but particularly as a first-line treatment in ROS1-positive NSCLC.

All patients underwent local diagnostic testing for ROS1 rearrangements. Fifty-one of the 53 patients (96.2%) were ROS1-positive by FISH. The remaining two patients were ROS1-positive by reverse transcriptase polymerase chain reaction (RT-PCR).[68] Available tissues samples (n=37 from 36 patients) were retrospectively tested for ALK rearrangement. In one patient, NGS showed that they were ROS1-negative. Another patient tested positive for ROS1 and ALK rearrangement under FISH testing, but was determined to be ROS1-negative after NGS.[7] These two patients who were retrospectively determined to be ROS1-negative were kept in the analysis, as the trial protocol specified patients' gene translocations to be classified according to local testing (initial testing).[69] The impact of the inclusion of data from these two patients is discussed in this section.

The two patients who were retrospectively determined to be ROS1-negative (of whom one patients was ALK-positive) by NGS experienced [redacted] and [redacted], respectively. The inclusion of these two ROS1-negative patients was a conservative approach, as these two patients showed a worse or comparable response compared to most other ROS1-positive patients.

The preliminary results from EUCROSS support the observations from PROFILE 1001, suggesting that the results from ROS1 patients in PROFILE 1001 are generalisable to the UK population. The ORR from EUCROSS was [redacted]) and therefore comparable with the ORR reported in PROFILE 1001.[67]

Figure 3. Waterfall plot of tumour shrinkage activity of crizotinib in individual patients based on derived-tumour assessment (n=51*)



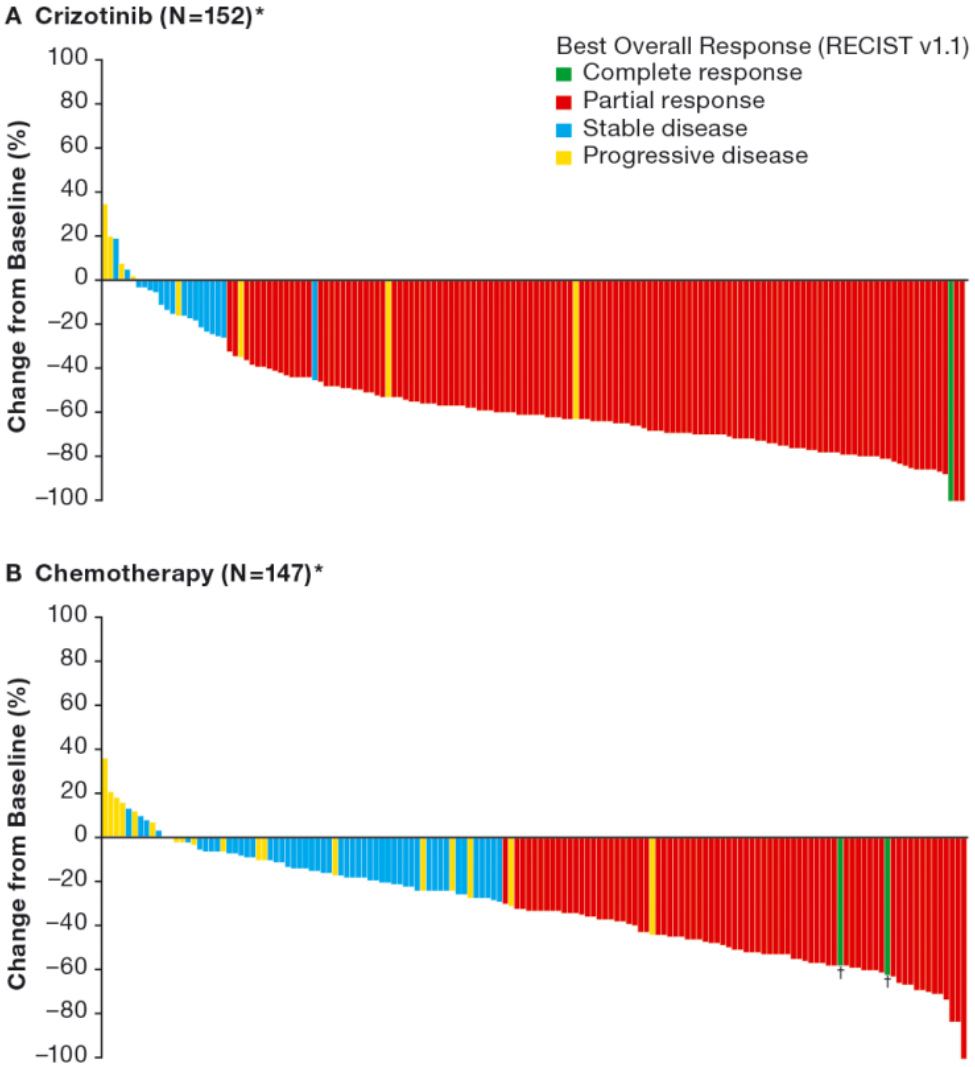
*n=51 based on the RE population, which excludes patients with early death or indeterminate response.
The three patients included from the AK-negative NSCLC cohort based on ROS1-positive status in retrospective review are marked with 'o'; derived tumour assessment for these patients uses RECIST version 1.1 criteria.
For patients enrolled into the ROS1-positive NSCLC cohort, derived tumour assessment is based on RECIST version 1.0 criteria.
Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; RE, response evaluable; RECIST, Response Evaluation Criteria In Solid Tumours.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

The ORR in crizotinib-treated patients from PROFILE 1007 and PROFILE 1014 was comparable with that observed in PROFILE 1001, and significantly better than in chemotherapy-treated patients

In PROFILE 1007, the ORR was significantly better in the crizotinib arm at 65.3% (n=112; 95% CI: 57.7–72.4), versus only 19.5% in the chemotherapy arm (n=34; 95% CI: 13.9–26.2, p<0.0001) for subsequent-line ALK-positive NSCLC patients. In PROFILE 1014, the ORR was significantly higher in the crizotinib arm at 74.4%, compared to 45% in the chemotherapy arm (p<0.001) for first-line ALK-positive NSCLC patients.

A waterfall plot showing the best tumour response in PROFILE 1014 is presented in Figure 4. This is comparable to the best tumour response observed in PROFILE 1001 (Figure 3). The superior tumour shrinkage with crizotinib in PROFILE 1014 was thought to be reflected by crizotinib's statistically significant improvement in HRQoL compared to pemetrexed plus platinum (see Section B.2.6.6).[5]

Figure 4. Summary of best overall response in change of tumour size in the ITT population in PROFILE 1014



*Assessed in the ITT population; only data for patients whose tumours were classified as an objective response, stable disease or progressive disease are shown; data for patients with an indeterminate response, non-measurable disease or who died early, are not shown.
†Signifies a complete response of <100% change from baseline – this can occur when lymph nodes are included as target lesions.
Abbreviations: ITT, intention-to-treat; RECIST, Response Evaluation Criteria In Solid Tumours.
Source: Solomon et al. (2014b) – Supplementary material: Figure S2[98]

B.2.6.2 Progression-free survival

Progression-free survival was high, along with probability of survival at 12 months in ROS1 patients

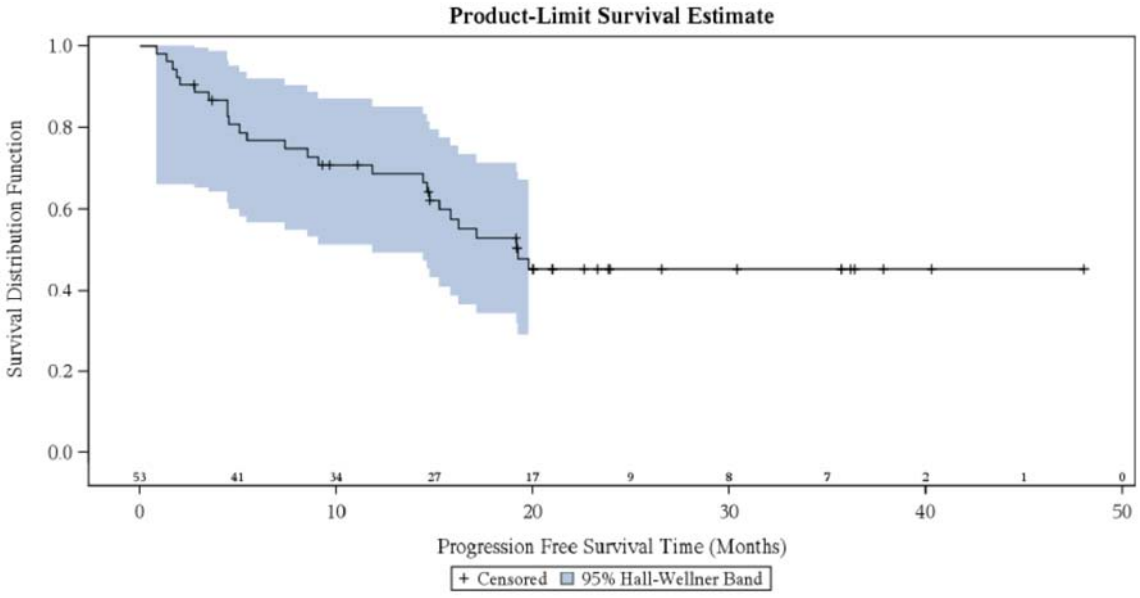
Median PFS was 19.3 months (95% CI: 14.8–NR), with 27 censored patients (50.9%), and 21 patients (39.6%) still on follow-up for disease progression at the data cut-off date in PROFILE 1001 (30th November 2014) (Figure 5).[7] The PFS from the preliminary EUCROSS results was [redacted] months (95% CI: [redacted])[67], which is comparable with the median PFS observed in PROFILE 1001.

At the data cut-off date in PROFILE 1001, three (42.9%) of the seven previously untreated patients had experienced an event (n=2 with objective progression, n=1 death without objective progression). Amongst previously treated patients (n=46), 23 patients (50.0%) had experienced an event by the data cut-off date (n=21 with objective progression, n=2 death without objective progression).

The probability of being alive and progression-free at 12 months was 79.0% (95% CI: 65.3–87.8).[68]

As mentioned above, the two patients who were retrospectively determined to be ROS1-negative (one of whom was ALK-positive) by NGS were included in the PROFILE 1001 analysis. The PFS durations of these patients were [redacted] (ALK-negative) and [redacted] (ALK-positive), respectively.[69] The inclusion of these patients in the PFS analysis was a conservative approach, and would not have biased the outcomes in favour of crizotinib, as these two ROS1-negative patients had a shorter or comparable PFS, respectively, compared to the ROS1-positive patients.

Figure 5. Kaplan-Meier plot of progression-free survival in ROS1-positive NSCLC patients (n=53)[7]



Abbreviations: NSCLC, non-small cell lung cancer.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

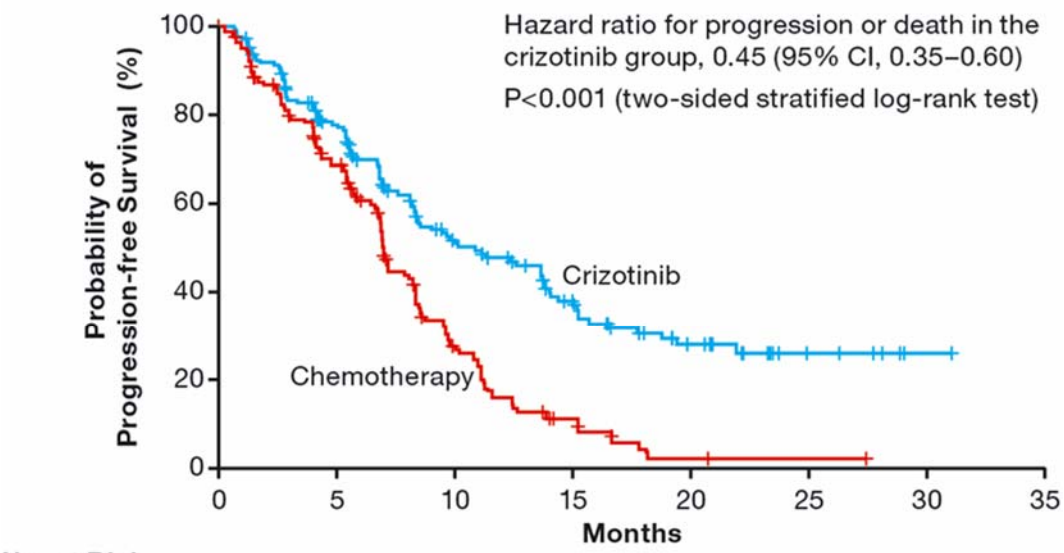
PROFILE 1007 and 1014 met their primary endpoints of a significant improvement in prolonging PFS versus chemotherapy

In PROFILE 1014 there was a significant improvement in prolonging PFS with crizotinib compared to chemotherapy. ALK-positive NSCLC patients in the crizotinib group had an increase in median PFS of 3.9 months compared to patients in the chemotherapy group (hazard ratio [HR]: 0.45; 95% CI, 0.35–0.60; p<0.001).[5] The Kaplan-Meier plot of PFS in first-line ALK-positive NSCLC patients from PROFILE 1014 is presented in Figure 6.

Based on evidence from PROFILE 1007, crizotinib also significantly increased the median PFS in ALK-positive patients compared to chemotherapy in the subsequent-line setting by 3.7 months

(HR: 0.487; 95% CI: 0.371–0.638; p<0.0001).[8] The results for prolonging survival without progression in PROFILE 1007 and 1014 support the high median PFS observed in PROFILE 1001, and therefore the similarities between ALK and ROS1 patient populations.

Figure 6: Kaplan-Meier plot for progression-free survival in the ALK-positive ITT population in PROFILE 1014



No. at Risk

Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

Abbreviations: ALK, anaplastic lymphoma kinase; ITT, intention-to-treat.
Source: Solomon *et al.* (2014a)[73]

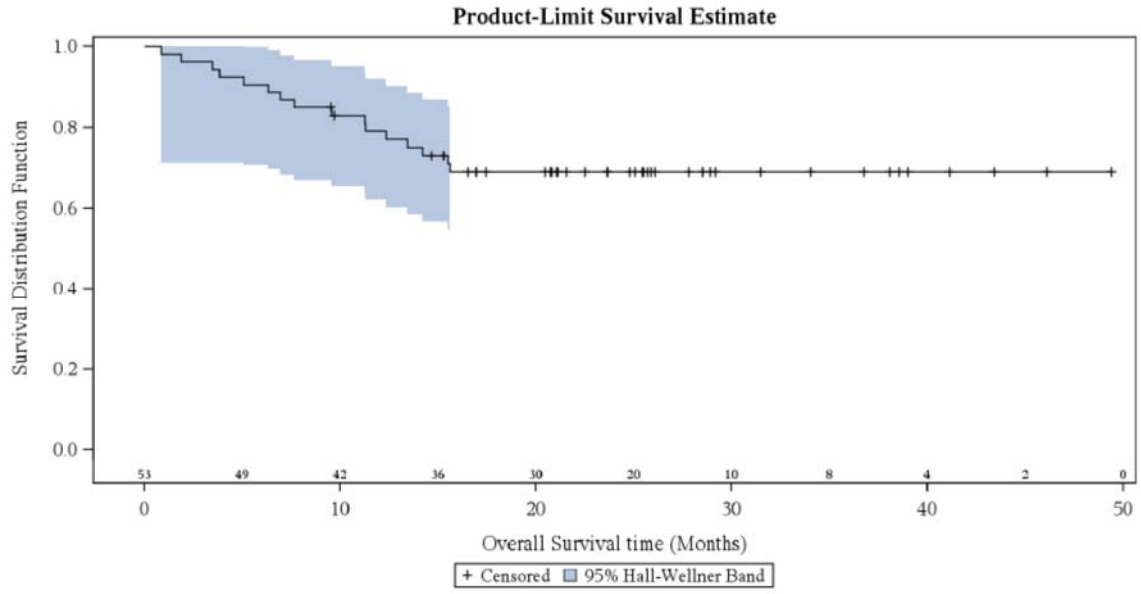
B.2.6.3 Overall survival

Median overall survival was not reached by the time of data cut-off in PROFILE 1001

At the time of the data cut-off, the median duration of OS follow-up (reverse Kaplan-Meier method) was 25.4 months (95% CI: 22.5–28.5).[7] The median OS was not reached by data cut-off (30th November 2014), where 16 deaths had been recorded and 37 patients were censored (Figure 7). However, the probability of survival at six months (based on Kaplan-Meier estimates) was determined to be 90.6% (95% CI: 78.8–96.0), decreasing to 79.0% (95% CI: 65.3–87.8) over 12 months. This is comparable with the probability of survival at 12 months from EUCROSS ([redacted]), and also reported 24-month survival data of [redacted]).[67]

As mentioned above, the two patients who were retrospectively determined to be ROS1-negative (one of whom was ALK-positive) by NGS were included in the PROFILE 1001 analysis. The OS was [redacted] for the ROS1-negative, ALK-negative patient, whilst the OS was censored at [redacted] for the ROS1-negative, ALK-positive patient.[69] The inclusion of these patients in the OS analysis was a conservative approach, and would not have biased the outcomes in favour of crizotinib, as these two ROS1-negative patients had shorter or comparable OS, compared to the median duration of follow-up for OS reported for all the patients included in PROFILE 1001.

Figure 7. Kaplan-Meier Plot of overall survival in ROS1-positive NSCLC patients (n=53)[7]



Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Median OS results from PROFILE 1007 and PROFILE 1014 show crizotinib to provide an OS advantage compared to chemotherapy in ALK-positive NSCLC

In PROFILE 1007, the median OS reached at the final data cut-off date of 31st August 2015 was 21.7 months (18.9–30.5), compared to 21.9 months (16.8–26.0) in the chemotherapy arm. The Kaplan Meier curve is show in Figure 8.There was a numerical improvement in OS in the crizotinib arm (unadjusted HR: 0.854; 95% CI: 0.66–1.10; p=0.01145). The crossover adjusted HR showed the median OS of patients treated with crizotinib to be longer than the median OS of patients treated with chemotherapy (crossover adjusted HR: 0.383 [95% CI: 0.283–0.518], see Section B.3.3.4).

[redacted] The crossover adjusted HR from PROFILE 1014 showed the median OS of patients treated with crizotinib to be significantly longer than the median OS of patients treated with chemotherapy (crossover adjusted HR: [redacted]).

Figure 8: Kaplan-Meier curve of overall survival in subsequent-line ALK-positive NSCLC patients from PROFILE 1007

B.2.6.4 Time to treatment failure results

Median time to treatment failure (TTF) was high for the majority of patients in PROFILE 1001.

The majority of patients [redacted] were treated with crizotinib for at least 12 months.[69] At the time of the data cut-off date, the median duration of crizotinib treatment was 23.2 months (95% CI: [redacted]), with [redacted] of patients still actively receiving crizotinib.[69]

B.2.6.5 Other efficacy results from PROFILE 1001

Disease control rate at Week 8 and Week 16 was high and time to tumour response was generally rapid in ROS1-positive NSCLC patients treated with crizotinib

Disease control rate (DCR) was 86.8% (95% CI: 74.7–94.5) and 79.2% (95% CI: 65.9–89.2) at Week 8 and Week 16, respectively, of the study.[7]

Time to tumour response (TTR) to crizotinib was generally rapid, with a median TTR of 7.9 weeks (range 4.3–32.0) amongst responders (n=37).[7] This corresponded with the approximate time of the first on-treatment tumour scan.[68] These results show that most patients who receive crizotinib gain rapid control of tumour growth and that treatment with crizotinib as a single agent has robust anti-tumour activity.[69]

Duration of response was not reached at data cut-off, suggesting it to be meaningful

The benefit from the high ORR (see above) is further supported by a meaningful duration of response (DR) beyond the data cut-off date of the study. Median DR for patients who were objective responders (n=37) could not be reported because the median DR was not reached at time of data cut-off in PROFILE 1001 (95% CI: 15.2–NR). The median duration of follow-up for OS was 25.4 months (95% CI: 22.5–28.5) at data cut-off,[7] suggesting the duration of response to be meaningful.

Time to tumour progression was high, including when compared to time to tumour progression on last prior therapy for previously treated patients

A median time to tumour progression (TTP) of 19.8 months (95% CI: 15.2–NR) was reported. Of the 53 ROS1-positive NSCLC patients, 43.4% had objective progression and the remaining (56.6%) were censored, including 39.6% who were still in follow-up for progression.[7]

A within-patient TTP analysis was performed for patients who had received prior therapy. In this, TTP on crizotinib compared with TTP on last prior therapy: the median TTP with crizotinib versus last prior therapy was 19.8 vs 8.1 months (HR: 0.588; 95% CI: 0.308–1.125; p-value=0.1089).[7] Although this result was not statistically significant, there was a numerical decrease in the risk of progression with crizotinib compared with last prior therapy.

B.2.6.6 Patient-report outcomes and health-related quality-of-life results

No HRQoL data was collected for ROS1-positive NSCLC in PROFILE 1001. However, due to the similarities between ROS1 and ALK patient populations (see Section B.1.3.1), data from the ALK-positive NSCLC can be used as a proxy for ROS1-positive NSCLC.

Both PROFILE 1007 and 1014 reported HRQoL data based on the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC-QLQ-C30) questionnaire and EORTC QLQ-Lung Cancer 13 (LC13) module, as well as EurQol-Five Dimensions (EQ-5D). As per the NICE reference case, data from the EQ-5D questionnaires were used in the economic model, with the results from each of the studies detailed below. For more information on HRQoL please refer to the respective NICE submissions for first-line and subsequent-line ALK-positive NSCLC.[48, 100]

PROFILE 1007

Completion rates of all questions of the EQ-5D questionnaire ranged [redacted]

Throughout the study, absolute EQ-5D index scores were [redacted] (Table 16). The difference between groups became [redacted] only found to be statistically significant for Cycles 6 and 7.

Table 16: EQ-5D index results by treatment arm – crizotinib vs. chemotherapy (FA population)

	EQ-5D absolute score		EQ-5D change from baseline	
Time point	Crizotinib 250 mg BID (N = 173) Mean (SD)	Chemotherapy (pemetrexed or docetaxel) (N = 174) Mean (SD)	Crizotinib 250 mg BID (N = 173) Mean (SD)	Chemotherapy (pemetrexed or docetaxel) (N = 174) Mean (SD)
[redacted]				

Note: End visit is based on the actual CRF visit label (END_OF_TREATMENT). Visit windows were applied for the EQ-5D data with the expected Day 1 of each cycle as the mid-point.
Abbreviations: BID, twice-daily; EQ-5D, EurQol 5-Dimensions; FA, Full analysis population; SD, standard deviation.
Source: PROFILE 1007 CSR[70]

Absolute EQ-5D index scores and the change from baseline in EQ-5D index scores for crizotinib compared to docetaxel are presented in Table 17. [redacted]

Table 17: EQ-5D index results by treatment arm – crizotinib vs. docetaxel (FA population)

	EQ-5D absolute score		EQ-5D change from baseline	
Time point	Crizotinib 250 mg BID (N = 173) Mean (SD)	Docetaxel (N = 72) Mean (SD)	Crizotinib 250 mg BID (N = 173) Mean (SD)	Docetaxel (N = 72) Mean (SD)
[redacted]				

Note: End visit is based on the actual CRF visit label (END_OF_TREATMENT). Visit windows were applied for the EQ-5D data with the expected Day 1 of each cycle as the mid-point.
Abbreviations: BID, twice-daily; EQ-5D, EurQol 5-Dimensions; FA, Full analysis population; SD, standard deviation.
Source: PROFILE 1007 CSR[70]

PROFILE 1014

Completion rates of all questions of the EQ-5D questionnaire from evaluable patients in PROFILE 1014 ranged from [redacted] for crizotinib (over the first 30 of a total of 50 cycles) and [redacted] for chemotherapy (over the maximum six cycles).[72] All but eight patients in the crizotinib group ([redacted]) and seven patients in the chemotherapy group ([redacted]) from the intention-to-treat (ITT) population completed all questions of the EQ-5D questionnaire at baseline.[72]

Whereas no statistically significant changes from baseline where observed in the chemotherapy group over six cycles, patients in the crizotinib group showed a significant improvement from baseline ([redacted]) in EQ-5D visual analogue scale (VAS) general health status scores in Cycles 3 to 16 and 18 to 21.[72] In a mixed-model analysis, crizotinib was associated with a statistically significant greater improvement in EQ-5D VAS scores compared to chemotherapy ([redacted]).[73]

In a mixed-model analysis the overall EQ-5D index score (utility) was found to be statistically significantly higher in the crizotinib group compared to chemotherapy ([redacted]); improvements from baseline in EQ-5D index scores were also statistically significantly greater in the crizotinib group relative to chemotherapy ([redacted]).[72]

Statistically significant improvements from baseline ([redacted]) in EQ-5D index scores were observed in some cycles in the crizotinib group (Cycles 2 to 20, 22, 24, 25, 29 and 30), but were not observed in any cycles in the chemotherapy group (Cycles 1 to 6).[72]

B.2.7 Subgroup analysis in PROFILE 1001

The pre-specified subgroup analysis required in PROFILE 1001 were reported in Section B.2.3.1. The results of the subgroup analysis of ORR by baseline characteristics are presented in Appendix E. The point estimate of the ORR was provided along with the corresponding 95% confidence intervals (CIs) using the exact method based on the F-distribution.[69]

These analyses demonstrate the broad clinical effectiveness of crizotinib across various subgroups of patients with ROS1-positive advanced NSCLC. The subgroup analysis by number of prior therapies received showed that patients with no prior advanced/metastatic therapy (n=6) had an ORR of 85.7% (95% CI: 42.1–99.6), compared to patients who had received at least one prior advanced/metastatic therapy (n=31), where the ORR was 67.4% (95% CI: 52.0–80.5).[68] However, due to the limited patient numbers, the ORR data by line of treatment is associated with high uncertainty. Because of the uncertainty associated with subgroup analysis by number of prior therapies, data in the rest of this submission are presented for the overall ROS1-positive NSCLC cohort, and are not broken down by line of therapy.

The uncertainty in the sub-group analysis by line of treatment in PROFILE 1001 further justifies the use of proxy data in the economic analysis from first-line and subsequent-line ALK patients in PROFILE 1014 and PROFILE 1007, respectively.

B.2.8 Meta-analysis

For each treatment comparison included in this submission there was only one study available, therefore no meta-analysis was performed. PROFILE 1001 was a single-arm study in 53 patients with ROS1-positive advanced NSCLC. PROFILE 1014 was the only RCT identified that investigated the comparison of crizotinib versus pemetrexed plus platinum therapy as a first-line treatment for adults with ALK-positive advanced NSCLC. PROFILE 1007 was the only RCT identified that investigated the comparison of crizotinib versus chemotherapy as a treatment for adults with previously treated ALK-positive advanced NSCLC. Pfizer do not have access to the individual patient data from the majority of the other trials identified in the systematic review, and therefore were unable to conduct the required statistical analysis.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

As PROFILE 1001 was a single arm study with a small sample size (n=53), the potential for indirect comparisons were limited. In the absence of a comparator arm in PROFILE 1001, there was no common comparator to link to studies of other treatments, therefore methods such as network meta-analysis could not be applied.

We considered unanchored matched adjusted indirect comparisons (MAIC) to compare crizotinib treated ROS1 patients in PROFILE 1001 with the pemetrexed plus platinum arm of PROFILE 1014 and with the chemotherapy arm (docetaxel/pemetrexed) of PROFILE 1007 in separate analyses. NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 recommends that for an unanchored MAIC matching should adjust for all effect modifiers and prognostic variables.[101] We considered it implausible to fit complex models including multiple variables given the small sample size in PROFILE 1001. The estimated effects of each covariate

would be based on very small patient numbers and any results from such a model would be subject to high uncertainty. Any attempt to adjust for differences between trial populations based on only one or two variables is unlikely to adequately address these differences. Furthermore, the results of any MAIC analysis would apply to the patient population in the target studies. For the two scenarios described here MAIC would provide the relative effects (HRs) of crizotinib compared to pemetrexed plus platinum in ALK-positive patients at first-line and for crizotinib compared to chemotherapy in ALK-positive patients at subsequent-line.

Estimates of these same hazard ratios could be obtained directly from the respective RCTs in ALK-positive patients (PROFILE 1014 and PROFILE 1007). Given the structural similarities between the ALK and ROS1 rearrangements and the comparable patients characteristics between ALK-positive and ROS1-positive NSCLC patients (as discussed in Section B.1.3.1), we preferred to use these HRs directly rather than attempt to estimate the same result based on complex methods with limited data. The published HRs from PROFILE 1014 reported the effect of crizotinib relative to pemetrexed plus platinum (Table 33 and Table 36 in Section B.3.3.4) and the published HRs from PROFILE 1007 reported the effect of crizotinib relative to chemotherapy (Table 34 and Table 37 in Section B.3.3.4). In an analysis presented in this submission, we calculated the inverse of the published HRs to give the effect of each comparator relative to crizotinib. To estimate OS and PFS for the comparator treatments, the HRs for pemetrexed plus platinum versus crizotinib from PROFILE 1014 and for chemotherapy versus crizotinib from PROFILE 1007 were applied to parametric survival curves fitted to crizotinib treated ROS1-positive patients at all lines of treatment from PROFILE 1001 (Section B.3.3.4).

B.2.9.2 Uncertainties in the indirect and mixed treatment comparisons

The approach described above makes two key assumptions:

1. The proportional hazards assumption holds for each treatment comparison.

2. The ROS1-positive and the ALK-positive populations are sufficiently similar that we can assume relative effects are constant between populations. For example, we assume that the HR for crizotinib versus pemetrexed plus platinum for OS observed in ALK-positive patients in PROFILE 1014 is the same as the HR that would have been observed in ROS1-positive patients if PROFILE 1001 had included a pemetrexed plus platinum therapy arm.

If we do not assume proportional hazards in this analysis, this would lead to fitting separate survival curves to the comparator arms of PROFILE 1014 and PROFILE 1007 and assuming that these are directly representative of ROS1-positive patients receiving the comparator treatments. We considered that the assumption of proportional hazards was preferable to naively comparing survival curves in the absence of sufficient data to support an MAIC approach.

In the NICE appraisal of crizotinib for untreated ALK-positive advanced NSCLC (TA406) the appraisal committee concluded that proportional hazards may not hold for the comparison of crizotinib versus pemetrexed plus platinum in PROFILE 1014 and that using separate parametric survival curves for each treatment group may be more appropriate. In the assessment of crizotinib for previously treated ALK-positive advanced NSCLC (TA422) the proportional hazards assumption was considered reasonable based on examination of the log cumulative hazards plots.[8]

In the base case, using PROFILE 1014 and PROFILE 1007 as a proxy for ROS-positive NSCLC, we have fitted separate curves to each arm in line with TA406. For consistency, we have taken this approach for all comparators since it would not make sense to assume proportional hazards for some comparisons but not others (B.3.3.4).

B.2.10 Adverse reactions

Summary of crizotinib safety and tolerability

- Crizotinib was well-tolerated by patients in PROFILE 1001; adverse events (AEs) from any cause associated with permanent discontinuation of study treatment occurred in 7.6% (n=4) of patients. These were disease progression (two patients, 3.8%), nausea (one patient, 1.9%) and pericardial effusion (one patient, 1.9%). Among these events, the only treatment-related AE was nausea.
- AEs that are known to occur with crizotinib can be managed primarily using dose reductions or temporary dose interruption, allowing patients to continue to benefit from the clinical improvements associated with crizotinib.
- The safety profile of crizotinib in ROS1-positive patients is generally comparable to that seen in other crizotinib studies, which is an improvement to that of chemotherapy.

PROFILE 1001 safety analysis

- The most frequently reported AEs in the crizotinib group were vision disorders (86.8%); no patients were reported to have grade 3 or 4 severity vision disorder AEs.
- Hypophosphataemia and neutropenia were the most common grade 3 treatment-related AEs (13.2% and 9.4%, respectively). No grade 4 treatment-related AEs as well as death considered related to crizotinib treatment were registered.
- Treatment-related serious AEs were bradycardia and gastrointestinal amyloidosis, each reported by one (1.9%) patient. None of these events were associated with permanent discontinuation of treatment.
- Toxicities experienced by ROS1-positive NSCLC patients were mostly manageable by short (<1 week) dose interruption and crizotinib dose reduction. There was only one patient in which treatment was permanently discontinued due to a drug-related AE. There was only one recorded case of discontinuation due to treatment-related AEs, which was due to a grade 2 AE.

Pooled safety analysis from across clinical trials

- A pooled safety analysis provides data from 1,722 patients who have received crizotinib across four clinical trials, including 1,669 patients with ALK-positive NSCLC.
- The safety profile of crizotinib in the ROS1-positive cohort is consistent with that from the pooled ALK-positive clinical trials population; no new safety issues emerged during PROFILE 1001.

The safety profile of crizotinib for the treatment of adults with ROS1-positive advanced NSCLC is based on the analysis of adverse events (AEs) that occurred in PROFILE 1001. As described in

Section B.2.3.1, PROFILE 1001 is a phase I clinical trial, which included a cohort of ROS1-positive patients enrolled to receive crizotinib at 250 mg twice daily (BID). Supportive evidence for the safety profile of crizotinib is provided based on the analysis of AEs from PROFILE 1007 and 1014, for ALK-positive NSCLC. As described in Section B.1.3.1, the patient characteristics of ALK- and ROS1-positive NSCLC patients, as well as the homology between the ROS1 and ALK RTKs with crizotinib binding with a high affinity to both, indicate that evidence from ALK studies can be used as supportive data for crizotinib in ROS1-positive NSCLC.

Safety data from across the clinical trial programme for crizotinib are presented as supportive evidence in this section and provides data from 1,722 patients, collectively. This analysis includes ALK-positive advanced NSCLC patients who received crizotinib at first-, second- or later lines of therapy as part of single-arm or active-controlled clinical trials (N=1,669) (see Table 22) and ROS1-positive NSCLC patients from PROFILE 1001 (N=53). Four other relevant studies identified in the systematic review also contained data on adverse events, as detailed in Appendix F. These studies report a consistent AE profile to those presented in PROFILE 1001, 1007 and 1014.

Safety analysis in PROFILE 1001 (ROS1 cohort)

The crizotinib safety profile in the ROS1-positive NSCLC population is based on data from the 53 patients treated in PROFILE 1001. Most of these patients (67.9%) received crizotinib for longer than 12 months, and the median treatment duration was 23.2 months (95% CI: 15.0–NR), with approximately half of patients (47.2%) still on treatment at the data cut-off date (30th November 2014).[7] Only events that occurred during the period from the first dose of study treatment until 28 days after the last dose of study treatment were included in the analysis. Unless stated otherwise, the analysis of safety in PROFILE 1001 was not adjusted for the duration of treatment.

Adverse events in PROFILE 1001

Generally, crizotinib was well-tolerated by patients in PROFILE 1001; AEs from any cause associated with permanent discontinuation of study treatment occurred in only 7.6% of patients. Of those AEs associated with permanent discontinuations, none were judged to have been related to study treatment by the investigator.[7] A summary of treatment-emergent AEs reported in PROFILE 1001 is presented in Table 18.

AEs of any cause that occurred in at least 10% of patients, are presented in Table 19. The most frequent AEs reported in PROFILE 1001 included vision disorder (86.8%), nausea (58.5%), oedema (54.7%) and vomiting (50.9%). Vision disorders were the most commonly reported AEs; all of the AEs were less than grade 3 in severity and only one patient reported a grade 2 all-causality event. No treatment discontinuations (temporary or permanent) or dose reduction due to visual disturbances were reported.[7] Most AEs were managed by short dose interruptions of less than one week, or by dose reductions. There was one permanent discontinuation of treatment associated with grade 2 nausea.[7]

All grade 3 or 4 AEs that occurred in at least 2% of patients in the treatment group are presented in Table 20. Hypophosphatemia, pulmonary embolism and neutropenia accounted for the majority of grade 3 and 4 AEs that occurred in patients. No deaths or grade 4 treatment-related AEs were considered to be related to crizotinib treatment.[7]

Table 18: Treatment-emergent AEs in the SA population in PROFILE 1001

Adverse event, No. of patients (%)[a]	Crizotinib (N=53)[a]	
	All causality	Treatment-related
Number of patients:[b]		
With AEs	53 (100)	52 (98.1)
With SAEs[c]	22 (41.5)	2 (3.8)
With grade 3 or 4 AEs	28 (52.8)	16 (30.2)
With grade 5 AEs	9 (17.0)	0
With AEs associated with:		
Permanent discontinuation	4 (7.5)	1 (1.9)
Dose reduction	6 (11.3)	6 (11.3)
Temporary discontinuation	24 (45.3)	13 (24.5)

[a]No. of patients in the SA population. [b]Patients are only counted once per treatment in each row. [c]According to investigator assessment.
Incidence of AEs were unadjusted for duration of treatment.
Abbreviations: AE, adverse events; SA, safety analysis; SAE, serious adverse event.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Table 19: Most frequent AEs in the SA population (≥10% in the SA population) in PROFILE 1001

Adverse event, No. of patients (%)[a]	Crizotinib (N=53)[a]	
	All-causality	Treatment-related
Vision disorder[b]	46 (86.8)	45 (84.9)
Nausea	31 (58.5)	26 (49.1)
Oedema[c]	29 (54.7)	24 (45.3)
Vomiting	27 (50.9)	20 (37.7)
Diarrhoea	24 (45.3)	22 (41.5)
Constipation	23 (43.4)	18 (34.0)
Dizziness[c]	21 (39.6)	10 (18.9)
Upper respiratory infection[§]	21 (39.6)	0
Elevated aminotransferases[§]	19 (35.8)	16 (30.2)
Fatigue	17 (32.1)	10 (18.9)
Neuropathy[c]	16 (30.2)	5 (9.4)
Dyspnoea[c]	15 (28.3)	1 (1.9)
Rash	14 (26.4)	7 (13.2)
Bradycardia[c]	14 (26.4)	11 (20.8)
Decreased appetite	13 (24.5)	6 (11.3)
Headache	13 (24.5)	0
Abdominal pain[c]	12 (22.6)	3 (5.7)
Dysgeusia	12 (22.6)	10 (18.9)
Cough[c]	11 (20.8)	0
Pyrexia	10 (18.9)	0

Disease progression	9 (17.0)	0
Hypophosphataemia	9 (17.0)	8 (15.1)
Neutropenia[c]	9 (17.0)	7 (13.2)
Arthralgia	8 (15.1)	0
Pneumonia	8 (15.1)	0
Back pain	7 (13.2)	0
Pulmonary embolism[c]	7 (13.2)	0
Pain in extremity	7 (13.2)	0
Pruritus	7 (13.2)	3 (5.7)
Blood creatinine increased[c]	6 (11.3)	2 (3.8)
Chest pain[c]	6 (11.3)	0
Dyspepsia	6 (11.3)	5 (9.4)
Fall	6 (11.3)	0
Stomatitis[c]	6 (11.3)	1 (1.9)
Wheezing	6 (11.3)	0

[a]Number of patients in the SA population. [b]The category of vision disorder comprised a cluster of AEs including: visual impairment, photopsia, blurred vision, vitreous floaters, reduced visual acuity, diplopia, visual field defect, halo vision, visual brightness, chromatopsia and photophobia. [c]This item comprised a cluster of AEs that may represent similar clinical symptoms or syndromes.
Incidence of AEs were unadjusted for duration of treatment.
Abbreviations: AE, adverse event; SA, safety analysis.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Table 20: Grade 3 or 4 AEs in the SA population (≥2% in the SA population) in PROFILE 1001

Grade 3 or 4 adverse event, No. of patients (%)[a]	Crizotinib (N=53)[a]	
	All-causality	Treatment-related
Hypophosphatemia	8 (15.1)	7 (13.2)
Neutropenia[b]	5 (9.4)	5 (9.4)
Headache	4 (7.5)	0
Dyspnoea[b]	3 (5.7)	0
Syncope	3 (5.7)	0
Vomiting	3 (5.7)	1 (1.9)
Electrocardiogram QC prolonged	2 (3.8)	1 (1.9)
Elevated transaminases[b]	2 (3.8)	2 (3.8)
Pneumonia	2 (3.8)	0
Pulmonary embolism[b]	6 (11.3)	0

All AEs are categorised as grade 3, apart from pulmonary embolism, where all of the cases were grade 4.
[a]Number of patients in the SA population. [b]This item comprised a cluster of AEs that may represent similar clinical symptoms or syndromes.
Abbreviations: AE, adverse event; SA, safety analysis.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Deaths from any cause reported in PROFILE 1001

Deaths that occurred from any cause between treatment start and 28 days after the last administration of study treatment are summarised in Table 21. No deaths were associated with

the study treatment. All nine deaths that occurred within 28 days of the last dose were associated with progression of study disease.[7] In total, 16 deaths were reported, with seven of these occurring more than 28 days after the last dose of crizotinib.[68]

Table 21: Deaths from any cause in the SA population in PROFILE 1001

Grade 5 (death) adverse events, No. of patients (%)[a]	Crizotinib (N=53)[a]
Disease progression (within 28 days of last dose)	9 (17.0)
Disease progression (>28 days of last dose)	7 (13.2)
Other:	
Unknown[b]	1 (1.9)
Death from all causes[c]	16 (30.2)

Includes grade 5 events (deaths) that occurred between the start of treatment and 28 days after the last administration of study treatment.
[a]Number of patients in the SA population. [b]Unknown cause of death includes not reported. Patient died eight months after last dose of crizotinib. [c]Excluding unknown death.
Abbreviations: SA, safety analysis.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Supportive safety data from ALK-positive trial populations

The safety and tolerability of crizotinib with ALK-positive advanced NSCLC has previously been evaluated across the clinical trial program for crizotinib (see Table 22 for a description of the trials). A pooled safety analysis of patients treated with crizotinib in these trials, as described in the EPAR, is presented below. This analysis includes data from 1,669 ALK-positive NSCLC patients who have received crizotinib and therefore provides substantial supportive evidence for the safety and tolerability of crizotinib.[7]

The ALK-positive NSCLC population includes ALK-positive patients from PROFILE 1014 (phase III treatment-naïve crizotinib only, including patients crossed over to crizotinib), PROFILE 1007 (phase III pre-treated patients, crizotinib only), PROFILE 1005 (phase II ALK-positive NSCLC), and PROFILE 1001 (R2PD, ALK-positive NSCLC).

Table 22: Summary of crizotinib clinical trials in ALK-positive patients from which ALK-positive pooled safety data is reported

Study name	Study design	Number of ALK-positive patients in the pooled analysis	Crizotinib line of treatment	Comparator
PROFILE 1014[73]	Phase III randomised controlled trial	280	First-line	Pemetrexed plus either cisplatin or carboplatin
PROFILE 1007[71]	Phase III randomised controlled trial	172	Second-line	Pemetrexed or docetaxel
PROFILE 1005[102]	Phase II single-arm trial	1,063	Second-line or later	None

PROFILE 1001 ALK cohort[103]	Phase I single arm-trial – dose escalation study and expanded cohort	154	First-, second- and later lines[a]	None

[a]Only 24/149 patients included in PROFILE 1001 (at the data cut-off: 1st June 2011) received crizotinib in the first-line setting.
Patients in all crizotinib clinical trials were predominantly of non-squamous histology.
Abbreviations: ALK, anaplastic lymphoma kinase.

The baseline characteristics for safety analysis (SA) patients in PROFILE 1001 were generally consistent with those of the ALK-positive NSCLC population (Table 23). Both populations had more female patients enrolled than males, and their mean age in years was similar at 54.1 years for the ROS1-positive cohort, and 51.9 years for the ALK-positive NSCLC population. In all trials, patients received the same dose of crizotinib (250 mg BID).

The AEs observed in the ROS1-postive cohort in PROFILE 1001 and the pooled ALK-positive NSCLC patient population are comparable. Table 24 presents AE data from PROFILE 1001 (previously shown in Table 19), alongside the pooled data from the ALK-positive NSCLC population. The proportion of patients who experienced nausea (58.5% for ROS1-positive, and 56.5% for ALK-positive) as well as vomiting and dysgeusia, are comparable across both groups. The increased proportion of vision disorders observed in the ROS1-positive cohort (86.8% vs. 62.2% in the ALK-positive population) may be due to the small size of the ROS1-positive cohort.[7]

There were no new safety concerns raised from the data of the ROS1-positive cohort, compared with previous data from ALK-positive cohorts receiving crizotinib. In summary, the ROS1-positive cohort confirmed the known safety profile for crizotinib, mainly characterised by manageable vision disorders, gastrointestinal disorders and general disorders.[7]

Table 23: Baseline characteristics of ROS1-positive patients in PROFILE 1001 and ALK-positive patients pooled from PROFILE 1014, 1007, 1005 and 1001

	ROS1-positive NSCLC (N=53)	ALK-positive NSCLC (N=1,669)
Sex – no. (%)		
Male	23 (43.4)	717 (43.0)
Female	30 (56.6)	952 (57.0)
Age – years		
Mean (SD)	54.1 (13.44)	51.9 (12.47)
Median (Range)	55.0 (25–81)	52.0 (19–86)
Age category – no. (%)		
<65 years	38 (71.7)	1404 (84.1)
≥65 years	15 (28.3)	265 (15.9)
Race – no. (%)		
White	30 (56.6)	853 (51.1)
Black	2 (3.8)	28 (1.7)
Asian	21 (39.6)	753 (45.1)

Smoking classification – no. (%)		
Never smoked	40 (75.5)	NR
Ex-smoker	13 (24.5)	NR

Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; SD, standard deviation.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Table 24: Adverse drug reactions of any grade, or of grades 3 or 4 in ROS1-positive and ALK-positive NSCLC patient populations

Adverse event, No. of patients (%)	ROS1-positive NSCLC (N=53)		ALK-positive NSCLC (N=1,669)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Vision disorder[a]	46 (86.8)	0	1038 (62.2)	6 (0.4)
Nausea	31 (58.5)	1 (1.9)	943 (56.5)	37 (2.2)
Oedema[a]	29 (54.7)	0	814 (48.8)	36 (2.2)
Vomiting	27 (50.9)	3 (5.7)	847 (50.7)	31 (1.9)
Diarrhoea	24 (45.3)	1 (1.9)	906 (54.3)	20 (1.2)
Constipation	23 (43.4)	0	720 (43.1)	15 (0.9)
Dizziness[a]	21 (39.6)	0	421 (25.2)	9 (0.5)
Elevated aminotransferases[a]	19 (35.8)	2 (3.8)	534 (32.0)	176 (10.5)
Fatigue	17 (32.1)	0	497 (29.8)	56 (3.4)
Neuropathy[a]	16 (30.2)	0	419 (25.1)	22 (1.3)
Bradycardia[a]	14 (26.4)	0	205 (12.3)	7 (0.4)
Rash	14 (26.4)	0	213 (12.8)	5 (0.3)
Decreased appetite	13 (24.5)	1 (1.9)	498 (29.8)	29 (1.7)
Dysgeusia	12 (22.6)	0	352 (21.1)	0
Neutropenia[a]	9 (17.0)	5 (9.4)	365 (21.9)	207 (12.4)
Dyspepsia	6 (11.3)	0	137 (8.2)	0
Blood creatinine increased[a]	6 (11.3)	0	132 (7.9)	4 (0.2)
Leukopenia[a]	3 (5.7)	0	247 (14.8)	48 (2.9)
Syncope	3 (5.7)	3 (5.7)	41 (2.5)	39 (2.3)
Electrocardiogram QT prolonged	2 (3.8)	2 (3.8)	62 (3.7)	25 (1.5)
Blood alkaline phosphatase increased	2 (3.8)	0	110 (6.6)	16 (1.0)
Renal cyst[a]	2 (3.8)	0	50 (3.0)	10 (0.6)
Interstitial lung disease[a]	1 (1.9)	0	49 (2.9)	18 (1.1)
Hepatic failure	0	0	5 (0.3)	4 (0.2)

[a]This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.
Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.
Source: EPAR Xalkori/crizotinib 21st July 2016[7]

Summary of safety evidence for crizotinib in ROS1-positive NSCLC

Safety data from PROFILE 1001 demonstrated that crizotinib is generally well-tolerated by patients receiving crizotinib for ROS1-positive advanced NSCLC, with AEs from any cause

associated with permanent discontinuation of study treatment occurred in only 7.6% of patients. No new safety concerns were identified by clinicians.

The most common AEs that occurred in the crizotinib group in PROFILE 1001 were vision disorders; these were mostly grade 1 or 2 in severity and could be managed with concomitant medication or subsequent dose reduction. Hypophosphataemia (15.1%) and pulmonary embolism (11.3%) accounted for the majority of all-causality grade 3 or 4 AEs and were primarily managed using dose interruptions or dose reductions.[7]

The safety profile of crizotinib observed in PROFILE 1001 is consistent with that observed in previous clinical trials with crizotinib, as demonstrated in the pooled safety analysis across four crizotinib trials earlier in this section. The most frequently reported AEs experienced by patients receiving crizotinib across these trials were vision disorders (62.2%) and nausea (56.5%), as was observed in PROFILE 1001.[7] No new safety concerns are therefore evident with crizotinib in ROS1-positive advanced NSCLC patients.[7]

Finally, given the improvements in patient HRQoL observed with crizotinib in ALK-positive advanced NSCLC patients and the similarities between ALK and ROS1 patients (described in Section B.1.3.1) it is likely that the improvement in patient HRQoL would also be observed in ROS1-positive advanced NSCLC. Crizotinib therefore represents an alternative treatment option for patients with ROS1-positive advanced NSCLC that is associated with a distinct and improved safety profile in comparison to the current standard of care therapy.

B.2.11 Ongoing studies

PROFILE 1001 is closed to further enrolment for patients with ROS1-positive advanced NSCLC and no further data cuts are expected. It was deemed unethical to conduct RCTs in ROS1-positive NSCLC patients due to the ultra-orphan nature of the disease, and the unequivocal efficacy of crizotinib in patients with ROS1-positive NSCLC from PROFILE 1001 was accepted by the EMA for the marketing authorisation of crizotinib in this patient population.[7]

[redacted]

The OX-ONC study was completed on [redacted] (data cut-off date). Updated results from the completed study has been included in Appendix D and Appendix F, alongside the interim data identified in the clinical SLR.

[redacted]

Recently, a UK national audit of patients with ROS1-positive advanced NSCLC was conducted by investigators at the [redacted]. The preliminary results from the [redacted] audit were presented to Pfizer by the lead investigator [redacted] during an advisory board in July 2017. This audit identified [redacted] patients with ROS1-positive NSCLC in the UK, of which [redacted] patients received first-line pemetrexed plus platinum and [redacted] patients received first-line and subsequent-line crizotinib. [redacted] The preliminary median PFS was [redacted] months for patients

treated by pemetrexed plus platinum and maintenance pemetrexed in the first-line setting, and [redacted] months with crizotinib in the first-line and subsequent-line settings. Median OS [redacted] for ROS1-positive advanced NSCLC patients treated by first- and subsequent-lines of crizotinib.

B.2.12 Innovation

A first-in-class targeted therapy for ROS1-positive patients

ROS1 represents a RTK related to ALK that is not usually highly expressed in normal lung tissue, but that becomes aberrantly activated in ROS1-positive NSCLC. ROS1 and ALK RTKs share 77% amino acid homology within their ATP binding sites; consistent with this, crizotinib is seen to bind with a high affinity to both ROS1 and ALK.[35] ROS1 gene rearrangements lead to the development of ROS1 fusion proteins which become oncogenic, driving the development of tumours, including NSCLC.[32] Crizotinib was granted marketing authorisation for ROS1-positive advanced NSCLC in August 2016 and is the only licensed targeted therapy available in the UK and Europe for ROS1-positive patients.[7]

Currently, unidentified patients with ROS1-positive advanced NSCLC will be treated according to the NICE guidelines for patients without a specific oncogenic driver (see Section B.1.3.2). This is a stark contrast to the situation for patients with EGFR mutant and ALK-positive advanced NSCLC, for whom there is access to targeted therapies with clinical effectiveness recognised by marketing authorities and NICE.[5, 8, 50, 54-56] Diagnosing oncogene aberrations in NSCLC and subsequent matching to molecular targeted tyrosine kinase inhibitors (TKIs) are now accepted as standard practice for ALK-positive and EGFR mutant advanced NSCLC. Clinicians have been clear that their preference would always be to give a targeted therapy for advanced lung cancer, if the cancer is driven by a specific gene rearrangement, and they recognise ROS1 gene rearrangements in ROS1-positive NSCLC as a key determinant to tumour response.[7, 32, 104-106] In this context, there is a clear unmet need for clinically effective therapies targeted at the ROS1 gene rearrangement.

An innovative therapy recognised at the regulatory level

The clinical benefits associated with crizotinib have been acknowledged in the European Union (EU)and United States (US) regulatory approval processes.[7, 107] Crizotinib for ROS1-positive NSCLC received “Breakthrough Therapy Designation” and was granted through “Priority Review” by the US Food and Drugs Administration (FDA).[107] Breakthrough therapy is described as a process to speed up the review of drugs deemed as substantial improvements over current available treatments.[108] Priority review is designed to take action on an application within six months of it being submitted.[108] The approval of crizotinib as part of these programs is demonstrative of a ‘step-change’ in the management of ROS1-positive NSCLC with crizotinib. In addition, the EMA approved crizotinib for use in ROS1-positive NSCLC based on the strength of the single-arm PROFILE 1001 study.[7]

A novel therapy which addresses current clinical unmet need: *response to treatment*

Current chemotherapy options that represent standard of care in UK clinical practice for unidentified ROS1-positive advanced NSCLC are not supported by a clinical evidence base in ROS1-positive NSCLC patients specifically. In ALK-positive advanced NSCLC, where clinical evidence is available, these chemotherapy treatment options have demonstrated only modest

impact on efficacy outcomes with ORRs of 19.5–45%, and median PFS of approximately 3–8 months across first- and second-line treatment (See Section B.2.6 for details from PROFILE 1007 and PROFILE 1014).[47, 64, 73] Most patients would therefore be unlikely to derive significant durable improvement in HRQoL with these treatments. The considerable toxicity associated with systemic chemotherapy would also be expected to impact on HRQoL.

In PROFILE 1001, the benefit observed in terms of ORR for patients with ROS1-positive advanced NSCLC treated with crizotinib was 69.8% (95%CI: 55.7–81.7). Six out of the seven previously untreated patients in this study achieved an objective response. Patients tended to respond early, with a median time to response of 7.9 weeks (i.e. at the first tumour re-assessment). This compares favourably to the ORR for the 46 ROS1-positive patients who had received prior therapy with ORR of 21.7% for prior first-line chemotherapy (29.4% with pemetrexed), 16.7% for prior second-line chemotherapy (30.8% with pemetrexed), and 23.7% for any line therapy with pemetrexed.[7] These responses to chemotherapy prior to receipt of crizotinib in ROS1-positive patients in PROFILE 1001 were similar to those observed in unselected NSCLC patients treated with current standard of care (9–35% across first- and second-line therapies),[109-113] and to those observed for ALK-positive patients treated with crizotinib (see Section B.2.6).

In PROFILE 1001, at the time of the data cut-off, the median PFS was 19.3 months (95% CI: 14.8–NR). A statistical analysis was also provided in which TTP on crizotinib was compared with TTP on last prior therapy: the median TTP with crizotinib vs last prior therapy was 19.8 vs 8.1 months (HR=0.59, 95% CI: 0.31–1.13).

Information regarding ORR and TTP/PFS with standard chemotherapies in ROS1-positive NSCLC was only available from the literature in studies which had a small sample size. Due to the small sample sizes, these data do not provide reliable evidence for the effect of chemotherapy on ROS1-positive patients.

Despite the small patient numbers, crizotinib demonstrated considerable anti-tumour activity in treatment-naïve patients. This is supported by the anti-tumour activity demonstrated in first-line ALK-positive NSCLC patients from PROFILE 1014, used as a proxy in this submission. Results from PROFILE 1014 clearly demonstrated that crizotinib provided statistically significant, robust, and clinically meaningful improvement in PFS and ORR in this patient population compared to chemotherapy.[73] The EMA concluded that based on the pre-clinical and anti-tumour similarities between ALK- and ROS1-positive NSCLC, there is "*no concern regarding the efficacy of crizotinib in the first line treatment for patients with ROS1-positive NSCLC*".[7] Available data are considered by the EMA to sufficiently support the efficacy of crizotinib in ROS1-positive NSCLC patients regardless of the line of treatment.[7]

A novel therapy which addresses current clinical unmet need: *depth of tumour response and quality of life*

Another advantage of crizotinib over chemotherapy is the depth of tumour response observed when patients receive a targeted therapy. Crizotinib-treated patients achieved a median best percentage reduction in target lesion size from baseline of -57.1% (from graph, see Figure 3).[7] Clinically this would be predicted to translate to a greater improvement in symptom control and associated quality of life, representing a true 'step-change' in the way patients are treated. This impact on HRQoL has been observed in patients with ALK-positive advanced NSCLC treated with crizotinib, who show a similar response to crizotinib and who share similar clinical

characteristics to those patients with advanced ROS1-positive NSCLC.[1, 17, 73] Treatment in advanced NSCLC is not curative, so palliation through the reduction of symptoms and improvements in HRQoL is considered to be a key goal of therapy, alongside extension of life.[114, 115] Clinicians believe that the benefit for crizotinib in terms of HRQoL will be similar to the improvement seen in patients who have received other TKIs, including those for EGFR-positive NSCLC.

A novel therapy which addresses current clinical unmet need: *life extending*

Life expectancy in ROS1-positive NSCLC patients is expected to be similar to ALK-positive patients, which historically has been shown to be between 6 and 22 months with chemotherapy (see Section B.1.3.1). In contrast to chemotherapy, crizotinib possesses an innovative, targeted mechanism of action that can elicit tumour size reductions and tumour responses that would be expected to translate to further delays to progression and death beyond that seen with chemotherapy.[7] In the phase I clinical trial PROFILE 1001, the median PFS was 19.3 months and the median OS was not reached, with 39.6% of patients still in follow-up for progression (median OS follow-up time at data cut-off was 25.4 months (95% CI: 22.5–28.5). In this study, the probability of survival at 12 months was 79.0% (95% CI: 65.3–87.8).[7] This was also demonstrated in the real world clinical setting in the observed preliminary OS results from the [redacted] audit in the UK (see Section B.2.11). Based on the economic analysis (see B.3.7.1), the estimated life extension with crizotinib is 2.39 years in the first-line and 1.36 years in the subsequent-lines.

Crizotinib therefore represents a life-extending medicine for patients with ROS1-positive advanced NSCLC who are otherwise at end-of-life with current therapy.[49] Full consideration of crizotinib as an end-of-life medicine is presented in Section B.2.13.2.

An orally-available targeted therapy, enabling greater autonomy for patients

The current standard of care for patients with ROS1-positive advanced NSCLC that has not been diagnosed as ROS1-positive is intravenously administered chemotherapy, given every three weeks. As an orally-available therapy, crizotinib offers patients a more convenient and less burdensome route of administration. This would be transformative for patients as they would no longer need to spend lengthy periods of time each month receiving chemotherapy infusions in secondary care, often in a chemotherapy suite; a healthcare appointment that usually represents an additional visit to a patient's regular outpatient review. This would also reduce the need for extra travel and time away from home for the patient and potentially their carer's. A preference for orally-available therapies amongst cancer patients has been previously demonstrated in several studies.[116, 117] Although the reductions in National Health Service (NHS) service requirements for crizotinib as an oral therapy are considered in the economic analysis presented in B.3.5, the patient benefit in terms of convenience and ease of use is not captured in the calculation of quality-adjusted life years (QALYs), and any personal out-of-pocket travel expenditure incurred by the patient is not incorporated under the perspective of the economic analysis.

Wider societal value of crizotinib

Patients with ROS1-positive NSCLC are typically younger than patients who are ROS1-negative unselected NSCLC with a median age in the mid-50s for ROS1-positive patients.[7] The clinical benefits associated with crizotinib, in particular with regards to global and functioning HRQoL

domains, may therefore allow working-age patients to return to employment. The economic benefits of this potential outcome (e.g. reduced costs associated with productivity loss) are not included in the cost-effectiveness analysis presented in this submission, which takes an NHS perspective. Cost-savings related to reduced productivity losses have previously been noted as a potential benefit from the use of targeted therapies over chemotherapy in advanced NSCLC.[118]

Alleviation in carer burden

The cost-effectiveness analyses also do not take into account the potential benefits that crizotinib may provide to patients' carers. The burden of NSCLC on carers in terms of HRQoL and cost is substantial, and has been shown to deteriorate over time with disease progression.[119, 120] Improvements in patient HRQoL were observed with crizotinib in ALK-positive NSCLC patients in the pivotal phase III trial PROFILE 1014 (see Section B.2.6.6). Given the homology between the kinase domains of ROS1 and ALK, similarity in patient clinical characteristics and evidence of response to crizotinib in both ROS1-positive and ALK-positive NSCLC patients, it is plausible to assume that treatment with crizotinib in ROS1-positive NSCLC would likely reduce the carer burden in a similar manner to ALK-positive advanced NSCLC when compared to current chemotherapy options in the short-term. This is especially important when considering the significantly prolonged time to deterioration in lung cancer symptoms with crizotinib, and the trend for HRQoL functioning domain scores to improve with crizotinib and deteriorate with chemotherapy.[73]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence

PROFILE 1001 provides the most relevant clinical evidence on the clinical effect of crizotinib for the treatment of adults with ROS1-positive advanced NSCLC. Despite the small study population size and the single-arm design of PROFILE 1001, this pivotal study was considered by the EMA to provide sufficient evidence for market authorisation, due ultra-orphan nature of ROS1-positive NSCLC. The preliminary results from the recently completed EUCROSS study in ROS1 patients provides supportive evidence with ORR and PFS comparable to PROFILE 1001. Based on the strong support by clinical experts, evidence from PROFILE 1007 and PROFILE 1014 was used to provide proxy data from the ALK-positive population to support the comparative analysis of crizotinib versus chemotherapy. The use of proxy data from ALK-positive NSCLC patients was possible due to the similarities between ROS1 and ALK NSCLC in terms of RTK amino acid homology, affinity of crizotinib to the RTK ATP-binding sides, patient characteristics and response to crizotinib (see Section B.1.3.1). Chemotherapy was considered to be the most relevant comparator for crizotinib in ROS1-positive NSCLC patients, as it is representative of routine clinical practice in the absence of targeted therapies to treat ROS1-positive NSCLC patients in the UK (see Section B.1.3.2). Without crizotinib, patients are expected to have a life expectancy of less than 22 months, based on proxy OS data from ALK patients. PROFILE 1001, PROFILE 1007 and PROFILE 1014 demonstrate that the response rate to crizotinib is high and that the OS is approximately 21.7 months. Crizotinib is therefore expected to offer a life-extending treatment option. This is supported by real world clinical data from the [redacted] audit (see Section B.2.11).

Objective response rate

Crizotinib has demonstrable anti-tumour activity in ROS1-positive tumours via the targeted inhibition of ROS1 fusion proteins and oncogenic variants.[32] In PROFILE 1001, the majority of patients treated with crizotinib achieved an objective response (69.8%). The response rate with crizotinib observed in PROFILE 1001 aligns with the ORR results in the ALK-positive trials, where 74.4% of patients treated with crizotinib in the first-line (PROFILE 1014) and 65.3% in the subsequent-line (PROFILE 1007) achieved an objective response.

The ORR observed in PROFILE 1001 is driven by the subsequent-line patients who account for most of the population of the trial (n=46). Given that the ORR appeared to be higher in first-line patients compared to subsequent-line patients in PROFILE 1001 (85.7% versus 67.4%, see Section B.2.6.1), the high overall ORR observed is a conservative estimate, especially in patients who may receive crizotinib treatment prior to other systemic therapies in practice. That said, when considering the ORR for the 46 patients in PROFILE 1001 who received crizotinib in the subsequent-line setting, the observed ORR of 67.4% was considerably higher than the objective response these patients achieved when they received prior chemotherapy treatment, which ranged from 16.7% to 30.8%.[7]

This improved tumour response was also reflected in the considerable median percentage reduction in target lesions achieved by patients treated with crizotinib in PROFILE 1001 (-57.1%; from graph, see Figure 3).[7] Such improvements in response with crizotinib treatment may translate into improved patient health at the time of RECIST-defined progression relative to treatment at initiation. In addition, a greater and more durable tumour response to treatment is believed to be associated with improvements in patient HRQoL.[85, 86]

Progression-free survival

At the time of the data cut-off, the median PFS was 19.3 months (95% CI: 14.8–NR) for patients with ROS1-positive advanced NSCLC treated with crizotinib in PROFILE 1001. A prolonged median PFS have also been previously observed in PROFILE 1014 and 1007, for first- and subsequent-line ALK-positive NSCLC, respectively (B.2.6.2).

In PROFILE 1014, first-line crizotinib was associated with a prolonged PFS in patients with ALK-positive advanced NSCLC. Improvements in PFS were significant (median PFS in crizotinib: 10.9 months; median PFS in chemotherapy: 7.0 months; HR=0.45; 95% CI: 0.35–0.60; p<0.001) and were independent of baseline characteristics, including race (Asian vs. non-Asian), ECOG performance status (0 or 1 vs. 2) and brain metastases (presence vs. absence).[73] In PROFILE 1007, subsequent-line crizotinib significantly improved median PFS compared to chemotherapy (pemetrexed or docetaxel) in previously treated patients with ALK-positive advanced NSCLC (crizotinib median PFS: 7.7 months; chemotherapy median PFS: 3.0 months; HR=0.487, 95% CI 0.371–0.638; p<0.0001).[71] The prolonged median PFS observed in the ALK-positive NSCLC population support the effect of crizotinib compared to chemotherapy, and can be used as a proxy considering the lack of data for chemotherapy in ROS1-positive NSCLC. The PFS results observed in ALK-positive NSCLC from PROFILE 1007 and PROFILE 1014 are supported by the PFS from the [redacted] audit, which was [redacted] for ROS1-positive patients treated with crizotinib in the first-line and subsequent-lines (see Section B.2.11). This is lower than that observed in PROFILE 1001. At a recent advisory board, where the current [redacted] audit data was reviewed, the discrepancy in the PFS seen in the [redacted] audit with the PFS from PROFILE 1001 was felt to be due to the real-world nature of the audit of UK patients.

Patient-reported outcomes and HRQoL

There are no data reported for patient-reported outcomes and HRQoL for ROS1-positive patients who have been treated with crizotinib. Given the homology between the kinase domains of ROS1 and ALK, similarity in patient clinical characteristics and comparable responses to crizotinib in both ROS1-positive and ALK-positive NSCLC patients, clinical experts considered the HRQoL data for crizotinib in ALK-positive NSCLC to be generalisable to the ROS1-positive NSCLC patients and therefore has been used as a proxy.

In PROFILE 1014, treatment with first-line crizotinib was associated with significantly higher utility scores, as measured by EQ-5D, and significantly greater improvements from baseline in HRQoL and symptom severity relative to chemotherapy. In particular, patients treated with crizotinib experienced significant and clinically relevant reductions in symptom-related scores, such as for dyspnoea, cough and pain in chest; this is reflective of beneficial effects of greater tumour reduction. A positive association between tumour response and HRQoL in NSCLC has been proposed previously.[85, 86]

In PROFILE 1007, crizotinib was associated with rapid and substantial improvement in global quality of life, and this improvement was significantly greater than for the chemotherapy arm ($p<0.001$).[71] PROFILE 1007 also reported a substantial and sustained improvement in EQ-5D index scores, which was statistically significantly greater than baseline in many cycles, unlike chemotherapy.[121]

Overall survival

Median OS for patients with ROS1-positive advanced NSCLC was not reached in PROFILE 1001, with only 30.2% of patients having died at the time of PFS analysis.[7] In this study, the median duration of follow up for OS was 25.4 months, and the 6 month and 12 month survival rates were 91% and 79%, respectively, which is comparable with preliminary real-world data from the [redacted] audit (see Section B.2.11). Median PFS can be used as a conservative proxy for the minimum OS for targeted therapies (Table 25). Median PFS for crizotinib in ROS1-positive NSCLC was 19.3 months, suggesting that OS with crizotinib will be at least this, and possibly considerably longer.[7]

In PROFILE 1007, the median OS for patients treated with crizotinib in the subsequent-line was 21.7 months, which showed a numerical improvement versus chemotherapy (median OS: 21.9 months). Of patients who were initially randomised to chemotherapy, 89% crossed-over to receive crizotinib. The crossover adjusted HR showed the median OS of patients treated with crizotinib to be significantly longer than for patients treated with chemotherapy (HR: 0.383 [95% CI: 0.283–0.518]) (see Figure 15).

[redacted] but the crossover adjusted HR showed the median OS of patients treated with crizotinib to be significantly longer than the median OS of patients treated with chemotherapy ([redacted])

Adverse events

Crizotinib was generally well-tolerated by patients in PROFILE 1001. Vision disorders were the most common AEs, but these were all grade 1 or 2 in severity and did not cause any permanent

or temporary discontinuations of crizotinib treatment. Monitoring processes are already described for known hepatic events, and in PROFILE 1001 these were managed primarily with dose reductions and interruptions. The safety profile of crizotinib observed in PROFILE 1001 was consistent with that reported across four crizotinib trials (1,669 patients), including PROFILE 1007 and PROFILE 1014, as detailed in the pooled analysis presented in Section B.2.10. As noted by UK clinical experts consulted at an advisory board for ALK-positive NSCLC,[5] the majority of AEs known to be associated with crizotinib can be managed by dose reductions or dose delay as recommended in the SmPC, thus allowing overall continuation of crizotinib treatment and the maintenance of the clinical benefits and improved HRQoL associated with crizotinib.

B.2.13.2 The strengths and limitations of the clinical evidence base for the technology

The clinical evidence base of crizotinib for the treatment of ROS1-positive NSCLC is primarily drawn from the results of the single-arm phase I trial PROFILE 1001. This trial provides a strong clinical evidence base for crizotinib, despite its limitations in terms of being a single-arm study with a small sample size. The EMA recognised the strengths of this study despite the limited evidence for crizotinib in ROS1-positive NSCLC, and it was used as the main evidence for the approval of crizotinib for ROS1-positive NSCLC by the EMA.[7] The evidence from PROFILE 1001 is supported by the two pivotal trials for crizotinib in ALK-positive NSCLC, PROFILE 1014 for first-line patients, and PROFILE 1007 for those treated in the subsequent-line. The evidence from these two trials in the ALK-positive NSCLC population have previously been accepted by NICE, and based on expert clinical opinion and the similarities between ROS1 and ALK, this evidence has been used as a highly appropriate proxy for the economic evidence in this submission, which is possible because of the homology between ALK and ROS1 oncogenes, where crizotinib binds with a high affinity to both, as well as the similarities in patient characteristics and comparable efficacy and safety results. PROFILE 1007 and PROFILE 1014 provide comparative data of crizotinib versus chemotherapy for the economic model, where there are limited data in the ROS1-positive NSCLC population.

The strengths and weaknesses of PROFILE 1001 as a source of evidence with regards to internal validity are discussed below.

Strengths of the evidence

PROFILE 1001 is an international, multi-centre, trial and the first to investigate crizotinib as a treatment for patients with ROS1-positive advanced NSCLC.

The internal validity of PROFILE 1001 is supported by the following:

- Although this was a single-arm trial, assessments of tumour response were evaluated by an independent, central, radiological review
- The outcomes assessed in the PROFILE 1001 trial are of relevance to clinical practice and are consistent with those presented previously for therapies in ALK-positive NSCLC and lung cancer more generally
- These outcomes are also endorsed by 12 UK clinicians and they are reflective of what has been observed in clinical practice for these patients

Further supportive evidence for the clinical effectiveness of crizotinib in ROS1-positive NSCLC patients is presented in Appendix D, and is based on other single-arm prospective and retrospective studies which are in the ROS1-positive NSCLC population. In addition, the evidence from published studies is also supported by real world clinical data from the [redacted] audit (see Section B.2.11).

As mentioned above, data from trials in ALK-positive NSCLC patients, PROFILE 1007 and PROFILE 1014, are used to support the clinical data from PROFILE 1001 and are used as a proxy in the economic evidence where no data of crizotinib versus chemotherapy in ROS1-positive NSCLC are available, with comparable results observed for key effectiveness endpoints. This also includes comparable data for crizotinib in terms of safety and tolerability, which are supported by pooled safety data from 1,669 ALK-positive patients who have received crizotinib as part of the wider clinical trial programme. The validity of these studies has been accepted previously, in TA422 and TA406, respectively.[5, 8]

Limitations of the evidence

The internal validity of PROFILE 1001 is limited by the following:

- PROFILE 1001 is a single-arm phase I trial, which means that there was no direct comparison to comparator therapies. However, this study was accepted by the EMA as providing sufficient clinical evidence for the approval of crizotinib in ROS1-positive NSCLC due to the breakthrough nature of crizotinib and due to the ultra-orphan nature of the disease, as it would be unethical to conduct further clinical trials prior to approval.[7]
- At the time of PFS analysis, OS data for PROFILE 1001 was immature with only 30% of patients having died at the latest data cut-off date (see Section B.2.6.2). No follow-up OS analysis is planned.

The external validity of PROFILE 1007 and 1014 is limited by the following:

- The control arm of PROFILE 1007 was composed of both docetaxel and pemetrexed-treated patients. Pemetrexed was not considered as a subsequent-line comparator in the appraisal of crizotinib for previously treated ALK-positive NSCLC.[8] From subgroup analysis in PROFILE 1007, the median PFS in patients who received pemetrexed was higher than for patients who received docetaxel (4.2 months [redacted] versus 2.6 months [redacted], respectively). As the mixed treatment data will be used as evidence for docetaxel monotherapy in ROS1-positive NSCLC, this efficacy estimate will be conservative from the perspective of determining cost-effectiveness of crizotinib due to the higher PFS observed in patients treated with pemetrexed.

- The validity of using data from ALK clinical trials to support evidence for crizotinib in ROS1-positive NSCLC is dependent on the assumption that it is possible to draw a direct analogy between two biologically similar, but distinct subtypes of NSCLC. This is possible due to the 77% amino acid homology of ALK and ROS1, with crizotinib binding to a high affinity to both, and similar patient demographics which have been accepted by the EMA for the approval of crizotinib in ROS1-positive NSCLC.[7] This was also validated by 12 leading clinical experts at a recent advisory board.[3]

As such, these limitations are not expected to considerably impact the current analysis.

Generalisability of results to patients in the UK and the relevance of the evidence presented to the decision problem

PROFILE 1001 is highly relevant to the decision problem in terms of patient population and outcomes considered, as detailed below:

- PROFILE 1001 included patients, with confirmed ROS1-positive advanced NSCLC, which is the patient population under consideration in this submission.
- According to UK clinical experts, the characteristics of patients in PROFILE 1001 are representative of the relevant patient population in clinical practice (i.e. younger, never-smokers). This is supported by data from the Viola *et al.* (2016) study, where UK patients were tested for ROS1-positivity. Those patients who were ROS1-positive were younger and mostly never-smokers.[122]
- Both treatment-naïve and treatment-experienced ROS1-positive NSCLC patients were included in PROFILE 1001. It is expected that both treatment-naïve and treatment-experienced ROS1-positive patients will be treated by crizotinib in clinical practice, with clinicians noting that treatment-experience patients receiving crizotinib would be due to whether or not ROS1-testing had been performed prior to initiating first-line therapy.

In addition, PROFILE 1007 and PROFILE 1014 are highly relevant to the decision problem in terms of patient population and outcomes considered, as detailed in Section B.1.3.1. The NICE committee has already accepted the generalisability of these trials to the UK population in the recommendations of crizotinib for first- and subsequent-line ALK-positive NSCLC.[5, 8]

The external validity of PROFILE 1001, PROFILE 1007 and PROFILE 1014 is supported by the use of the licensed dose of crizotinib as described in the SmPC.[10]

End-of-life criteria

Evidence to support the consideration of crizotinib as a 'life-extending treatment at the end of life' in the context of NICE's end-of-life criteria are summarised in Table 25. The relevant sources and sections within this submission from which information has been derived are also detailed.

Table 25: Summary of end-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	As detailed in Section B.1.3.1, there is a paucity of estimates of OS with current chemotherapy in the ROS1-positive advanced NSCLC population specifically. There is no conclusive evidence that ROS1-positivity is a better prognostic factor for survival, compared to unselected NSCLC.[14, 15, 123-126] Based on opinion from 12 leading clinical experts from the UK, the PFS in chemotherapy-treated ROS1-positive patients is similar to the PFS in chemotherapy-treated ALK-positive patients.[3] As there are limited data on OS for ROS1-positive advanced NSCLC patients, data from ALK-positive NSCLC have been used as supportive evidence, due to the generalisability of ALK and ROS1. Estimates for median OS in ALK-positive patients range from 6 to 22 months,[46] with median OS in the chemotherapy arm of PROFILE 1007 reaching 21.9 months at the final analysis. Based on the available evidence and support from 12 UK leading clinical experts,[3] the life expectancy of ROS1-positive advanced NSCLC patients is expected to be below 24 months.[127]

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS was not reached in PROFILE 1001, with only 30.2% of patients having died at the time of PFS analysis (30th November 2014). At this point, median PFS was 19.3 months, therefore this is expected to be the minimum value for OS.[7] In the previous appraisal of crizotinib as a subsequent-line therapy for ALK-positive NSCLC, it was acknowledged that PFS is considered a conservative indicator of OS for targeted therapies: *"[The Committee] discussed comments by the manufacturer that it is biologically plausible that the overall survival to PFS ratio would be higher with targeted therapy than with chemotherapy. The clinical specialists confirmed that in some patients there was a dramatic response to treatment and that targeted therapies such as crizotinib could reduce tumour size to below that at the beginning of therapy. Therefore, at progression, the size of the tumour could still be smaller than at the beginning of therapy and as a result, benefit would continue into the progressed disease stage. The Committee was persuaded by this evidence."*[8] Crizotinib demonstrated clear benefits in terms of tumour response (see Section B.2.6.1) in PROFILE 1001, which, based on the NICE Committee's previous considerations, is supportive of a continued survival benefit with crizotinib into progressed disease. As such, the observed PFS with crizotinib should be considered an absolute minimum estimate of overall survival. In both the first-line and the subsequent-line settings, NICE has accepted an extension of life of more than three months in ALK-positive NSCLC patients receiving crizotinib compared to standard care. The model predicts an extension to life associated with crizotinib in ROS1-positive patients of 2.39 years compared to pemetrexed plus platinum therapy and 1.36 years compared to docetaxel therapy, which therefore meets the NICE criteria for end-of-life.

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; UK, United Kingdom.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

As documented in Appendix G, no published cost-effectiveness analyses were identified for ROS1-positive advanced NSCLC.

B.3.2 Economic analysis

B.3.2.1 Patient population

In line with the decision problem outlined in the final scope for this appraisal, the objective of this economic assessment is to provide an evidence base reflective of the population for which crizotinib has been recently licensed, that is patients with ROS1-positive NSCLC (EU marketing authorisation, received 25th August 2016).[7]

Due to limitations in the ROS1-positive data from PROFILE 1001, and the extensive homology between ALK-positive and ROS1-positive NSCLC, ALK-positive data from PROFILE 1014 (first-line) and PROFILE 1007 (subsequent-line) are used as a proxy for ROS1-positive patients. This is discussed in detail in Section B.3.3.4.

The cost-effectiveness of crizotinib for its indication in ROS1-positive NSCLC is assessed versus two comparator populations, patients who have received no prior therapy (first-line) and patients who have received one or more prior therapies (subsequent-line). The relevant comparators of interest and corresponding cost, efficacy, and utility data are dependent on the patient population.

We have also considered in an alternative analysis (PROFILE 1001 analysis), where an 'all-lines approach' is taken based on a parametric survival analysis for crizotinib, using a ROS1 population consistent with the full clinical trial population (first- and subsequent-line patients) from the phase I pivotal single-arm trial, PROFILE 1001 (as discussed in Section B.3.3.4).

B.3.2.2 Model structure

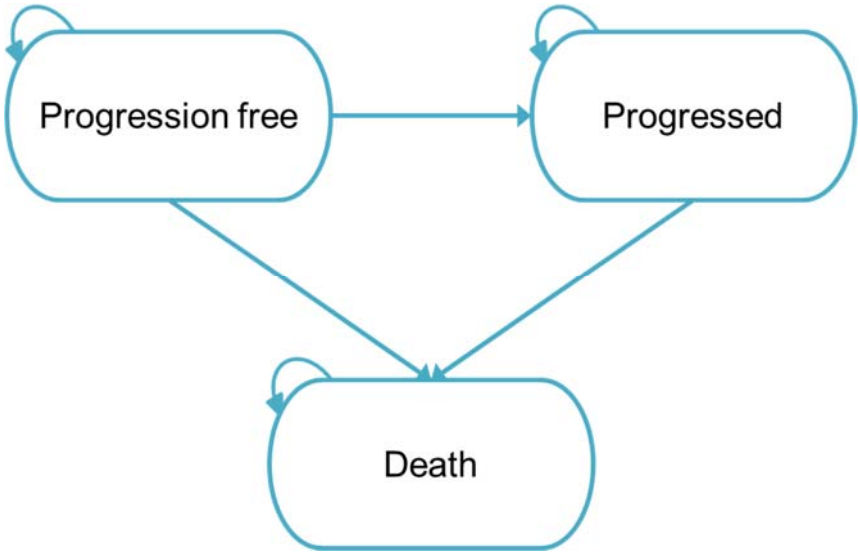
Model Structure

The cost-effectiveness model was developed in Microsoft Excel® using a "partitioned survival analysis". A probabilistic sensitivity analysis was conducted using 10,000 Monte Carlo simulations to capture stochastic uncertainty around key model outputs. The same model structure is applied to both the first- and subsequent-line models; however the relevant comparators and cost, efficacy, and utility inputs differ between populations.

The model structure schematic is presented in Figure 9. The model is based on three health states: progression-free disease, progressed disease, and death. All patients begin the model in the progression-free state and are at risk of progression. Transitions to the death state can occur from either the progression-free or progressed disease health states, and death is an 'absorbing state'. The progression free health state is designed to capture the relatively higher quality of life, whilst the disease is controlled prior to progression, where patients are receiving benefit from an active treatment. The progressed disease state is designed to capture the relatively poor quality

of life following disease progression and prior to death (although a proportion of patients may be treated beyond progression and thus continue to receive the benefit from an active treatment). The model therefore captures the changes in quality of life between pre- and post-progression.

Figure 9: Model Diagram



The model structure is fully aligned with two of the primary objectives of treatment in NSCLC, namely avoiding disease progression and prolonging life (see Section B.2.3.1). This model structure and the health states utilised are typical of modelling in oncology and were used in the previous appraisals for crizotinib in untreated and previously treated ALK-positive NSCLC (TA406 and TA422), in addition to numerous other NICE technology appraisals for NSCLC.[5, 8, 50, 53, 58, 59] The model structure, for both first- and subsequent-line patients, contains the three most relevant disease-related health states from a patient, clinician, and NHS perspective.

Patients receiving crizotinib as a first-line treatment

Progression free: within this state it is assumed that patients' disease is in a stable or responding state and not actively progressing. Progression was defined in both PROFILE 1001 and PROFILE 1014, and therefore subsequently in the model, using RECIST. Patients in this state are assumed to incur costs associated with treatment, including drug costs for crizotinib and pemetrexed plus platinum therapy, costs of drug administration, costs associated with medical management of the condition, and the management of grade 3/4 adverse events. A one-off cost for the testing of ROS1-positivity is also applied in the economic model. Details of the costs incurred are described in Section B.3.5.

Patients experience a higher utility weighting compared with *progressed disease*, as their tumour and related symptoms are controlled, and this utility weighting is treatment specific. However, if patients are treated beyond progression with crizotinib, they continue to receive the treatment benefit (based on observed utility for patients receiving crizotinib in PROFILE 1014). A summary of the utility values applied in the model is provided in Table 40.

Progressed disease: in this state, a patient's disease is assumed to have progressed (as defined by RECIST), and will move onto second-line treatment (docetaxel monotherapy) and then third-line BSC before death.

The current assumption in the model is that second-line therapy post-progression for patients who are not treated beyond progression is docetaxel monotherapy for both treatment arms. This is aligned with routine clinical practice in England and Wales, reflects the existing NICE recommendation for docetaxel monotherapy for NSCLC within the second-line setting,[57] and this assumption was previously accepted in TA406.[5] However, a "basket of therapies" based on the subsequent therapies in PROFILE 1014 is also considered in scenario analysis (described in Section B.3.5.4).

In PROFILE 1001 (87% at data cut-off 2014) and PROFILE 1014 (73% at data cut-off 2013), some patients could continue receiving treatment with crizotinib beyond progression. In the base case, this is based on time on treatment data from PROFILE 1014. This approach is consistent with the previous appraisal for crizotinib in untreated ALK-positive NSCLC (TA406). Time on treatment data from PROFILE 1001 is used in the "PROFILE 1001" analysis also presented in this submission, which uses parametric survival curves based on the 53 ROS1-positive PROFILE 1001. This approach has been taken to ensure that the time on treatment data is aligned with the efficacy data.

In line with the previous appraisal for crizotinib in untreated ALK-positive NSCLC (TA406), patients continue to incur costs of crizotinib (if treated beyond progression) or docetaxel monotherapy, in addition to administration costs and costs associated with medical management of the condition.[5] Patients who go on to receive docetaxel will experience a lower utility weighting (based on observed docetaxel utilities in the PROFILE 1007) than in the progression free-state. Patients who are treated beyond progression continue to have the 'treatment with crizotinib' utility observed in PROFILE 1014, as described in Section B.3.4.5.

Death: this is an absorbing health state.

Patients receiving crizotinib as a subsequent-line treatment:

Progression free: within this state it is assumed that patients' disease is in a stable or responding state and not actively progressing. Progression was defined in both PROFILE 1001 and PROFILE 1007, and therefore subsequently in the model, using RECIST. Consistent with the first-line model, patients are assumed to incur drug costs for crizotinib and docetaxel, administration costs, costs associated with medical management of the condition, and management of grade 3/4 adverse events. A one-off cost for the testing of ROS1-positivity is also applied in the economic model. Patients experience a higher utility value compared with *progressed disease* (0.81 on crizotinib vs 0.66 on docetaxel following progression), unless treated beyond progression with crizotinib whereby patients continue to receive the treatment benefit.[121]

Progressed disease: in this state, a patient's disease is assumed to have progressed (defined by RECIST). Consistent with the first-line model, patients may either continue to receive treatment beyond progression with crizotinib, followed by third-line BSC or move directly onto third-line BSC before death.

Death: this is an absorbing health state.

The proportion of patients within the cohort in each health state at each point in time is calculated directly from parametric survival function equations for PFS and OS (described in Section B.3.3.4).

In the base case, ROS1-testing for the crizotinib arm is assumed to take place along with other diagnostic testing prior to first-line treatment in non-squamous patients; hence the modelled patients' ROS1 status is known upon entry into the model. The costs of screening for ROS1-positivity have been included in the model as per the testing strategy recommended as a "cost-effective approach" in the European Society for Medical Oncology (ESMO) guidelines (IHC test, with positive tests being confirmed by FISH). It is understood from discussions with clinical experts at an advisory board that this is a commonly used strategy in the UK.[63] This is applied in the model in terms of the expected cost per patient to identify one ROS1-positive patient from a cohort of all patients with non-squamous NSCLC. The more expensive, and so most conservative, costing option is selected in the base case. A sensitivity analyses using a sequential testing assumption (whereby the population being tested excludes ALK-positive and EGFR-positive patients) is tested in sensitivity analysis (described in section B.3.5.4).

Features of the de novo analysis

The analyses were conducted from a NHS and personal social services (PSS) perspective in England and Wales. The model uses 30-day cycles, with a half-cycle correction applied. Within each cycle, costs were adjusted to account for the difference in treatment cycle length compared with the model cycle length. That is, crizotinib treatment costs were based on clinical trial measurement points and pack size, while for chemotherapies the treatment cycle length of 21 days was adjusted to match the 30-day model cycle length. A time horizon of 20 years was chosen. This aligns with the maximum life expectancy of the cohort predicted by parametric survival analysis and, clinically, it is unlikely for patients with ROS1-positive advanced NSCLC to survive beyond 20 years. In the first- and subsequent-line deterministic model base cases and alternative analyses using PROFILE 1001 data, less than 6% of patients remained alive across all treatment arms at the time horizon. The impact of the selection of the time horizon on results is explored in sensitivity analysis. A discount rate of 3.5% per annum was applied for costs and benefits. The perspective chosen, time horizon assessed, and the discount rates used are all in line with the NICE reference case.[128]

There are no prior NICE technology appraisals for the treatment of ROS1-positive NSCLC. The similar characteristics of ALK- and ROS1-positive NSCLC patients, as well as the extensive homology between the ROS1 and ALK RTKs are considered by clinicians to be supportive of the use of ALK-positive studies as a proxy for crizotinib in ROS1-positive NSCLC (Section B.1.3.1). As a result, technology appraisals for crizotinib (TA406 and TA296 [Replaced by TA422]) and ceritinib (TA395) in ALK-positive NSCLC are relevant as comparative precedence.[5, 8, 50]

The features of the *de-novo* analysis, compared with the features of the previous technology appraisals for ALK-positive untreated NSCLC (TA406) and previously treated ALK-positive NSCLC (TA422 and TA395) are presented in Table 26.[5, 8, 50]

Table 26: Features of the economic analysis

Factor	Previous appraisals			Current appraisal	
	TA406	TA296 (replaced by TA422)	TA395	Chosen values	Justification
Model Structure	Partitioned survival analysis with 3 health states	Partitioned survival analysis with 3 health states	Partitioned survival analysis with 3 health states	Partitioned survival analysis with 3 health states	Reflects 3 most disease relevant health states. Structure typical of NSCLC modelling; used in several previous NICE appraisals.
Time horizon	15 years	15 years	10 years	20 years	Due to new mature PROFILE 1014 data, the previously accepted 15-year time horizon was deemed insufficient for this cost-effectiveness analysis. Therefore, 20 years is considered adequately long that the majority of patients (>96%) have died by the end of the modelled time horizon in all analyses. 20 years is also long enough to reflect all differences in costs and outcomes in line with the NICE reference case.
Source of utilities	PROFILE 1014 PROFILE 1007 Nafees *et al.* (2008)	PROFILE 1007	ASCEND trials (mapped EORTC QLQ-C30 to EQ-5D) Chouaid *et al.* (2013) Nafees *et al.* (2008)	PROFILE 1014 PROFILE 1007 Nafees *et al.* (2008)	Utility values were derived from EQ-5D data collected in PROFILE 1014 and PROFILE 1007; in line with the NICE reference case. Where not available in the relevant clinical trials, EQ-5D data were sourced from literature in line with NICE reference case. Due to the similarities in the characteristics of ROS1- and ALK-positive patients, utility values from PROFILE 1014 (for crizotinib and pemetrexed plus platinum therapy) and PROFILE 1007 (for docetaxel) are considered appropriate proxies.
Source of drug costs	MIMS eMit (generics)	BNF	BNF eMit (generics)	MIMS eMit (generics)	In line with the NICE reference case, the public list prices for technologies should be used.

Factor	Previous appraisals			Current appraisal	
	TA406	TA296 (replaced by TA422)	TA395	Chosen values	Justification
					As described in the NICE reference case, the CMU publishes information of the price paid by the NHS for generics through eMit.
Source of other costs	NHS reference costs (monitoring and adverse event costs) PSSRU (monitoring costs, palliative care costs)	NHS reference costs (monitoring costs) PSSRU (monitoring costs)	NHS reference costs (administration, monitoring and adverse event costs) PSSRU (monitoring costs)	NHS reference costs (administration, monitoring and adverse event costs) PSSRU (administration, monitoring and palliative care costs)	Consistent with NICE reference case (resources should be valued using the prices relevant to the NHS).
Cycle length	30 days	30 days	1 month	30 days	Based on clinical trial measurement points and pack size for crizotinib (30 days). For chemotherapies with cycle length of 21 days, costs were adjusted to account for the difference in treatment cycle length compared with the model cycle length.
Health effects measure	QALYs	QALYs	QALYs	QALYs	Consistent with NICE reference case
Discount rate for costs and QALYs	3.5%	3.5%	3.5%	3.5%	Consistent with NICE reference case
Perspective	NHS/PSS	NHS	NHS/PSS	NHS/PSS	Consistent with NICE reference case
Half cycle correction applied?	Yes	Yes	Yes	Yes	Consistent with NICE reference case

Factor	Previous appraisals			Current appraisal	
	TA406	TA296 (replaced by TA422)	TA395	Chosen values	Justification

Abbreviations: BNF, British national formulary; CMU, Commercial medicines unit; eMit drugs and pharmaceutical electronic market information MIMS, monthly index of medical specialities; NHS, National Health Service, NICE, National Institute for Health and Care Excellence; PSS, personal social services; PSSRU personal social services research unit; QALY, Quality-adjusted life year; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

Crizotinib is a single agent oral chemotherapy with a recommended dose of 250 mg taken twice daily (available in 250 mg and 200 mg capsules) which may be used to treat patients with advanced stage ROS1-positive NSCLC. Patients who are treated with crizotinib may be first-line, meaning they have not received any prior therapy, or subsequent-line, whereby they have received one or more prior therapies.

As discussed in Section B.2.4, treatment with crizotinib was continued until disease progression or clinical deterioration in the pivotal clinical studies (PROFILE 1001, PROFILE 1014 and PROFILE 1007). Treatment beyond progression was, however, permitted in the study at the investigators discretion.[68] Therefore, the model considers the cost and benefit of this and assumes treatment beyond progression occurs (and the corresponding costs and effects) for a duration in line with what was observed in the clinical trials (Section B.3.3.4). This method of modelling treatment beyond progression with crizotinib is in line with the accepted approach for the appraisals of crizotinib in untreated and previously treated ALK-positive NSCLC (TA406 and TA422).[5, 8]

In the base case, crizotinib the final accepted time on treatment curves from TA406 and TA422, were used for first-line and subsequent-line, respectively. In the “PROFILE 1001” analysis presented in this submission, the time on treatment data from PROFILE 1001 for crizotinib is used.

Patients receiving crizotinib as a first-line treatment:

The final scope for this appraisal includes the following comparators for untreated ROS1-positive NSCLC:

- Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with carboplatin or cisplatin
    - With pemetrexed maintenance (for non-squamous NSCLC patients), or
    - Without pemetrexed maintenance
- Pemetrexed in combination with carboplatin or cisplatin (for non-squamous NSCLC patients)
    - With pemetrexed maintenance (following cisplatin-containing regimen), or
    - Without pemetrexed maintenance
- Single agent chemotherapy with a third-generation drug (for patients who cannot tolerate platinum-based chemotherapy)

As discussed in Section B.1.3.2, based on feedback from UK clinical experts the main comparator of interest based on clinical practice for first-line ROS1-positive patients is pemetrexed plus platinum therapy. Pemetrexed in combination with cisplatin has been assessed, and recommended for use by NICE as a first-line treatment for patients with NSCLC.[6] It was also considered as a relevant comparator in the appraisal for crizotinib for untreated ALK-positive NSCLC (TA406).[5] As demonstrated in the recent NICE appraisal (TA406),[5] clinician preference for either cisplatin or carboplatin is largely based on patient fitness/tolerability and ease of administration, with comparable efficacy between regimens having been detected in recent meta-analyses.

Therefore, due to the extensive homology between ALK-positive and ROS1-positive NSCLC, it is assumed that the comparative efficacy observed between crizotinib and pemetrexed plus platinum therapy observed in PROFILE 1014 is applicable for ROS1-positive NSCLC patients at first-line (discussed further in Section B.1.3.1).

As described in Section B.1.3.2, clinical experts have suggested that approximately 15% of patients with advanced NSCLC would be eligible for pemetrexed maintenance after platinum doublet first-line chemotherapy, based on fitness. Given the small proportion of patients who receive maintenance therapy, this was not considered as a comparator in this submission, as per the NICE submission for crizotinib for the first-line treatment of ALK-positive NSCLC. It was not possible to compare to the other comparators due to the lack of clinical evidence for the comparator in a ROS1-positive or ALK-positive population. ROS1-positive NSCLC is fundamentally different to unselected NSCLC, and therefore a meaningful comparison cannot be made between the two, including their comparators (see Section B.1.3.1).

Patients receiving crizotinib as a subsequent-line treatment:

In the subsequent-line patient population, the final scope includes the following comparators:

- Docetaxel
    - With nintedanib (for adenocarcinoma histology), or
    - Without nintedanib
- Best supportive care

NICE guidance recommends that docetaxel monotherapy is appropriate as a second-line treatment for patients with locally advanced or metastatic NSCLC, in whom relapse has occurred after prior chemotherapy. Docetaxel was also considered as a relevant comparator for crizotinib in patients with ALK-positive NSCLC at second line in a previous NICE appraisal (TA422).[8]

Therefore, docetaxel monotherapy is considered as the subsequent-line treatment comparator in the economic model for patients with ROS1-positive NSCLC, using comparative efficacy data observed in PROFILE 1007, given the similarities between ROS1-positive and ALK-positive NSCLC (discussed further in Section B.1.3.2).

As described in Section B.1.3.2, it was not possible to compare to the other comparators due to the lack of clinical evidence for the comparator in a ROS1-positive or ALK-positive population. ROS1-positive NSCLC is fundamentally different to unselected NSCLC (see Section B.1.3.1), and therefore a meaningful comparison cannot be made between the two, including their comparators.

B.3.3 Clinical parameters and variables

B.3.3.1 Clinical data incorporated into the model

An attempt has been made in this submission to use the ROS1-positive specific data from PROFILE 1001. However, survival data from PROFILE 1001 for the key clinical endpoints of PFS and OS were based on a small sample size (n=53) and were considered immature, as only 30% of patients had died at the date of data cut-off (Table 27).

Table 27: Summary of number of patients and events in PROFILE 1001

	Number of patients	Number of events
OS	53	16
PFS	53	26

Abbreviations: OS, Overall survival; PFS, progression-free survival

Due to the uncertainty associated with the limited PROFILE 1001 data for crizotinib (described above and in section B.3.3.4 in detail), ALK-positive NSCLC data (from PROFILE 1014 and PROFILE 1007) is used as a proxy for ROS1-positive patients, in the base case. Using ALK-positive NSCLC data as a proxy is appropriate due to the extensive homology between the ALK gene rearrangement and the ROS1 gene rearrangement in NSCLC. This assumption has been supported by 12 clinical experts attending an advisory held in July 2017.[3] Using ALK-positive data as a proxy is also considered to be more robust given that the data comes from RCTs with a much larger sample size rather than a single arm study with only 53 patients. Further to this, the data from PROFILE 1014 and PROFILE 1007 has already been assessed and approved by NICE. Therefore, we have utilised the best available evidence for a rare condition with high unmet need.

An alternative analysis is presented in this submission ("PROFILE 1001 analysis") where crizotinib outcomes are modelled based on ROS1-positive patients from PROFILE 1001, with comparator outcomes modelled using the inverse HRs from ALK-positive patients from PROFILE 1014 (first-line, pemetrexed plus platinum therapy) and PROFILE 1007 (subsequent-lines, chemotherapy).

In the base case, the final accepted OS and PFS curves from TA422 were used to estimate the proportion of crizotinib patients in each health state at subsequent-line. The final accepted PFS curve from TA406 and OS curves from the latest PROFILE 1014 data cut (2017) were used to estimate the proportion of crizotinib patients in each health state at first-line.

A proportion of patients could receive treatment with crizotinib beyond progression, therefore the costs and outcomes associated with crizotinib for these progressed patients must be accounted for. In the base case, crizotinib time on treatment was estimated using the final accepted time on treatment curves from TA406 and TA422, for first-line and subsequent-line, respectively.

AE data from PROFILE 1014 and PROFILE 1007 were used to estimate the proportion of patients experiencing treatment-related grade 3/4 AEs in the crizotinib and comparators arms of the model for first-line and subsequent line, respectively. In the alternative 'PROFILE 1001 analysis' presented in the submission, AE data was taken from PROFILE 1001 for the crizotinib arms in both the first- and subsequent-line model.

In line with the previous appraisals for crizotinib in ALK-positive NSCLC (TA406 and TA422),[5, 8] baseline characteristics of patients were included in the model if they had an impact on the model output. As such, body surface area (BSA), or height and weight data to calculate BSA when not available, were included in the model and used for dosing calculations. In the base case, these were taken from TA406 (1.73 m^2) and TA422 (1.80 m^2) for the first-line and subsequent-line analyses, respectively.[5, 8] The BSA taken from the previous submissions for crizotinib were closely aligned to that reported in PROFILE 1001 (1.80 m^2).

Patients receiving crizotinib as a first-line treatment

As described in Section B.2.2, no evidence was identified for pemetrexed plus platinum therapy, the first-line comparator for this submission, or for docetaxel monotherapy, the subsequent-line comparator for this submission, in a ROS1-positive population. The PROFILE 1014 study provided a head-to-head comparison of crizotinib against pemetrexed plus platinum therapy in previously untreated ALK-positive patients[73]. Due to the extensive homology between the kinase domain of the ALK and ROS1 tyrosine kinase receptors, and the likenesses in the characteristics of ALK-positive and ROS1-positive NSCLC patients, (as discussed in Section B.1.3.1), it is assumed that the ALK-positive data is an appropriate proxy for ROS1-positive NSCLC. This assumption has been supported by 12 clinical experts attending an advisory held in July 2017.[3]

Due to the uncertainty associated with the PROFILE 1001 data for crizotinib (described above and in section B.3.3.4) ALK-positive NSCLC data from PROFILE 1014 has been used as a proxy for ROS1-positive NSCLC in the base case. This is achieved by using the final accepted extrapolated, PFS and time on treatment curves for crizotinib and pemetrexed plus platinum therapy as accepted in TA406. Following this submission, a more recent 2017 data cut of OS data from PROFILE 1014 has become available. Parametric curves have been fitted to the updated OS data for this submission (Section B.3.3.4).

Data from PROFILE 1014 were also used to inform the proportion of patients who experience treatment-related Grade 3/4 adverse events in the crizotinib and pemetrexed plus platinum therapy arms. This data was previously used and was accepted by the committee in TA406.[5]

An alternative analysis (PROFILE 1001 analysis) has been presented in this submission where, data from the PROFILE 1001 trial were used to estimate the proportion of crizotinib patients in each health state (using an extrapolation of PFS and OS Kaplan Meier [KM] data). In this analysis, the HRs from PROFILE 1014 reporting the effect of crizotinib relative to pemetrexed plus platinum therapy were used. We calculated the inverse of the published HRs to give the effect of pemetrexed plus platinum therapy relative to crizotinib. These HRs were applied to the OS and PFS curves estimated for ROS1-positive patients treated with crizotinib in PROFILE 1001 to estimate OS and PFS for patients receiving pemetrexed plus platinum therapy (Section B.3.3.4). TTF data from the PROFILE 1001 study was extrapolated to estimate time on crizotinib in the “PROFILE 1001 analysis”. PROFILE 1001 data was used to estimate the proportion of patients experiencing treatment-related grade 3/4 AEs in the crizotinib arm of the model. BSA data is taken from PROFILE 1001, in this analysis.

Patients receiving crizotinib as a subsequent-line treatment

The PROFILE 1007 study provided a head-to-head comparison of crizotinib against pooled chemotherapy (pemetrexed or docetaxel) in previously-treated ALK-positive patients. As for the comparison with pemetrexed plus platinum therapy described above, due to the extensive homology between ALK-positive and ROS1-positive NSCLC, ALK-positive OS and PFS data from PROFILE 1007 are assumed to be a reasonable estimate for the relative efficacy of crizotinib versus docetaxel monotherapy in a ROS1-positive population. This assumption has been supported by 12 clinical experts attending an advisory held in July 2017.[3]

As for the first-line population, due to the uncertainty associated with the PROFILE 1001 data for crizotinib (described in section B.3.3.4) using ALK-positive data from PROFILE 1007 as a proxy for ROS1-positive NSCLC is used in the base case. This is achieved by using the final accepted

extrapolated OS, PFS and time on treatment curves, for crizotinib and pooled chemotherapy (for docetaxel monotherapy), as accepted in TA422.[8]

Data from PROFILE 1007 was also used to inform the proportion of crizotinib and docetaxel monotherapy patients who experience treatment-related grade 3/4 adverse events in the docetaxel monotherapy arm. This data was previously used and was accepted by the committee in TA422.[8]

An alternative analysis (PROFILE 1001 analysis) has been presented in this submission where, data from the PROFILE 1001 trial were used to estimate the proportion of crizotinib patients in each health state (using an extrapolation of PFS and OS Kaplan Meier [KM] data). In this analysis, the inverse of published HRs from PROFILE 1007 are applied to the OS and PFS curves estimated for ROS1-positive patients treated with crizotinib in PROFILE 1001 to estimate the OS and PFS of patients receiving docetaxel monotherapy. Crossover adjusted HRs for OS for crizotinib versus docetaxel alone are not available from the PROFILE 1007 analyses, therefore, the crossover-adjusted HR for the pooled chemotherapy arm from PROFILE 1007 is used and assumed to be equivalent for docetaxel monotherapy for OS (using ROS1-positive data from PROFILE 1001). Given that patients in PROFILE 1007 performed better on pemetrexed than docetaxel,[48, 71] the use of a pooled chemotherapy arm is a conservative assumption as it is likely to overestimate the treatment effect of docetaxel monotherapy on OS. This assumption was accepted in the previous appraisal for crizotinib in previously treated ALK-positive NSCLC patients (TA422). TTF data from the PROFILE 1001 study was extrapolated to estimate time on crizotinib in the “PROFILE 1001” analyses. PROFILE 1001 data was used to estimate the proportion of patients experiencing treatment-related grade 3/4 AEs in the crizotinib arm of the model. BSA data is taken from PROFILE 1001, in this analysis.

B.3.3.2 Estimation of transition probabilities from the clinical data

The area underneath the OS curve represented the proportion of patients that were still alive over time, while the proportion of patients in the progression-free state was identified by the patients located underneath the PFS curve. The area between the OS and PFS curve indicates the proportion of patients in the progressed disease state. For crizotinib patients, the area between the TTF and PFS curves represents the proportion of patients who are treated beyond progression, whilst the area between the OS and TTF curves indicates proportion of progressed patients who are no longer being treated with crizotinib.

B.3.3.3 Transition probabilities over time

Examination of survival functions from the pivotal clinical studies (PROFILE 1014, PROFILE 1007 and PROFILE 1001) and other oncology studies indicates that transition probabilities are likely to vary over the course of the disease. The parametric survival method used to model transition probabilities allows for flexibility in the rate of change of the survival functions over time.

B.3.3.4 Extrapolation of data

Using ALK-positive data as a proxy for ROS1-positive NSCLC (base case)

As highlighted in detail in Section B.1.3.1, there is extensive homology between ROS1-positive and ALK-positive NSCLC patients. There is also a much larger evidence base available for patients with ALK-positive NSCLC receiving crizotinib (first- and subsequent lines), pemetrexed

plus platinum therapy (first-line) and docetaxel monotherapy (subsequent-line), based on PROFILE 1014 (first-line) and PROFILE 1007 (subsequent-lines). Given this, the survival data estimated in previous appraisals for crizotinib, TA406 and TA422 (based on PROFILE 1014 and PROFILE 1007, respectively),[5, 8] along with the updated PROFILE 1014 data is considered a more robust estimate of survival for crizotinib versus pemetrexed plus platinum therapy (first-line) and docetaxel monotherapy (subsequent-line) in patients with ROS1-positive NSCLC. Therefore, in the base case, ALK-positive OS, PFS and time on treatment data is used as a proxy for ROS1-postive patients.

Overall Survival

First-line

Crossover adjustment methods were employed to adjust the pemetrexed plus platinum therapy arm to estimate the effect of treatment on overall survival in PROFILE 1014 had crossover not been permitted. At the time of first data cut for OS analysis, the rank-preserving structural failure time model (RPSFTM), the Iterative Parameter Estimation (IPE) and the two-stage method were applied to adjust for the impact of crossover and estimate the treatment effect for OS in PROFILE 1014. However, at the time of new OS analysis only the RPFSTM method was performed to adjust for the effect of crossover on OS to obtain the unbiased estimate of treatment effect on OS. The RPSFTM and the IPE methods both represent randomization-based methods for estimating counterfactual survival outcomes (i.e. survival times that would have been observed in the absence of crossover). The two methods are comparable except that the IPE method uses a parametric likelihood approach to estimate the acceleration factor for the counterfactual survival outcome. Therefore, given the similarity between methods and the almost identical results at the time of first OS analysis, the IPE model was not implemented at the time of final analysis.

The results of two-stage analysis performed at the time of first OS analysis were also comparable to the results of the first two methods, however, for the two-stage method to provide a valid estimate of the treatment effect on OS, it must be assumed that the post-progression survival (PPS) of non-crossover patients is representative of the PPS of crossover patients had they not crossed over. At the time of final OS analysis, [redacted] patients randomised to pemetrexed plus platinum therapy had progressed. Of these, [redacted] patients received subsequent crizotinib and [redacted] did not. The number of pemetrexed plus platinum therapy patients with progressed disease and without subsequent crossover is therefore very small [redacted] As the two-stage method relies on the PPS outcome of these [redacted] patients to represent what the PPS of [redacted] would have been had they not crossed over, the uncertainty associated with treatment effect estimates derived using this methodology may be high and the two–stage method was considered inappropriate for the new data cut of PROFILE 1014.

Therefore, adjusted survival times were estimated using two variations of the RPSFT method; log rank and Wilcoxon. The results (Table 28) demonstrate a strong, consistent estimate of clinical benefit across the different crossover adjustment methods. The Wilcoxon method was selected in the base case as this provided the most conservative treatment effect.

Table 28: Overall survival crossover adjustment methods use in parametric modelling, with treatment effect estimates

Crossover adjustment method	Analysis	Abbreviation	Crizotinib versus pemetrexed plus platinum therapy HR (95% CI)
RPSFT	Wilcoxon text method	RW	[redacted]
	Log-rank test method	RL	[redacted]

In the accepted base case for the appraisal of crizotinib in untreated ALK-positive NSCLC (TA406), a retrospective real-world cohort study conducted by Davis *et al.* (2015) was used to provide the baseline patient characteristics for covariate adjustment in the parametric modelling.[127] This was because, in TA406, the characteristics were considered more representative of patients seen in current UK clinical practice than those in PROFILE 1014 (see Table 29 for a comparison of patient characteristics).

In the updated data cut from PROFILE 1014, used for OS in the first-line base case, the adjustment of the survival curves to be more reflective of that patient in UK clinical practice, as accepted in TA406, is again applied. As PFS and time on treatment curves used in the base case are the final accepted ALK-positive curves from the previous submission (TA406), the real-world adjustment that was previously applied and accepted by the committee in TA406 is already applied to these curves. Therefore, adjusting for the characteristics in Davies *et al*. (2015) in the OS curves provides consistency with the PFS and time on treatment curves used.

The following covariates, which are the same as used in TA406, are included in the survival models:

- Race [Asian vs. non-Asian]
- Eastern Cooperative Oncology Group [ECOG] status [2 vs. 1 or 0]
- Brain metastases [yes vs. no])
- Age group (≥65 vs. <65)
- Sex (male vs. female)
- Smoking status (never smoked vs. former smokers or current smoker)
- Adenocarcinoma (yes vs. no).

Table 29: Baseline demographics and patient characteristics for covariate-adjustment

Covariate	Real-world data (Davis *et al.* [2015])	Crizotinib (PROFILE 1014)	Pemetrexed plus platinum therapy (PROFILE 1014)	Pooled treatments (PROFILE 1014)
% non-Asian	87.6%	55.2%	53.2%	54.2%
% age ≥ 65	29.2%	13.4%	18.7%	16.0%
% male	67.9%	39.5%	36.8%	38.2%
% smoker or ex-smoker	62.8%	38.4%	34.5%	36.4%
% ECOG PS 0-1	78.1%	94.2%	95.3%	94.7%
% ECOG PS 2	21.9%*	5.8%	4.7%	5.3%
% with brain metastases	NR	26.2%	27.5%	26.8%
% non-adenocarcinoma	NR	6.4%	5.8%	6.1%

*16.8% of patients were ECOG PS 2, and 5.1% were ECOG PS 3. However, due to only ECOG PS 0–1 and 2 included in the PROFILE 1014 trial, the covariate effect of ECOG PS 3 on outcomes was not determinable. Consequently, the n=7 (5.1%) ECOG PS 3 patients have been pooled into the ECOG PS 2 category.
Abbreviation: ECOG, Eastern Cooperative Oncology Group; NR, not reported; OS, overall survival; PFS, progression-free survival; PS, performance status.

Parametric survival curves were fitted to OS data from the latest data cut from PROFILE 1014 (2017), separately for crizotinib and pemetrexed plus platinum therapy (based on the preferences by the committee in TA406). Survival curve fitting was conducted in line with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[101] All standard parametric models were considered and compared. These included exponential, Weibull, log-normal, log-logistic, gompertz and generalised gamma. The fit of the alternative models was assessed by considering:

- visual inspection of fitted curves
- comparisons of Akaike information criterion (AIC) and Bayesian information criterion (BIC) between the model types, and
- the plausibility of long-term extrapolation based on clinical expert opinion, and expected survival from other data sources.

Survival curves were predicted by using the parameter estimates and underlying statistical equations for each statistical model, and applying covariate estimates to represent the survival for the population being 'predicted'; i.e. proportions of patients observed in PROFILE 1014 with respect to the covariates were used to produce predicted curves for PROFILE 1014. Following this, the 'real-world' proportions of patients for each covariate were used to adjust curves for the 'real-world' population.

The AIC and BIC for the crizotinib OS curves, including the covariates for prognostic factors, are provided in Table 30 and for pemetrexed plus platinum therapy in Table 31; lower values are preferred for the best statistical fit. The OS curve fits (using characteristics from PROFILE 1014) for crizotinib are shown alongside the KM curve in Figure 10 and the OS curve fits (using PROFILE 1014 characteristics) for pemetrexed plus platinum therapy are shown alongside the KM curve in Figure 12. The OS curves for crizotinib and pemetrexed plus platinum therapy that have been adjusted using real-world characteristics are presented in Figure 11 and Figure 13, respectively.

The exponential curve has been selected for the base case, as this was the best fitting curve (based on the AIC and BIC estimates), which also provided the most clinically plausible estimates for both crizotinib and pemetrexed plus platinum therapy. The selected curves are presented in Figure 14. Alternative curve fits are tested in sensitivity analysis.

Table 30: AIC and BIC for crizotinib OS

Model	AIC	BIC
Exponential	1203.6	1228.8
Generalised Gamma	1207.3	1238.8
Gompertz	1205.6	1234.0
Log-logistic	1205.2	1233.6
Log-normal	1209.4	1237.8
Weibull	1205.6	1233.9

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival

Figure 10: OS – Crizotinib (estimated using PROFILE 1014 data for patient characteristics [unadjusted])

Abbreviations: OS, Overall survival; KM, Kaplan Meier

Figure 11: OS – Crizotinib (estimated using real-world data for patient characteristics [adjusted])

Abbreviations: OS, Overall survival; KM, Kaplan Meier

Table 31: AIC and BIC for pemetrexed plus platinum therapy OS

Model	AIC	BIC
Exponential	1141.6	1166.7
Generalised Gamma	1138.9	1170.3
Gompertz	1143.1	1171.4
Log-logistic	1135.0	1163.3
Log-normal	1137.3	1165.6
Weibull	1142.5	1170.7

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival

Figure 12: OS (using crossover method RPSFT: Wilcoxon) – pemetrexed plus platinum therapy (estimated using PROFILE 1014 data for patient characteristics [unadjusted])

Abbreviations: OS, Overall survival; KM, Kaplan Meier; RPSFT, Rank Preserving Structural Failure Time

Figure 13: OS (using crossover method RPSFT: Wilcoxon) – pemetrexed plus platinum therapy (estimated using real-world data for patient characteristics [adjusted])

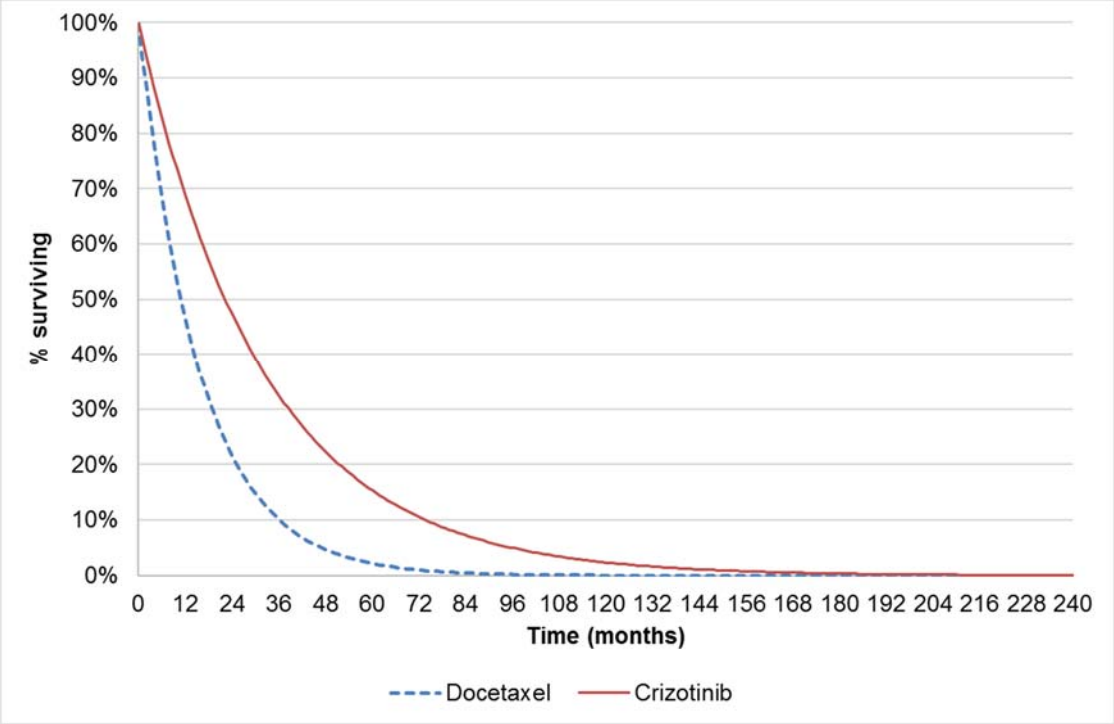
Abbreviations: OS, Overall survival; KM, Kaplan Meier; RPSFT, Rank Preserving Structural Failure Time

Figure 14: Selected curves for crizotinib and pemetrexed plus platinum therapy (exponential), with real world adjustment

Subsequent Line

The PROFILE 1007 OS data and extrapolations have already been appraised and accepted by NICE in TA422.[8] Therefore, only the final accepted curves have been modelled for crizotinib and pemetrexed plus platinum therapy. In the second-line appraisal for crizotinib in ALK-positive NSCLC (TA422), the curve used to estimate OS in the docetaxel arm in the preferred base case was exponential. The HR applied to the docetaxel arm in order to estimate OS in the crizotinib arm that was selected was 0.49 (0.37, 0.64). These curves are shown in Figure 15.

Figure 15: Final accepted OS curves for crizotinib and docetaxel from TA422



Abbreviations: OS, Overall survival; TA, technology appraisal
Source: NICE TA422[8]

Progression Free Survival

First line

The PROFILE 1014 PFS data and extrapolations have already been appraised and accepted by NICE in TA406.[5] Therefore, only the final accepted curves have been modelled for crizotinib and pemetrexed + platinum therapy. Fully stratified log-normal and generalised gamma curves (for crizotinib and pemetrexed + platinum therapy, respectively) which independently adjusted for covariates (and therefore did not assume proportional hazards between treatment groups) were used in this base case analysis which best reflected the committee's preferences. The curves, which used data from PROFILE 1014, were adjusted to reflect the characteristics of patients in England, using data from a retrospective cohort study in the US and Canada.[127] These curves are shown in Figure 16.

Figure 16: Final accepted PFS curves for crizotinib and pemetrexed plus platinum therapy from TA406

Abbreviations: PFS, progression-free survival; TA, technology appraisal
Source: NICE TA406[5]

Subsequent Line

Similarly, the PROFILE 1007 PFS data and extrapolations have already been appraised and accepted by NICE in TA422.[8] Therefore, only the final accepted curves have been modelled for crizotinib and chemotherapy. PFS was assumed to follow Weibull and log-normal distributions in the crizotinib and chemotherapy arms, respectively, in the accepted base case in TA422. These curves are shown in Figure 17.

Figure 17: Final accepted PFS curves for crizotinib and docetaxel from TA422

Abbreviations: PFS, progression-free survival; TA, technology appraisal
Source: NICE TA422[8]

Time on Treatment

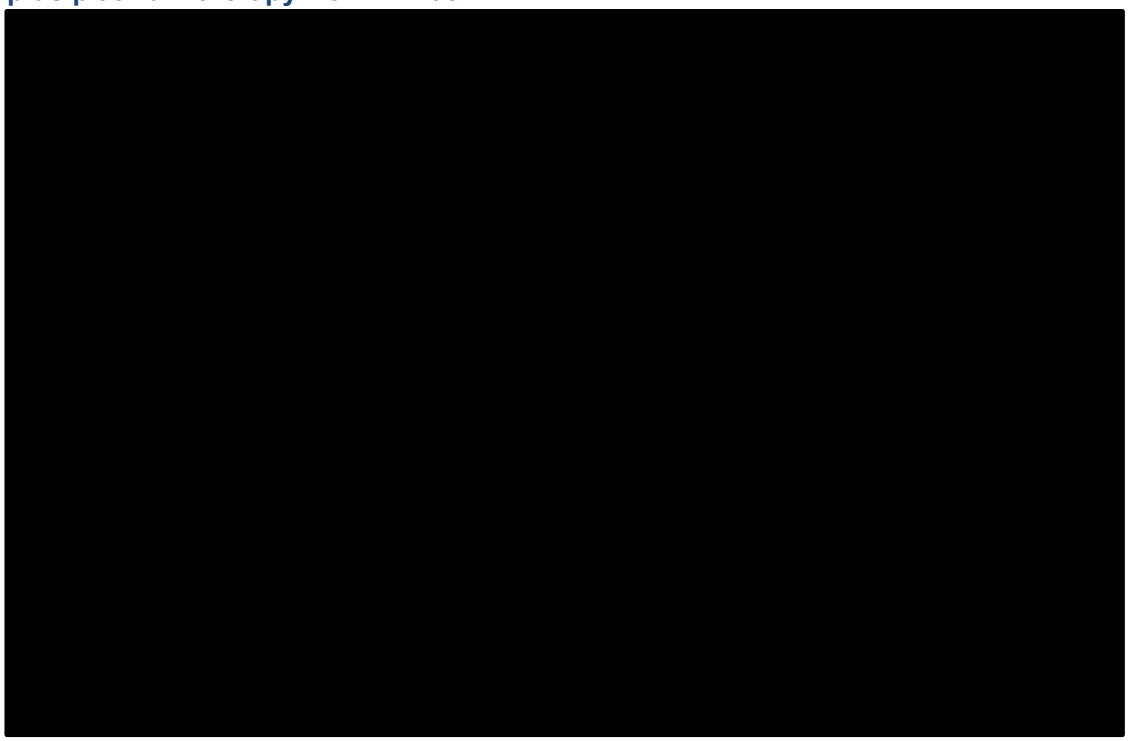
First-line

The PROFILE 1014 time on treatment data and extrapolations have already been appraised and accepted by NICE in TA406.[5] Therefore, only the final accepted curves have been modelled for crizotinib and pemetrexed plus platinum therapy. In the committee's preferred base case, fully stratified (independent) exponential and gompertz curves (for crizotinib and pemetrexed + platinum therapy, respectively) which were adjusted to reflect the population in England were used to estimate time on treatment.[127] These curves, along with the final accepted OS and PFS curves are shown in Figure 18 and Figure 19, respectively.

Figure 18: Updated PROFILE 1014 OS and final accepted PFS and TTD curves for crizotinib from TA406

Abbreviations: OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TTD, time to treatment discontinuation
Source: NICE TA406[5]

Figure 19: Updated PROFILE 1014 OS and final accepted PFS and TTD curves pemetrexed plus platinum therapy from TA406



Abbreviations: OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TTD, time to treatment discontinuation
Source: NICE TA406[5]

Subsequent-line

The PROFILE 1007 time on treatment data and extrapolations have already been appraised and accepted by NICE in TA422.[8] Therefore, only the final accepted curves have been modelled for crizotinib. For crizotinib, time on treatment was estimated using a Weibull curve in the final accepted base case in TA422. These curves, along with the final accepted OS and PFS curves are shown in Figure 20. Time on treatment curves for docetaxel were not used as part of TA422. A maximum of 3 doses of docetaxel is assumed in both base case analyses, in line with TA422 (discussed in Section B.3.5.1).

Figure 20: Final accepted PFS, TTD and OS curves for crizotinib from TA422

Abbreviations: OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TTD, time to treatment discontinuation
Source: NICE TA422[8]

Using the ROS1 data from PROFILE 1001 (PROFILE 1001 analysis)

For OS, PFS, and TTF, standard parametric curve fitting for data from the PROFILE 1001 trial was conducted to estimate outcomes in the long-term (beyond the end of the trial) for crizotinib. The inverse of the published HRs from PROFILE 1014 and PROFILE 1007 were then applied to estimate long-term PFS and OS for pemetrexed plus platinum therapy (first-line patients) and docetaxel monotherapy (subsequent-line patients), respectively (as described in Section B.3.3.1).

Survival curve fitting was conducted in line with the NICE DSU TSD 14.[101] All standard parametric models were considered and compared. These included exponential, Weibull, log-normal, log-logistic, gompertz and generalised gamma. The fit of the alternative models was assessed by considering:

- visual inspection of fitted curves
- comparisons of AIC and BIC between the model types, and

- the plausibility of long-term extrapolation based on clinical expert opinion, and expected survival from other data sources.

Parametric survival modelling for crizotinib was explored including a covariate for line of treatment within the PROFILE 1001 trial (first-line versus subsequent-lines); allowing for an estimation of OS, PFS, and TTF in first- and subsequent-line crizotinib patients separately. However, as there were only seven ROS1-positive patients receiving crizotinib as a first-line therapy in the PROFILE 1001 trial, with only two events of interest for OS, three events for PFS, and four events for TTF, the data were not considered robust. The KM data for OS, PFS, and TTF, by line, are presented in Figure 21, Figure 22 and Figure 23, respectively.

Figure 21: PROFILE 1001 KM data for OS, by line

Abbreviations: 1L, first-line; 2L+, subsequent-line; KM, Kaplan-Meier; OS, Overall survival.

Figure 22:PROFILE 1001 KM data for PFS, by line

Abbreviations: 1L, first-line; 2L+, subsequent-line; KM, Kaplan-Meier; PFS, Overall survival.

Figure 23: PROFILE 1001 KM data for TTF, by line

Abbreviations: 1L, first-line; 2L+, subsequent-line; KM, Kaplan-Meier; TTF, Overall survival.

An approach estimating the OS, PFS, and TTF of crizotinib in 'all lines' was therefore considered to be more robust. The 'all lines' approach applies standard parametric curves to all ROS1-positive patients in the PROFILE 1001 trial, resulting in an estimation of OS, PFS, and TTF for crizotinib patients across all lines of treatment. This assumes that the efficacy of crizotinib is equal irrespective of whether it is received as a first-line or subsequent-line treatment. The majority of the patients in PROFILE 1001 were second line or later and therefore these patients drive the survival estimates. Therefore, the "all line" approach is considered conservative for treatment-naïve patients, who would be expected to have greater survival estimates.

While an 'all lines approach' is less uncertain than a separate first- and second-line approach with the PROFILE 1001 data, a large amount of uncertainty associated with the parametric survival modelling based on these data persists. This is primarily due to the small sample size of the combined first-line and subsequent-line populations (n=53 patients), an artefact of the rarity of ROS1 NSCLC as a disease. Further to this, the immaturity of the PROFILE 1001 (only 30% of patients had died at completion) contributes to the uncertainty.

Overall survival

Crizotinib (All lines) – PROFILE 1001 analysis

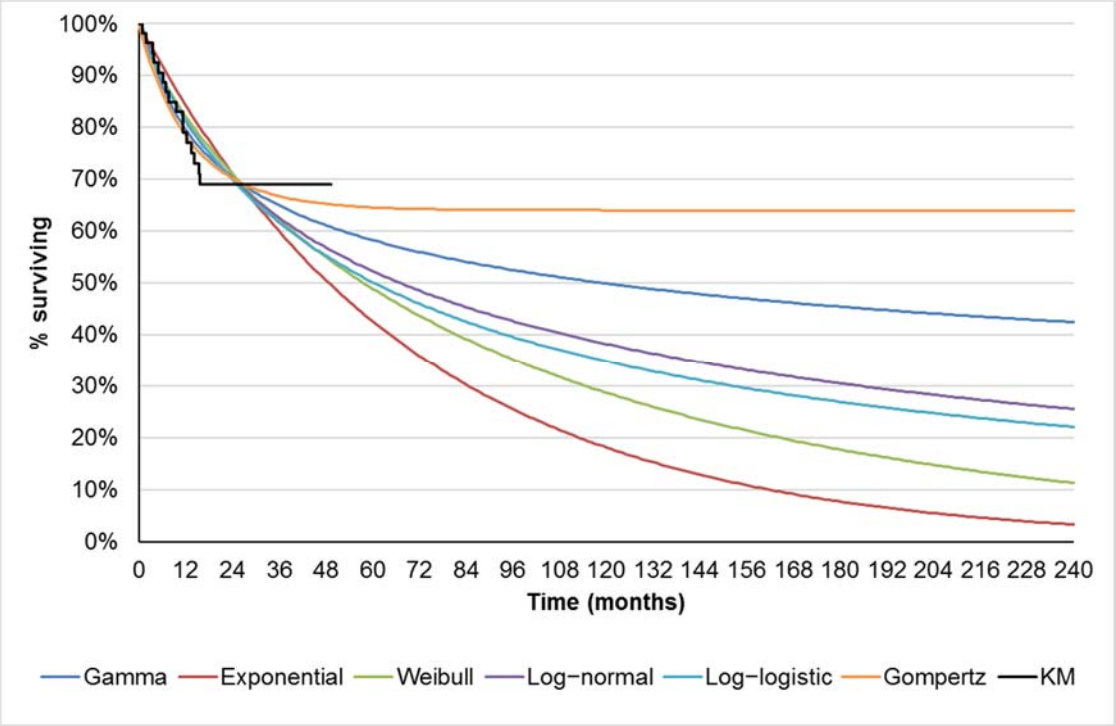
The AIC and BIC for the crizotinib OS curves are provided in Table 32; lower values are preferred for the best statistical fit. The OS curve fits for crizotinib are shown alongside the KM curve in Figure 24.

Table 32: AIC and BIC for OS

Model	AIC	BIC
Exponential	279.41	281.38
Generalised Gamma	278.59	284.50
Gompertz	276.54	280.48
Log-logistic	279.34	283.28
Log-normal	278.01	281.95
Weibull	280.42	284.36

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival

Figure 24: Parametric curve fits to ROS1-positive crizotinib OS data from PROFILE 1001 (all lines)



Abbreviations: KM, Kaplan-Meier; OS, Overall survival

The curves generated were assessed using AIC and BIC, considering the clinical plausibility of the projections and by visual inspection before a suitable curve was selected for the base-case.

For all curves, the AIC and BIC points were within 5 points which indicated that there is no substantial difference between curves in terms of statistical fit to the data. There was however large variation in the long-term OS predicted by the curves. The curves were then examined for clinical plausibility. Only the exponential curve appeared potentially clinically plausible, while all other curves examined predict longer, more unrealistic OS estimates over the long-term than can be substantiated. Clinical experts, at an advisory board held in July 2017, stated that exponential was the most, potentially, clinical plausible, but is still considered to predict optimistic survival estimates. Despite this, visual inspection suggests that the exponential curve does not fit the data well and therefore it could be argued that none of the curves fit to the PROFILE 1001 data to provide a plausible estimation of the OS for crizotinib in ROS1-positive patients. Considering the information and limitations of the three assessment techniques, and that it predicted the most conservative survival estimates, the exponential curve was ultimately selected for the “PROFILE 1001” analysis. The Weibull parametric curve fit was tested in a scenario analysis (B.3.8.3). In summary, the results of the PROFILE 1001 analysis should be treated with caution.

Pemetrexed plus platinum therapy (first-line) – PROFILE 1001 analysis

OS for pemetrexed plus platinum therapy is estimated by applying the inverse of the crossover adjusted HRs for crizotinib versus pemetrexed plus platinum therapy from PROFILE 1014 (which account for potential confounding from patients crossing over from chemotherapy to crizotinib).[73] Since TA406, a later data cut has been made available and so is used in this submission. As discussed in Section B.3.3.4 (base case OS [first-line]), two variations of the RPSFTM method have be conducted; Wilcoxon and Log-rank. Two variations of the RPSFTM method have be

conducted; Wilcoxon and Log-rank. The Wilcoxon method is selected as the preferred option for the PROFILE 1001 analysis as this was the most conservative estimate. The impact of applying alternative method is explored in scenario analysis (Section B.3.8.3). The HRs used in the economic model are reported in Table 33.

Table 33: HRs from PROFILE 1014 used in the PROFILE 1001 analysis

	Crossover Method	
	RPSFTM – Wilcoxon (base case)	**RPSFTM – Log-rank (scenario analysis)**
HR (95% CI)	[redacted]	[redacted]
Inverse HR applied to the crizotinib OS curve (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; RPSFTM, rank-preserving structural failure time models.

Applying the inverse HR from PROFILE 1014 to the crizotinib curves from PROFILE 1001 relies on two key assumptions:

- The relative treatment effect of crizotinib compared to pemetrexed plus platinum therapy in the first-line ALK-positive population can also be applied to the ROS1-positive NSCLC population.
- Applying the HRs to survival curves assumes the hazards remain proportional over time between the two treatment arms; i.e. that the assumption of proportional hazards holds between treatments and between populations. The limitations of this assumption are discussed in B.2.9.2.

Figure 25 displays the exponential curves used to inform the efficacy of crizotinib alongside the curve used to inform the efficacy of pemetrexed plus platinum therapy (based on the application of the inverse HR described above).

Figure 25: PROFILE 1001 analysis - OS crizotinib and pemetrexed plus platinum therapy - Selected curves (Exponential)

Abbreviations: OS, Overall survival

Docetaxel monotherapy (subsequent-line) – PROFILE 1001 analysis

In an alternative analysis using PROFILE 1001 data for crizotinib, docetaxel monotherapy OS is estimated by applying the inverse of the published HR for crizotinib versus pooled chemotherapy (pemetrexed or docetaxel) from PROFILE 1007. As discussed in Section B.3.3.1, the crossover adjusted HR for OS of crizotinib versus docetaxel alone are not available from the PROFILE 1007 analyses, therefore, it is assumed that the crossover-adjusted HR for the pooled chemotherapy arm from PROFILE 1007 is equivalent to docetaxel monotherapy for OS in this base case analysis. Given that patients in PROFILE 1007 performed better on pemetrexed than docetaxel,[48, 71] the use of a combined chemotherapy arm is a conservative assumption as it is likely to overestimate the treatment effect of docetaxel monotherapy on OS and therefore underestimate the relative effect of crizotinib. This assumption was accepted in the previous appraisal for crizotinib in previously treated ALK-positive NSCLC patients (TA422).[8]

There are three RPSFTM crossover methods available for crizotinib versus combined chemotherapy from PROFILE 1007; Wilcoxon, Log-rank and Cox. In this analysis, the RFSFTM – Log-rank HR is applied; which was used in the previous appraisal for ALK-positive crizotinib patients (TA422).[8] The impact of applying alternative HRs is explored in scenario analysis (Section B.3.8.3). The HRs used in the economic model are reported in Table 34.

Table 34: HRs from PROFILE 1007 used in the PROFILE 1001 analysis

	Crossover Method		
	RPSFTM – Log-rank (base case)	RPSFTM – Wilcoxon	RPSFTM – Log-rank (base case)
HR (95% CI)	0.38 (0.04,0.99)	0.40 (0.07,0.97)	0.35 (0.04,0.85)
Inverse HR applied to the crizotinib OS curve (95% CI)	2.61 (1.01, 23.81)	2.49 (1.03, 14.49)	2.84 (1.17, 27.03)

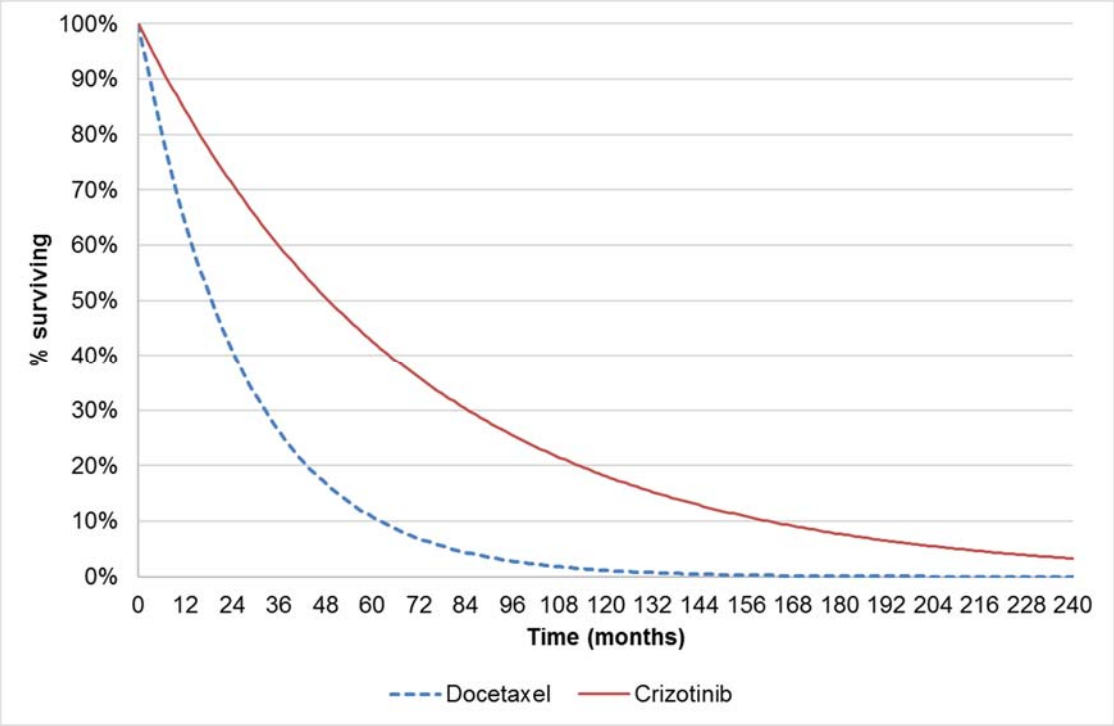
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; RPSFTM, rank-preserving structural failure time models.

Applying HRs from PROFILE 1007 to the crizotinib curves from PROFILE 1001 requires three key assumptions:

- The relative treatment effect of crizotinib compared to pooled chemotherapy in the second-line ALK-positive population can also be applied to the ROS1-positive NSCLC population.
- The relative treatment effect of crizotinib versus pooled chemotherapy (pemetrexed or docetaxel) can be used as a proxy for crizotinib versus docetaxel monotherapy.
- Applying the HR to the crizotinib parametric survival curve estimates that the hazard remains proportional over time between the two treatment arms; i.e. that the assumption of proportional hazards holds between treatments and between populations.

Figure 26 displays the exponential curves used in the base-case economic model to inform the efficacy of crizotinib alongside the curve used to inform the efficacy of pooled chemotherapy which is used as a proxy for docetaxel monotherapy (based on the application of the HR described above). Clinical experts felt that the resulting estimation for docetaxel monotherapy (median OS=48 months) was overly optimistic and that median OS would be expected to be <12 months.

Figure 26: PROFILE 1001 analysis - OS crizotinib and docetaxel monotherapy - selected curves (Exponential)



Abbreviations: OS, overall survival.

Progression-free Survival

Crizotinib (all lines) – PROFILE 1001 analysis

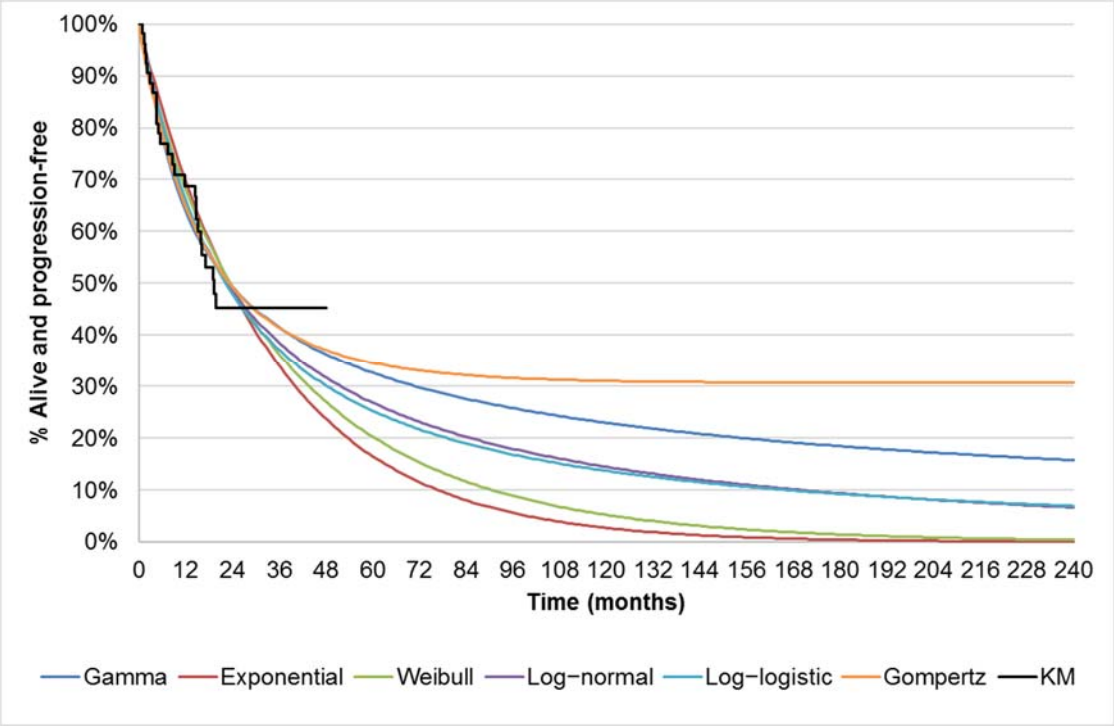
The AIC and BIC for the crizotinib PFS curves are provided in Table 35; lower values are preferred for the best statistical fit. The PFS curve fits for crizotinib are shown in alongside the KM curve in Figure 27.

Table 35: AIC and BIC for PFS

Model	AIC	BIC
Exponential	414.00	415.97
Generalised Gamma	413.51	419.42
Gompertz	413.27	417.21
Log-logistic	413.60	417.54
Log-normal	412.36	416.30
Weibull	415.48	419.42

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, Progression-free survival

Figure 27: Parametric curve fits to crizotinib ROS1-positive PFS data from PROFILE 1001 (all lines)



Abbreviations: KM, Kaplan Meier; PFS, Progression-free survival.

For all curves, the AIC and BIC were within 5 points which indicated that there is no substantial difference between curves in terms of goodness-of-fit to the data. Exponential and Weibull were the most, potentially, clinically plausible long-term outcomes. i.e. all other curves predict longer, more unrealistic PFS estimates over the long-term. The exponential curve was selected for the PROFILE 1001 analysis, as it had a slighter better statistical fit to the data, according to the AIC and BIC estimates, compared to Weibull and was also considered to be the most conservative estimate. Clinical experts, at an advisory board held in July 2017, supported the exponential as the most plausible curve, however still felt that this was optimistic. The Weibull curve is tested as an alternative, plausible parametric curve in scenario analysis.

Pemetrexed plus platinum therapy (first-line) – PROFILE 1001 analysis

PFS for pemetrexed plus platinum therapy is estimated by applying the inverse of the HR for crizotinib versus pemetrexed plus platinum therapy from PROFILE 1014 to the extrapolated PFS curves for crizotinib from PROFILE 1001.[73] The HR used in the economic model are reported in Table 36.

Table 36: HRs for PFS from PROFILE 1014 used in the economic model

	PROFILE 1014 (base case)
HR (95% CI)	0.45 (0.35,0.60)
Inverse HR applied to the crizotinib PFS curve (95% CI)	2.20 (1.68, 2.89)

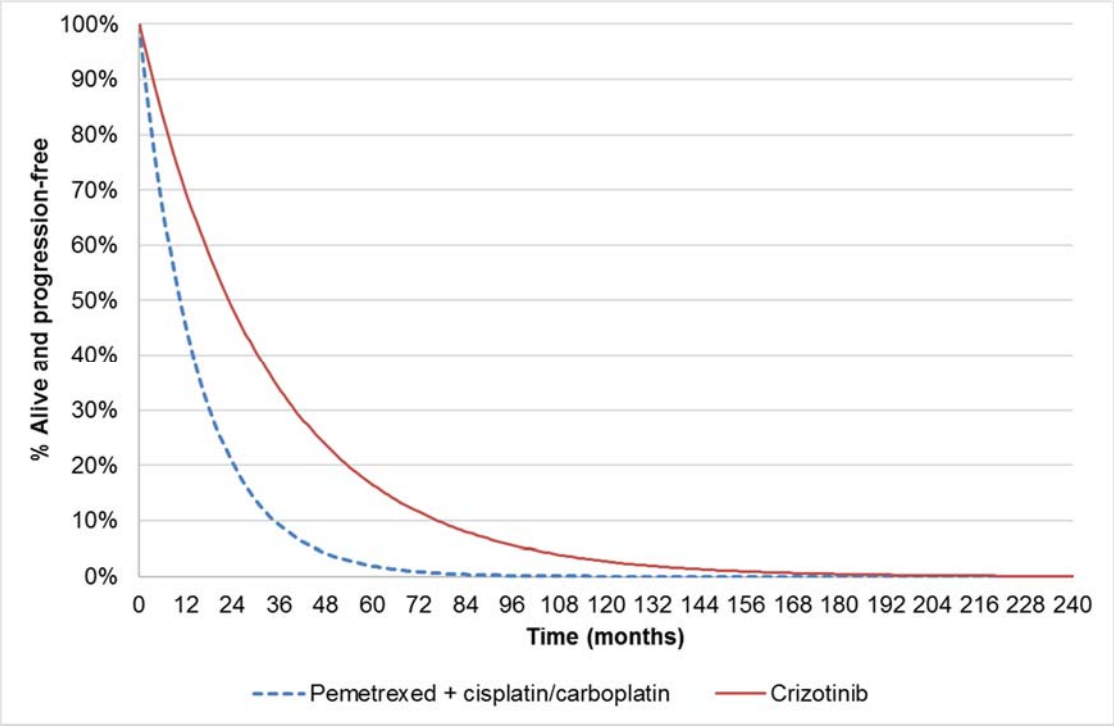
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, Progression-free survival.

Applying HRs from PROFILE 1014 to the crizotinib curves from PROFILE 1001 relies on two key assumptions:

1. The relative treatment effect of crizotinib compared to pemetrexed plus platinum-based chemotherapy in the first-line ALK-positive population can also be applied to the ROS1-positive NSCLC population.
2. Applying the HRs to survival curves estimates the hazards remain proportional over time between the two treatment arms; i.e. that the assumption of proportional hazards holds between treatments and between populations. The limitations of this assumption are discussed in Section B.2.9.2.

Figure 28 displays the exponential curves used in the PROFILE 1001 analysis to inform the efficacy of crizotinib alongside the curve used to inform the efficacy of pemetrexed plus platinum therapy (based on the application of the inverse HR described above).

Figure 28: PROFILE 1001 analysis - PFS crizotinib and pemetrexed plus platinum therapy - Selected curves (Exponential)



Abbreviations: PFS, Progression-free survival.

Docetaxel monotherapy (subsequent-line) – PROFILE 1001 analysis

The PFS curve for docetaxel monotherapy is estimated using the inverse of the HR for crizotinib versus chemotherapy (pemetrexed and docetaxel) from PROFILE 1007 and applied to the extrapolated PFS data for crizotinib from PROFILE 1001. As discussed previously, the crossover adjusted HR for OS are unavailable for docetaxel alone, therefore for consistency, the HR for pooled chemotherapy is also used for docetaxel monotherapy for PFS. Given that patients in PROFILE 1007 performed better on pemetrexed than docetaxel,[48, 71] the use of a pooled chemotherapy arm is a conservative assumption as it is likely to overestimate the treatment effect of docetaxel monotherapy. This assumption was accepted in the previous appraisal for crizotinib in previously treated ALK-positive NSCLC patients (TA422). The inverse of the HR for crizotinib versus docetaxel alone for PFS is applied in scenario analysis (Section B.3.8.3).

Table 37: HRs for PFS from PROFILE 1007 used in the economic model

	PROFILE 1007 (chemotherapy) (base case)	PROFILE 1007 (docetaxel)
HR (95% CI)	0.49 (0.37,0.64)	0.30 (0.21,0.43)
Inverse HR applied to the crizotinib PFS curve (95% CI)	2.05 (1.57, 2.70)	3.33 (2.33, 4.76)

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Applying HRs from PROFILE 1007 to the crizotinib curves from PROFILE 1001 requires three key assumptions:

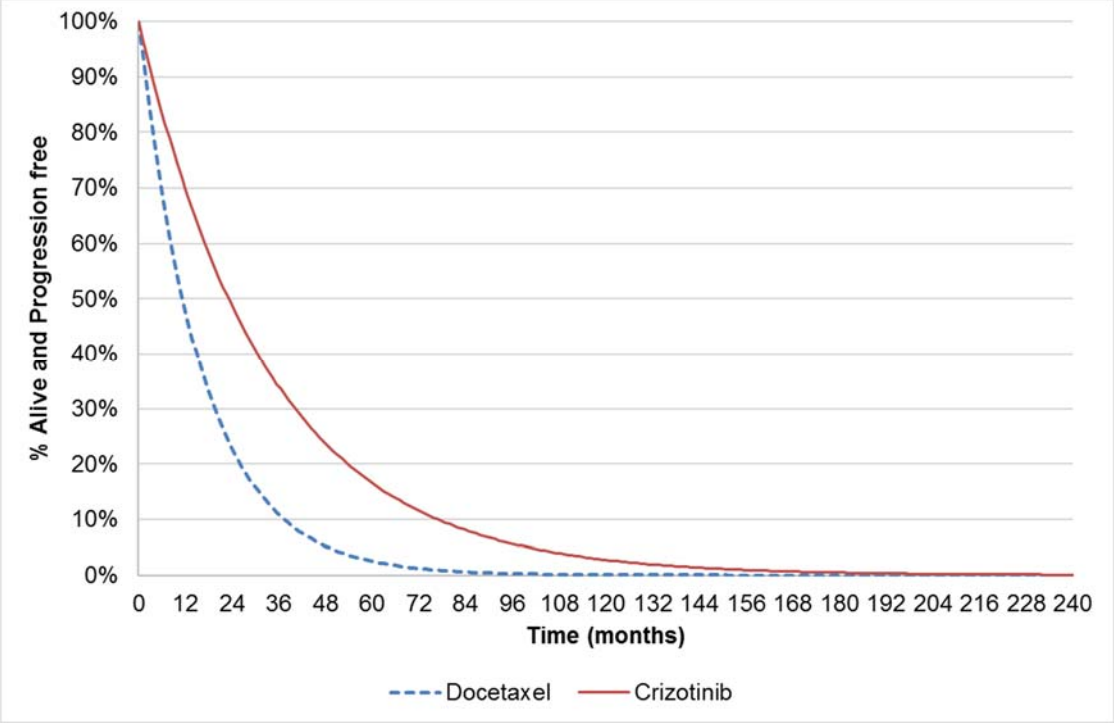
1. The relative treatment effect of crizotinib compared to pooled chemotherapy in the second-line ALK-positive population can also be applied to the ROS1-positive NSCLC population

2. The relative treatment effect of crizotinib versus pooled chemotherapy (pemetrexed or docetaxel) can be used as a proxy for crizotinib versus docetaxel monotherapy

3. Applying the HR to the crizotinib parametric survival curve estimates that the hazard remains proportional over time between the two treatment arms; i.e. that the assumption of proportional hazards holds between treatments and between populations

Figure 29 displays the exponential curve used in the PROFILE 1001 analysis to inform the efficacy of crizotinib alongside the curve used to inform the efficacy of pooled chemotherapy (which is assumed equivalent to docetaxel monotherapy), based on the application of the inverse HR described above.

Figure 29: PROFILE 1001 analysis - PFS crizotinib and pooled chemotherapy (as a proxy for docetaxel monotherapy) - selected curves (Exponential)



Abbreviations: PFS, Progression-free survival.

Time to treatment failure

Crizotinib (all lines) – PROFILE 1001 analysis

In PROFILE 1001, some patients could receive treatment with crizotinib beyond progression. Parametric curves were fitted to TTF data from PROFILE 1001. The AIC and BIC for the crizotinib TTF curves are provided in Table 40; lower values are preferred for the best statistical fit. The TTF curve fits for crizotinib are shown in alongside the KM curve in Figure 30.

Table 38: AIC and BIC for TTF

Model	AIC	BIC
Exponential	464.71	466.68
Generalised Gamma	467.39	473.30
Gompertz	466.03	469.97
Log-logistic	465.89	469.83
Log-normal	465.43	469.37
Weibull	466.37	470.31

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTF, Time to treatment failure.

Figure 30: TTF parametric curve fits to crizotinib ROS1 data from PROFILE 1001 (all lines)

Abbreviations: KM, Kaplan-Meier; TTF, Time to treatment failure.

For all curves, the AIC and BIC were within 5 points which indicated that there is no substantial difference between curves in terms of statistical fit to the data. The exponential and Weibull curves gave the most clinically plausible estimates, i.e. the other parametric curves predict longer, more unrealistic TTF estimates. The exponential curve was selected for the base case as it had a slightly better statistical fit to the data than the Weibull. Alternative parametric curve fits, including the Weibull curve, are considered in scenario analysis. Crizotinib time on treatment

estimated based on the PROFILE 1001 trial data was substantially longer than that estimated based on PROFILE 1014 and PROFILE 1007. This results in substantially increased crizotinib treatment costs in the PROFILE 1001 analysis compared with the base case analysis.

The selected TTF curve alongside PFS and OS for crizotinib is presented in Figure 31.

Figure 31: PROFILE 1001 analysis - PFS, TTF and OS for crizotinib (all lines) based on the assumption for the PROFILE 1001 analysis

Abbreviations: OS, Overall survival; PFS, Progression-free survival; TTF, Time to treatment failure.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Crizotinib received its marketing authorisation for ROS1-positive patients based on evidence from a Phase I, safety, pharmacokinetic and pharmacodynamic study designed for regulatory purposes. Therefore, the clinical trial evidence base does not contain HRQoL data.

Due to the extensive homology and significant similarities in the characteristics of ALK-positive and ROS1-positive NSCLC patients, utility data from PROFILE 1014 and 1007, which were used and accepted in the appraisals for crizotinib in untreated and previously-treated ALK-positive NSCLC (TA406 and TA422) respectively,[5, 8] are assumed to also be appropriate for utility value estimates in the ROS1-positive population.

Utility was collected in PROFILE 1014 and PROFILE 1007 using the EQ-5D questionnaire. The EQ-5D was scored according to its scoring manual. Each dimension of the health state profiles (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) included the proportion of patients reporting “no health problems” “moderate health problems” and “extreme

health problems". A health utility index score was calculated using the standard algorithm provided in the manual.[129]

The EQ-5D is a standardised and validated generic instrument, and the preference elicitation is based on a time trade off algorithm, which corresponds to the NICE reference case.[128]

For PROFILE 1014, to calculate the mean utility for each treatment arm, the EQ-5D scores were calculated using repeated measures mixed-effects analyses to compare overall VAS and index scores between treatments, controlling for baseline (i.e. the models contained a baseline covariate). The resulting calculated figures gave a mean (SE) 'treatment with crizotinib' utility of 0.806 (0.008) and pre-progression utility 0.720 (0.010) for pemetrexed plus platinum therapy. For PROFILE 1007, mean (SD) overall EQ-5D utility index scores on treatment were reported as 0.82 (0.01) for crizotinib and 0.66 (0.04) for docetaxel monotherapy.[121]

The marginally higher mean utility values in second-line versus first-line treatment could be explained by the impact on health from first line therapy. In patients responding to therapy, the outcome of tumour volume shrinkage may translate to an improvement in clinical symptoms and performance status and an increase in utility. If progression is defined according to radiological criteria on first line treatment, then there may not be associated clinical deterioration and an associated fall in health utility. The health utility on commencement of second line therapy may therefore be higher than baseline.

B.3.4.2 Mapping

Mapping was not used within this economic evaluation.

B.3.4.3 Health-related quality-of-life studies

In the base case, the utility values used to inform the economic model were taken from PROFILE 1014 for crizotinib in the first- and subsequent-line models (0.81) and pemetrexed plus platinum therapy (0.72) and from PROFILE 1007 for docetaxel (0.66). A summary of the utility values used in the economic analysis is provided in Table 40.

A total of 33 publications on 22 unique studies were included in the SLR. In the vast majority of studies, the patient population were not from the UK, and did not specify the ROS1 genetic subtype being appraised in this submission. Therefore, the HRQoL data from this submission has been taken from the crizotinib in ALK-positive NSCLC pivotal studies PROFILE 1007 and 1014 as proxy, which have been previously appraised by NICE.[5, 8] Full details of the systematic review for health-related quality-of-life data are located in Appendix H.

B.3.4.4 Adverse reactions

The following section describes the impact of adverse reactions on patient HRQoL. Several studies indicated that adverse events have a detrimental impact on HRQoL. Doyle *et al.* (2008) conducted standard gamble interviews with 101 healthy participants from the Greater London area and used a mixed model analysis to estimate utility values for different combinations of symptoms and disease states.[130] It was demonstrated that symptoms such as pain, cough and dyspnoea have a detrimental effect on HRQoL.

Nafees *et al.* (2008) also performed standard gamble interviews with members of the UK general population.[25] Clinicians described adverse events and the impact that these were likely to have

at different stages of disease. All participants rated 12 health states, including the anchor states (stable and responding disease with no adverse effects, progressive disease), half of the remaining states (a combination of the three anchor states and one or more adverse events), current health and worst health. A mixed model with random effects on the participant level was used for the analysis of the health state valuations to allow the researchers to determine the change in utility associated with the different disease stages with or without toxicities. It was found that all toxicities were associated with a significant decline in utility compared to stable disease with no toxicity (Table 39).

Table 39: Utility values for the anchor health states and utility decrements associated with adverse events – results of the mixed model analysis

Parameter	Utility values	Parameter estimate	SE	Degrees of freedom	t-value	P value
Intercept		0.6532	0.02223	99	29.39	<0.0001
Progressive	0.473	-0.1798	0.02169	99	-8.29	<0.0001
Response	0.673	0.0193	0.006556	99	2.94	0.004
Stable		0	-	-	-	-
Neutropenia		-0.08973	0.01543	99	-5.82	<0.0001
Febrile Neutropenia		-0.09002	0.01633	99	-5.51	<0.0001
Fatigue		-0.07346	0.01849	99	-3.97	0.0001
Diarrhoea		-0.0468	0.01553	99	-3.01	0.0033
Hair Loss		-0.04495	0.01482	99	-3.03	0.0031
Rash		-0.03248	0.01171	99	-2.77	0.0066

Abbreviation: SE: Standard error.
Source: Nafees *et al.* (2008)[25]

Thomas et al. (2011) reported that a CTCAE score of >2 was associated with a greater risk of worsening HRQoL.[131] Whilst, the congress abstract, Billingham *et al*. (2011), reported an association between improvements in pain, cough, haemoptysis, insomnia, appetite loss and emotional functioning, and improvements in measures of global HRQoL.[132]

The utility estimates included in the economic model for the crizotinib, pemetrexed plus platinum therapy and docetaxel arms are taken directly from patients on treatment in the PROFILE 1014 and PROFILE 1007 trials, and hence this HRQoL reporting is expected to already reflect the negative changes in utility incurred through the adverse event profiles of the treatments. The impact of including a disutility due to adverse events could be deemed 'double-counting'. This assumption was accepted in TA406.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The HRQoL of a patient with NSCLC is affected by pain, mobility functionality and symptom burden.[133] The symptoms of lung cancer may include: cough, shortness of breath (dyspnoea), coughing up phlegm with signs of blood in it, an ache or pain when breathing or coughing, loss of appetite, fatigue, weight loss, and recurrent or persistent chest infection.[134] Less common symptoms of lung cancer, which may be associated with more advanced disease, include:

hoarse voice, difficulty swallowing, finger clubbing, swelling in the face caused by superior vena cava obstruction, and swelling due to enlarged lymph nodes.[134]

A study that used standard gamble (SG) techniques to elicit utilities from a UK population with NSCLC (Doyle *et al.* [2008]) found that health state values declined by 0.069 with the addition of pain, 0.050 with dyspnoea, and 0.046 with cough.[130]

Additionally, chemotherapy is associated with severe side effects that have a negative impact on patients' quality of life (alopecia, nausea, neutropenia) despite improvement in progression-free survival or overall survival.[6]

Pre-progression and treatment with crizotinib beyond progression

First-line

Within the cost-effectiveness model, first-line patients are expected to incur different utility values in the progression-free health state dependent on the treatment received. Patients receiving crizotinib are expected to have higher utility than patients receiving pemetrexed plus platinum therapy. This was observed in PROFILE 1014 where utility for patients on crizotinib was higher than those receiving pemetrexed plus platinum therapy (0.81 vs. 0.72).[72] This is likely because crizotinib reduces symptoms of the disease more so than chemotherapy, and is associated with fewer and less severe side effects. This assumption was accepted by the committee in the previous appraisal for crizotinib in previously untreated ALK-positive NSCLC (TA406).[5] Therefore, in all base case analyses, a utility value of 0.81 from PROFILE 1014 is applied to patients receiving crizotinib.[121]

The crizotinib utility value was measured based on the average utility of patients who are receiving treatment with crizotinib in PROFILE 1014. Therefore, it is reflective of patients who are either progression-free whilst receiving, or following, crizotinib treatment, or who are in the progressed disease health state but are receiving crizotinib treatment beyond progression.

The pemetrexed plus platinum therapy utility of 0.72, from PROFILE 1014, was applied for patients who were progression free whilst receiving or following pemetrexed plus platinum treatment only, as there is no treatment beyond progression for pemetrexed plus platinum.

The utility values used in the economic model are summarised in Table 40. Alternative utility values are tested in scenario analysis (Section B.3.8.3).

Subsequent-line

Within the subsequent-line model, patients are again expected to incur different utility values in the progression free health state dependent on the treatment received. The utility value for docetaxel monotherapy is taken from PROFILE 1007 and was used previously in TA406 as the utility for patients receiving docetaxel at second line.[5]

Patients receiving crizotinib are expected to have higher utility than patients receiving docetaxel monotherapy (0.82 vs. 0.66 [PROFILE 1007]). This is because crizotinib reduces symptoms of the disease more so than chemotherapy, and is associated with fewer and less severe side effects.

The utility value for patients who are progression-free whilst receiving crizotinib treatment or who are in the progressed disease health state but are receiving crizotinib beyond progression is taken from PROFILE 1014, as described above. This is because it is unlikely patients who are subsequent-line will have a higher utility (0.82) than those who are first-line (0.81).

The utility values used in the economic model are summarised in Table 40.

Post-progression

First-line

As previously discussed, in PROFILE 1001, some patients could continue treatment with crizotinib beyond progression. These patients continue to have the 'treatment with crizotinib' utility (0.81) observed in PROFILE 1014, for the time for which they are receiving crizotinib. Patients who have not received, or have stopped receiving, treatment beyond progression with crizotinib face a decrease in HRQoL with disease progression.

Following progression, patients who were not or no longer treated with crizotinib and patients who received pemetrexed plus platinum therapy received docetaxel monotherapy as a second-line treatment. This is consistent with the appraisal for crizotinib in untreated ALK-positive patients (TA406). For consistency with the cost-effectiveness model in subsequent-line patients (TA422), the utility for patients receiving subsequent-line treatment with docetaxel monotherapy were also obtained from the PROFILE 1007 trial. The duration of docetaxel monotherapy treatment (hence the duration the related utility value was incurred for) was assumed to be equal to the median PFS of second-line docetaxel treatment from PROFILE 1007.

Following this period, patients received BSC and utility was assumed to be consistent with the utility for progressive disease following second-line treatment from Nafees *et al.* (2008).[25] Nafees *et al.* (2008) used SG techniques to elicit preferences of members of the UK general population for health states associated with metastatic NSCLC.[25, 92] It was shown that progressive disease showed lower utility (0.473) compared with stable disease with no toxicity (0.653).[92] To allow for an incremental comparison between first-line therapies, utility values for the progressed disease health state were assumed to be consistent across treatment arms with patients receiving a set next-line therapy after progressing, thus allowing the differences in modelled results to be reflective of the incremental differences in current-line therapy only.

Subsequent-line

As in the first-line model, patients who continue to receive treatment with crizotinib beyond progression continue to have the 'treatment with crizotinib' utility (0.81) observed in PROFILE 1014, for the time for which they are receiving crizotinib.

Following progression, patients who were not or were no longer treated with crizotinib and patients who received docetaxel monotherapy went on to receive BSC as third-line treatment. For consistency with the first-line model, patients who progressed to BSC also had a utility value of 0.473 in line with that reported in Nafees *et al.* (2008).[25]

Health-related quality of life over time

Within the cost-effectiveness model, HRQoL is assumed to decrease over time as patients experience disease progression, as described above. Within each disease state, a designated

HRQoL is assigned, with disease states in further lines of therapy carrying lower utility scores. This assumption has been made because symptoms are directly related to the progression of a tumour; whilst a patient is in the progression free health state they would not be expected to experience a worsening of symptoms and hence there is no expected change in HRQoL.

Baseline health-related quality of life

No single baseline HRQoL was used within the economic model.

Adjustments to health state utility values

The utility values applied within the economic model are as observed from the PROFILE 1014, PROFILE 1007 trial or from the literature. No adjustments have been made to these values.

Health effects excluded from the cost-effectiveness analysis

The impact of adverse events on utilities has not been considered in either the base case analysis or the PROFILE 1001 analysis, as discussed above. No other health effects were identified that were excluded from the cost-effectiveness analysis.

Summary of utility values chosen for the cost-effectiveness analysis

The utility values used within the economic model base case are shown in Table 40.

Table 40: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission	Justification
First-line model				
Treatment with crizotinib	0.81 (0.01)	(0.79, 0.82)	B.3.4.1	Observed in PROFILE 1014 (measured whilst on treatment) Due to similarity in the characteristics of ROS1-positive and ALK-positive NSCLC patients Utilities from PROFILE 1014 are used as a proxy.
Progression-free: Pemetrexed plus platinum therapy	0.72 (0.01)	(0.70,0.74)	B.3.4.1	Observed in PROFILE 1014 Due to similarity in the characteristics of ROS1-positive and ALK-positive NSCLC patients
Progressed: second-line treatment with docetaxel monotherapy	0.66 (0.02)	(0.61,0.70)	B.3.4.1	Observed in PROFILE 1007 Due to similarity in the characteristics of ROS1-positive and ALK-positive NSCLC patients

State	Utility value: mean (SE)	95% CI	Reference in submission	Justification
Progressed: third-line treatment with BSC	0.47 (0.05)	(0.38,0.56)	B.3.4.5	Nafees *et al.* (2008) provides utility values for third-line treatment of NSCLC As per NICE reference case, if utility data is unavailable from trials, it may be sourced from literature
Subsequent-line model:				
Treatment with crizotinib	0.81 (0.01)	(0.79, 0.82)	B.3.4.1	Observed in PROFILE 1007 (measured whilst on treatment) Due to similarity in the characteristics of ROS1-positive and ALK-positive NSCLC patients Consistent with first-line model
Progression free on docetaxel	0.66 (0.02)	(0.61,0.70)	B.3.4.1	Observed in PROFILE 1007 Due to similarity in the characteristics of ROS1-positive and ALK-positive NSCLC patients Consistent with first-line model
Progressed – third line treatment with BSC	0.47 (0.05)	(0.38,0.56)	B.3.4.5	Nafees *et al.* (2008) provides utility values for third-line treatment of NSCLC As per NICE reference case, if utility data is unavailable from trials, it may be sourced from literature Consistent with first-line model

Abbreviations: CI, confidence interval, NSCLC; Non-small cell lung cancer; SE, standard error.
Source: PROFILE 1014; PROFILE 1007; Nafees et al. (2008)

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Resource use and unit costs for the economic model were based on a number of sources, including: data from PROFILE 1007 and PROFILE 1014, national databases, previous technology appraisals of crizotinib in first- and subsequent-line ALK-positive NSCLC and clinical advice. These are described in more detail below. In the absence of any additional sources of evidence, assumptions were made for cost/resource inputs included in the model where necessary and were validated through discussions with clinicians.

Full details of the systematic review to identify relevant cost and healthcare resource data are located in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

The acquisition costs associated with each treatment are presented in Table 41. Prices were taken from the Monthly Index of Medical Specialities (MIMS) for branded products, and the electronic market information tool (eMit) for generic products.[135, 136]

Table 41: Unit costs of interventions and comparators

Treatment	Unit	Unit cost (list price)	Reference	Dose per cycle (treatment cycle length)	Cost per treatment cycle (cost with PAS)
Crizotinib	60 x 20 0mg tablets	£4,689.00	MIMS, accessed 10/07/2017[135]	2 x 250 mg per day (30 days)	£4,689.00 without PAS [redacted] with PAS
	60 x 250 mg tablets	£4,689.00			
Pemetrexed	100 mg vial	£160.00		500 mg/m^2 = 500*1.73 = 866 mg (21 days)	£1,465.40 with wastage £1,385.40 without wastage
	500 mg vial	£800.00			
Cisplatin	10 mg (10ml vial)	£1.99	eMit, accessed 10/07/2017[136]	75mg/m^2 = 75*1.73 =130 mg (21 days)	£14.64 with wastage £10.97 without wastage
	50 mg (50 ml vial)	£6.48			
	100 mg (100 ml vial)	£8.45			
Carboplatin	50 mg (5 ml vial)	£3.25		Target AUC = 5, dose = 500 mg (21 days)[6]	£23.64 with wastage £22.66 without wastage
	150 mg (15 ml vial)	£7.49			
	450 mg (45 ml vial)	£20.39			
	600 mg (60 ml vial)	£27.89			
Docetaxel	20 mg (1 ml vial)	£3.85		75mg/m^2 = 75*1.80 =135 mg (21 days)	£20.59 with wastage £17.25 without wastage
	80 mg (4 ml vial)	£12.39			
	140 mg (7 ml vial)	£20.62			
	160 mg (8 ml vial)	£20.44			

Abbreviations: CI, confidence interval; eMit, electronic market information tool; MIMS, Monthly Index of Medical Specialities; NSCLC; Non-small cell lung cancer; SE, standard error.

As discussed in Section B.3.2.2, in the pivotal clinical trials, some patients could continue treatment with crizotinib beyond progression, therefore crizotinib is costed in the model using duration of treatment data. Time on treatment data were taken from the final accepted curves

from TA406 (first-line) or TA422 (subsequent-line), in the base case and from PROFILE 1001 in the PROFILE 1001 analysis (Section B.3.3.4). The cost of crizotinib per treatment cycle is applied to the proportion of patients treated with crizotinib based on the extrapolated curve. A simple patient access scheme (PAS) of [redacted], agreed with the Patient Access Scheme Liaison Unit (PASLU) and Department of Health (DH), is applied to the acquisition cost of crizotinib.

For the pemetrexed plus platinum therapy treatment arm, the distribution of patients across the two platinum regimens is assumed to be as per the final accepted proportion from TA406. In PROFILE 1014 patients were eligible to receive either cisplatin (54%) or carboplatin (46%) based on the investigator's choice. The split observed in the study was expected to reflect clinical practice. This is in line with previous appraisal for crizotinib (TA406).[5] In line with TA406, a sensitivity analysis is presented in Section B.3.8.3 that examines the effect on the ICER whereby 75% of patients received pemetrexed plus carboplatin, and 25% received pemetrexed plus cisplatin; the impact was negligible.[5]

Dosing for pemetrexed and cisplatin were based on the body surface area (BSA) reported, and accepted, in TA406 (1.73 m^2) in the base case analysis at first-line, this used the Mosteller equation to calculate the BSA from height and weight data. The BSA for the subsequent-line model was sourced from TA422 (1.80 m^2). Therefore, a BSA of 1.80 m^2 was used to calculate dosing for docetaxel. In the PROFILE 1001 analysis, BSA was based on patients in PROFILE 1001 at all lines (BSA=1.80 m^2). Carboplatin dosing is based on a target area under the curve (AUC) of 5–6. In the absence of data from PROFILE 1001 and PROFILE 1014 to estimate the target AUC, previous NICE submissions were reviewed for their assumptions regarding the dosing of carboplatin. TA181 and TA406 estimated that a target AUC of 5 would result in a dose of 500 mg, and TA347 estimated that a target AUC of 5 would result in a dose of 750 mg.[5, 6, 53] The dose of 500 mg was selected in both base case analyses as a conservative assumption as this results in the lower cost for carboplatin. The model does not assume any impact on efficacy. This approach was accepted in the previous submission for crizotinib in untreated ALK-positive NSCLC.

In line with the previous appraisals for crizotinib in ALK-positive NSCLC (TA406 and TA422), drug wastage has been assumed in the base case, as this is more likely to reflect the use of therapies in practice. Costs for pemetrexed, cisplatin and docetaxel were calculated using the method of moments given the mean BSA. As carboplatin dosing is fixed at 500 mg, its cost was calculated assuming that clinicians will use the optimum combination of vials to reach the target dose, rounding up to the nearest full vial.

In the base case, duration of pemetrexed plus platinum is determined by the final accepted time on treatment curves from TA406.[5] In the PROFILE 1001 analysis presented in this submission, 6 cycles of pemetrexed plus platinum therapy cycles were allowed. This is based on the median number of cycles of pemetrexed plus platinum therapy received in the PROFILE 1014 trial.[72] The SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy.[137] A sensitivity analysis is presented assuming only 4 cycles of pemetrexed plus platinum therapy are given; this sensitivity is conservative as it assumes no change to efficacy.

Docetaxel was assumed to be received for a maximum of 3 model cycles, based on the median progression-free survival of 2.6 months observed in the PROFILE 1007 trial and reported in the manufacturers submission for TA442.

In addition to drug acquisition costs, the cost of administration was considered for crizotinib and comparators (Table 42). Crizotinib is an oral therapy and does not require hospital administration however; crizotinib has a dispensing cost, associated with 12 minutes of hospital pharmacist time.[138] This cost was reported as £14.40 in the PSSRU 2015 however no comparable cost was reported in PSSRU 2016. Therefore, the cost was uplifted to 2015/16 prices (£14.59) using the HCHS index.[139] This cost was the preferred value by the committee in TA406.[5]

Cisplatin-containing regimens were assumed to incur a day case administration appointment, whereas carboplatin-containing regimens and docetaxel monotherapy were assumed to incur an outpatient administration appointment. This is based on assumptions made in previous NICE technology appraisals for pemetrexed and crizotinib (TA406) due to the more complex administration required for cisplatin.[5, 6]

The costs associated with treatment administration are summarised in Table 42.

Table 42: Drug administration costs for crizotinib and comparators

Treatment	Setting	Cost code	Description	Unit cost
Crizotinib	N/A	N/A	Dispensing cost (12 minutes pharmacist time)	£14.59
Pemetrexed plus cisplatin	Day case and regular day/night	SB14Z	Deliver Complex Chemotherapy, including Prolonged In fusional Treatment, at First Attendance	£406.63
Pemetrexed plus carboplatin	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Docetaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30

Abbreviations: N/A, not applicable.

Table 43: First-line unit costs associated with the technology in the economic model (base case)

Items	Crizotinib (CI)	Reference in submission	Pemetrexed plus cisplatin /carboplatin (CI)	Reference in submission
Technology Cost per treatment cycle	£4,689.00 list price [redacted] (with PAS)	B.3.5.1	£1,484.19 (£1,484.05, £1,484.34)	B.3.5.1
Mean cost of technology treatment	[redacted] (median TTF of [redacted] cycles) [redacted] (with PAS; assuming median TTF of [redacted] cycles)	B.3.5.1 B.3.3.4	£8,905.14 (£8,904.30, £8,906.04) (median TTF of 4 model cycles [6 pemetrexed plus platinum cycles])	B.3.5.1
Administration Cost per treatment cycle	£14.59 (£11.58, £17.22)	B.3.5.1	£359.40 (£288.96, £429.84)	B.3.5.1
Mean cost of technology administration	£160.49 (£127.38, £189.42)	B.3.5.1 B.3.3.4	£2,156.40 (£1,733.76, £2,579.04)	B.3.5.1
Monitoring cost	N/A – monitoring is expected to be based on health state rather than treatment	B.3.5.2	N/A – monitoring is costed in the health state	B.3.5.2
ROS1 testing, cost per treated patient	£4,287.92 (£4,047.90, £4,535.44)	B.3.5.4	N/A – no testing costs are required for pemetrexed treatment	N/A
Total	[redacted] ([redacted]) With PAS	N/A	£11,061.54 (£10,638.06, £11,485.08)	N/A

Abbreviation: CI; confidence interval, N/A, not applicable; TTF, time to treatment failure.

Table 44: Subsequent-line unit costs associated with the technology in the economic model (base case)

Items	Crizotinib (CI)	Reference in submission	Docetaxel (CI)	Reference in submission
Technology Cost per treatment cycle	£4,689.00 list price [redacted] (with PAS)	B.3.5.1	£20.59 (£20.13, £21.05)	B.3.5.1
Mean cost of technology treatment	[redacted] (median TTF of [redacted] cycles) [redacted] (with PAS; assuming median TTF of [redacted] cycles)	B.3.5.1 B.3.3.4	£61.77 (£60.40, £63.14) (fixed 3 cycles of docetaxel)	B.3.5.1
Administration Cost per treatment cycle	£14.59 (£11.58, £17.22)	B.3.5.1	£304.30 (£244.65, £363.94)	B.3.5.1
Mean cost of technology administration	£175.08 (£138.96, £206.64)	B.3.5.1 B.3.3.4	£912.89 (£733.95, £1,091.82)	B.3.5.1
Monitoring cost	N/A – monitoring is expected to be based on health state rather than treatment	B.3.5.2	N/A – monitoring is costed in the health state	B.3.5.2
ROS1 testing, cost per treated patient	£4,287.92 (£4,047.90, £4,535.44)	B.3.5.4	N/A – no testing costs are required for docetaxel treatment	N/A
Total	[redacted] ([redacted]) With PAS	N/A	£974.66 (£794.35, £1,154.96)	N/A

Abbreviation: CI; confidence interval, N/A, not applicable; TTF, time to treatment failure.

Table 45: First-line unit costs associated with the technology in the economic model (PROFILE 1001 analysis)

Items	Crizotinib (CI)	Reference in submission	Pemetrexed plus cisplatin /carboplatin (CI)	Reference in submission
Technology Cost per treatment cycle	£4,689.00 list price [redacted] (with PAS)	B.3.5.1	£1,539.07 (£1,538.92, £1,539.21)	B.3.5.1
Mean cost of technology treatment	[redacted] (median TTF of [redacted] cycles) [redacted] (with PAS; assuming median TTF of [redacted] cycles)	B.3.5.1 B.3.3.4	£9,234.42 (£9,233.52, £9,235.26) (6 cycles of pemetrexed)	B.3.5.1
Administration Cost per treatment cycle	£14.59 (£11.58, £17.22)	B.3.5.1	£359.40 (£288.96, £429.84)	B.3.5.1
Mean cost of technology administration	£364.75 (£289.50, £430.50)	B.3.5.1 B.3.3.4	£2,156.40 (£1,733.76, £2,579.04)	B.3.5.1
Monitoring cost	N/A – monitoring is expected to be based on health state rather than treatment	B.3.5.2	N/A – monitoring is costed in the health state	B.3.5.2
ROS1 testing, cost per treated patient	£4,287.92 (£4,047.90, £4,535.44)	B.3.5.4	N/A – no testing costs are required for pemetrexed treatment	N/A
Total	[redacted] ([redacted]) With PAS	N/A	£11,390.82 (£10,967.28, £11,814.30)	N/A

Abbreviation: CI; confidence interval, N/A, not applicable; TTF, time to treatment failure.

Table 46: Subsequent-line unit costs associated with the technology in the economic model (PROFILE 1001 analysis)

Items	Crizotinib (CI)	Reference in submission	Docetaxel (CI)	Reference in submission
Technology Cost per treatment cycle	£4,689.00 list price [redacted] (with PAS)	B.3.5.1	£20.62 (£20.16, £21.08)	B.3.5.1
Mean cost of technology treatment	[redacted] (median TTF of [redacted] cycles) [redacted] (with PAS; assuming median TTF of [redacted] cycles)	B.3.5.1 B.3.3.4	£61.86 (£60.48, £63.24) (3 cycles of docetaxel)	B.3.5.1
Administration Cost per treatment cycle	£14.59 (£11.58, £17.22)	B.3.5.1	£304.30 (£244.65, £363.94)	B.3.5.1
Mean cost of technology administration	£364.75 (£289.50, £430.50)	B.3.5.1 B.3.3.4	£912.89 (£733.95, £1,091.82)	B.3.5.1
Monitoring cost	N/A – monitoring is expected to be based on health state rather than treatment	B.3.5.2	N/A – monitoring is costed in the health state	B.3.5.2
ROS1 testing, cost per treated patient	£4,287.92 (£4,047.90, £4,535.44)	B.3.5.4	N/A – no testing costs are required for docetaxel treatment	N/A
Total	[redacted] ([redacted]) With PAS	N/A	£974.75 (£794.43, £1,155.06)	N/A

Abbreviation: CI; confidence interval, N/A, not applicable; TTF, time to treatment failure.

B.3.5.2 Health-state unit costs and resource use

The details of the health state costs are described in Table 47. Separate costs are presented for:

Patients in the *progression free* health state or the *progressed disease* health state whilst receiving second-line treatment

Patients in the *progressed disease* health state who are receiving third-line treatment with best supportive care

In the previous submission for crizotinib in untreated ALK-positive NSCLC (TA406), clinical experts confirmed that resource utilisation (monitoring costs) are expected to be the same for patients receiving first-line and second-line treatment for NSCLC.[5] Therefore, there is assumed to be no difference in monitoring costs for patients receiving crizotinib (in the first- and subsequent-line models), pemetrexed plus platinum therapy and docetaxel. In the model, resource utilisation assumptions were sourced from TA406 and TA296 (replaced by TA422), which used values from TA162 and TA258.[5, 48, 56, 140] These estimates were viewed as the best available estimates in the literature as they have been informed by expert opinion (four UK clinical experts specialising in the treatment of NSCLC and with experience of using crizotinib), have been subject to review by NICE ERGs and appraisal committees on four previous occasions and, although not all specifically focusing on patients with an ROS1 mutation, are applicable for second-line NSCLC patients receiving treatment with an oral agent.

It is assumed that all patients are assigned a standard cost for palliative care before death. This is assumed to cover hospital care in the 90 days before dying, based on Georghiou and Bardsley (2014).[141] The costs of terminal care included services such as district nurse, nursing and residential care, hospice care, and Marie Curie nursing. This cost was applied as a one-off cost at the point of death. The total cost is estimated to be £7,415 (see Table 48). This is in line with previous NICE appraisal in untreated ALK-positive NSCLC, TA406.[5]

Table 47: List of health states and associated costs in the economic model

Health State	Resources Required	Frequency	Reference (frequency)	Unit cost	Reference
Patients in progression free health state and patients in progressed disease health state receiving second-line treatment	Outpatient Visit	0.75 visits per month	TA406	£151.12	NHS reference costs 2015-16 Outpatient Attendances Data - medical oncology (370) [142] [141] [141] [141] [140] [126]
	GP visit	10% of patients per month		£27.00	PSSRU 2016[139] - Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	20% of patients receive 1 per month		£69.20	NHS reference costs 2015-16 Nurse cancer relate adult face-to-face (N10AF)
	Complete Blood Count	0.75 per month		£3.10	NHS reference costs 2015 -16 Direct Access: Pathology Services (DAPS05)
	Biochemistry	0.75 per month		£1.18	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS04)
	CT scan	30% patients receive 0.75 per month		£132.19	NHS reference costs 2015-16 Direct Access: Pathology Services (RD26Z) [142] [141] [141] [141] [140] [126]
	Chest X-ray	0.75 per month		£30.26	NHS reference costs 2015-16 Direct Access Plain Film (DAPF)
Total cost per month (first- and second-line treatment)				**£185.53**	
Patients in progressed disease health state receiving third-line treatment	Oncologist Visit	1 visit	TA406	£151.12	NHS reference costs 2015-16 Outpatient Attendances Data - medical oncology (370) [142] [141] [141] [141] [140] [126]
	GP visits	28% patients (1 visit)		£27.00	PSSRU 2016[139] - Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	10% patients (1 visit)		£69.20	NHS reference costs 2015-16 Nurse cancer relate adult face-to-face (N10AF)
	Complete Blood Count	All patients, 1 per month		£3.10	NHS reference costs 2015 -16 Direct Access: Pathology Services (DAPS05)

Health State	Resources Required	Frequency	Reference (frequency)	Unit cost	Reference
	Biochemistry	All patients, 1 per month		£1.18	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS04)
	CT scan	5% of patients, 0.75 per month		£132.19	NHS reference costs 2015-16 Direct Access: Pathology Services (RD26Z) [142 141 141 141 140 126]
	X-ray	30% of patients, 0.75 per month		£30.26	NHS reference costs 2015-16 Direct Access Plain Film (DAPF)
Total cost per month, Progressed Disease				**£181.65**	

Abbreviation: BSC, Best supportive care; CT, Computed tomography; GP, General practitioner; NHS, National Health Service; NA, Not applicable; PCT, Primary care trust; PSSRU, Personal Social Services Research Unit.

Table 48: Cost of palliative care

Cost	Unit cost	Reference	2015/16 Uplifted cost (PSSRU 2016)[139]
District nurse	£278	Georghiou and Bardsley (2014)[141]	£298
Nursing and residential care	£1,000		£1,106
Hospice care – inpatient	£550		£590
Hospice care – final 3 months of life	£4,500)		£4,830
Marie Curie nursing service	£550		£590
Total cost			**£7,415**

Abbreviation: PSSRU, Personal Social Services Research Unit.

B.3.5.3 Adverse reaction unit costs and resource use

Consistent with accepted practice for oncology cost-effectiveness models, treatment-related adverse events of Grade 3/4 occurring in ≥5% of patients in PROFILE 1014 for crizotinib and pemetrexed plus platinum therapy (first-line) and PROFILE 1007 for crizotinib and docetaxel monotherapy (subsequent-line) were used in the model. Grade 1 and 2 adverse events would not be expected to require hospitalisation or other costly interventions. Treatment related Grade 3/4 adverse events identified in ≥5% of patients in PROFILE 1014 for crizotinib first-line and pemetrexed plus platinum therapy and/or PROFILE 1007 for crizotinib subsequent-line and docetaxel monotherapy were elevated transaminases, neutropenia, anaemia, leukopenia, thrombocytopenia, and pulmonary embolism. In the PROFILE 1001 analysis, adverse events of Grade 3/4 occurring in ≥5% of patients were taken from PROFILE 1001 for the first- and subsequent-line crizotinib arms. In PROFILE 1001, hypophosphatemia was identified as an additional Grade 3/4 adverse event that occurred in ≥5% of patients.

For adverse events occurring with crizotinib, clinical expert opinion presented in TA442 indicated that neither elevated transaminases or neutropenia caused by crizotinib treatment would require pharmacological intervention. This is because these would be managed by dose reduction, dose interruption, or “watch and wait” monitoring; this is also considered to be relevant to previously-untreated patients receiving first-line crizotinib; in line with the untreated ALK-positive submission (TA406).[5]

Leukopenia is assumed to be managed in the same way as neutropenia (based on TA181), and therefore, no cost is assumed for incidences of leukopenia caused by crizotinib treatment.[6] There were no incidences of anaemia (in first-line patients) or thrombocytopenia caused by crizotinib treatment. To be conservative, there is no alteration the cost of crizotinib to allow for any dose reduction, yet the efficacy estimates from the trial already encompass patients having dose reductions from the side effect profile.

Adverse events related to pemetrexed plus platinum therapy and docetaxel monotherapy treatment have been costed to be consistent with the costings used in previous NICE technology appraisals (TA406 and TA442), but the chemotherapy related neutropenia is assumed managed by dose reduction in line with the assumption for crizotinib.

The proportions of patients experiencing each adverse event are provided in Table 49. The costs associated with treating adverse events are described in Table 50.

Table 49: Proportions of patients experiencing each adverse event

Adverse event	% patients with adverse event				
	Crizotinib, First-line (PROFILE 1014)	Crizotinib, subsequent-line (PROFILE 1007)	Crizotinib, Used in PROFILE 1001 analyses (PROFILE 1001)	Pemetrexed plus platinum therapy (PROFILE 1014)	Docetaxel monotherapy (PROFILE 1007)
Elevated transaminases	14.04%	15.70%	0.00%	2.37%	2.34%
Neutropenia	11.11%	13.37%	9.43%	15.38%	19.30%
Anaemia	0.00%	2.33%	0.00%	8.88%	5.26%
Leukopenia	1.75%	1.16%	0.00%	5.33%	4.68%
Thrombocytopenia	0.00%	0.00%	0.00%	6.51%	0.00%
Hypophosphatemia	0.00%	0.00%	13.21%	0.00%	0.00%
Pulmonary embolism	6.43%	5.23%	0.00%	6.51%	1.75%

Source: Crizotinib: PROFILE 1001; pemetrexed plus platinum therapy: PROFILE 1014; docetaxel monotherapy: PROFILE 1007

Table 50: Cost of treating adverse events

Adverse event	Resource required	Reference	Unit cost	Total cost	Reference for unit cost
Anaemia	1.7 hospitalisation days	Consistent with TA296 (replaced by TA422) and TA406	£335.57 per day	£570.47	NHS reference costs 2015/16; Iron Deficiency Anaemia with CC Score 0-1 SA04L
Thrombo-cytopenia	2.0 hospitalisation days		£303.52 per day	£607.04	NHS reference costs 2015/16; Thrombocytopenia with CC Score 0-1 SA12K
Neutropenia	Managed by dose reduction		-	-	-
Hypophosphatemia	1 hospitalisation day	Assumption	£287.19 per day	£287.19	NHS reference costs 2015/16; Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N
Pulmonary embolism	1 hospitalisation day	Assumption	£26.34 per day	£26.34	NHS reference costs 2015/16; Weighted average of Percutaneous Transluminal, Embolectomy or

Adverse event	Resource required	Reference	Unit cost	Total cost	Reference for unit cost
					Thrombolysis, of Blood Vessel, with CC Score 0-4 (YR23B) and Anticoagulant Services (Total Outpatient Attendances)

Abbreviation: CC, complication and comorbidity; NHS, National Health Service; TA: technology appraisal.The costs associated with treating adverse events are described in Table 50 and the total cost of treating adverse events for crizotinib and each comparator treatment are summarised in Table 51, which are based on the proportion of patients experiencing each adverse event. In line with TA406, these were applied within the model as a one-off cost during the first cycle of the model.

Table 51: Total cost of adverse events, by treatment

Treatment	One-off total cost of treating adverse events
Crizotinib (First-line)	£1.69
Crizotinib (Subsequent-line)	£14.64
Crizotinib (All lines - used in PROFILE 1001 analysis only)	£37.93
Pemetrexed plus platinum therapy	£91.86
Docetaxel monotherapy	£30.49

B.3.5.4 Miscellaneous unit costs and resource use

ROS1 Testing Costs

Introduction of crizotinib to treat ROS1-positive advanced NSCLC patients would require additional resource use for ROS1 testing. Upfront testing was considered in both the base case and PROFILE 1001 analysis, and sequential testing was considered in a scenario analysis. The upfront testing scenario is used for both first and subsequent-line as this was the most expensive, and thus conservative option. Sequential testing is an alternative approach, whereby patients who have previously been tested for ALK- and EGFR-positivity and found to be negative are subsequently tested for ROS1-positivity. In both the base case and scenario analysis, testing was modelled as IHC followed by confirmatory FISH, which is considered to be the most pragmatic strategy by UK clinical experts, and recognised as a robust screening tool. Only acquisition costs of the tests were considered, as the NHS already has the infrastructure in place to perform and analyse IHC and FISH.

Based on the 83% specificity and 100% sensitivity of IHC for ROS1 testing, the false-positive rate and false-negative rate of IHC was calculated to be 17% (100% - 83% = 17%) and 0% (100% - 100% = 0%), respectively.[122] The diagnostic accuracy of FISH for ROS1 testing was assumed to be perfect, as FISH was the reference test in the diagnostic accuracy study providing the specificity of IHC in ROS1 testing.[122]

A ROS1-positive adenocarcinoma incidence of 1.8% was used to calculate the ROS1 incidence in non-squamous patients.[14] Based on the proportion of non-squamous patients in NSCLC lung cancer (67.6%) and the proportion of NSCLC patients who are adenocarcinoma histological

subtype (63.5%), the ROS1 incidence in non-squamous patients was calculated to be 1.69%. The assumption that all ROS1-positive patients are non-squamous is conservative, as the true positive test results would be fewer, leading to lower FISH testing costs, if a small proportion of ROS1-patients are squamous and therefore not identified for confirmatory FISH. The calculated incidence rates of ROS1-, EGFR- and ALK-positive NSCLC amongst non-squamous patients are shown in Table 52.

Table 52: Incidence rates of ROS1-, EGFR- and ALK-positive NSCLC

Patient population	Incidence rate	Incidence rate in non-squamous NSCLC
ROS1 (incidence rate in adenocarcinoma)	1.8%[14]	Assume all ROS1 patients to be adenocarcinoma[1, 13, 15] Proportion of adenocarcinoma patients amongst non-squamous patients = 63.5%[12] / 67.6%[12] ROS1 incidence in non-squamous NSCLC: 1.69%
EGFR (incidence rate in NSCLC)	16.6%	Assume all ROS1 patients to be non-squamous Proportion of non-squamous patients amongst advanced NSCLC patients = 67.6%[12] EGFR incidence: (16.6% x 100%) / 67.6% = 24.5%
ALK (incidence rate in NSCLC)	3.4%[12]	Proportion of non-squamous patients amongst ALK-positive patients = 94%[a73] Proportion of non-squamous patients amongst advanced NSCLC patients = 67.6%[12] ALK incidence: (3.4% x 94%) / 67.6% = 4.7%

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Base case – upfront testing

Clinical experts from the UK have confirmed that the preferred testing strategy would be upfront testing of all advanced non-squamous NSCLC patients for ROS1-positivity, alongside of EGFR and ALK testing. This strategy is preferred due to its optimal use of tissue and faster turnaround time to avoid delays in access to therapy. Therefore, upfront testing has been used as the base case for both lines.

In the base case, the cost of IHC testing was calculated by applying the cost of IHC (£50) to all non-squamous NSCLC patients who would be tested upfront.[143] The cost of confirmatory FISH (£120) was then applied to 1.69% of the patients who are expected to be ROS1-positive (true-positive patients) and to 17% of the patients who are expected to receive a false-positive IHC result. The total testing cost per ROS1-positive patient diagnosed is expected to be £4,287.92 (Table 53).

Table 53: Upfront ROS1 testing cost (base case)

Test	Cost
IHC	Cost per IHC test: £50
FISH	Cost per FISH test: £120[144] Proportion of true-positive and false-positive patients from IHC: (1.69%+17%)= 18.7% Cost of FISH testing: £120*18.7% = £22.44

Total cost of testing	£50 + £22.44 = £72.44
Total cost per ROS1-positive patient diagnosed	ROS1 incidence in non-squamous patients: 1.69% £72.44 / 1.69% = £4,287.92

Abbreviations: FISH, fluorescent in situ hybridisation; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

Scenario analysis – sequential testing

A sequential testing strategy whereby advanced non-squamous NSCLC patients, with confirmed EGFR-negativity and ALK-negativity, are selected for testing, was included as a scenario analysis.

In the scenario analysis, the cost of IHC testing was applied to non-squamous NSCLC patients who are negative for EGFR and ALK mutations. ROS1-positivity, EGFR-positivity and ALK-positivity were assumed to be mutually exclusive. Based on this assumption, the proportion of patients with true positive IHC tests who receive confirmatory FISH is expected to still be 1.69%. In addition, 17% of the EGFR-negative and ALK-negative patients tested for ROS1 by IHC are expected to have false negative IHC results and therefore the patients also undergo confirmatory FISH testing. The total testing cost per ROS1-positive patient diagnosed in the scenario analysis is expected to be £3,068.08. in (Table 54).

Table 54: Sequential (method 1) ROS1 testing cost (scenario)

Test	Cost
IHC	Cost per IHC test: £50 Number of EGFR-negative and ALK-negative non-squamous NSCLC patients: (100% - 24.54% - 4.73%)= 70.73% Cost of IHC testing: £50*47.84% = £35.37
FISH	Cost per FISH test: £120 Number of true-positive and false-positive patients from IHC: (70.73%*17%)+1.69% = 13.72% Cost of FISH testing: £120*13.72% = £16.50
Total cost of testing	£35.37 + £16.50 = £51.84
Total cost per ROS1-positive patient diagnosed	£51.84 / 1.69% = £3,068.08

Abbreviations: FISH, fluorescent in situ hybridisation; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

Subsequent treatment

First Line

Base case – All patients receive docetaxel

Following progression of disease, all patients were expected to receive second-line treatment with docetaxel, based on expert clinical opinion that stated that this is the most reflective of clinical practice since treatment choices are severely limited in this patient population. Second-line treatment with docetaxel was assumed to be received for a maximum of 3 model cycles, based on the median progression-free survival of 2.6 months observed in the PROFILE 1007 trial and reported in the manufacturer's submission for TA296. [145] Following treatment with docetaxel

all patients were assumed to receive best supportive care (consisting of monitoring only) until death. These assumptions are consistent with the approach, and accepted in TA406.

Scenario Analysis – Patients receive "basket of therapies" based on what was received in PROFILE 1014

In PROFILE 1014, many patients went on to receive subsequent therapies after first-line treatment with crizotinib or pemetrexed plus platinum therapy.[98] The proportion of patients receiving each treatment, used in the model, is presented in Table 55. Only treatments received by >1% of patients, are available in the UK were included. Some patients received more than one treatment. Crizotinib was excluded as a subsequent therapy, despite a large proportion of patients on the pemetrexed plus platinum therapy arm receiving it. This is because crossover adjustment provides the estimated survival outcomes for pemetrexed plus platinum therapy patients who did not cross-over to crizotinib and so including costs for this would bias against the pemetrexed plus platinum therapy arm. The unit costs for the included subsequent therapies are reported in

Table 56 and administration costs in Table 57. Data on subsequent therapies in PROFILE 1014 has only become available in the new data cut available for this submission and so this scenario was not previous tested in TA406.

Table 55: Proportion of patients receiving subsequent therapy, by arm.

Agent	Crizotinib	Pemetrexed plus platinum
Pemetrexed	[redacted]	[redacted]
Ceritinib	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]

Table 56: Unit costs of subsequent therapies

Agent	Size	Cost	Source
Pemetrexed	100mg vial	£160.00	MIMS, accessed 19/06/2017
	500mg vial	£800.00	
Ceritinib	150-tab pack (150mg)	£4,923.45	
Cisplatin	10mg (10ml vial)	£1.99	eMit, accessed 10/07/2017
	50mg (50ml vial)	£6.48	
	100mg (100ml vial)	£8.45	
Carboplatin	50mg (5ml vial)	£3.25	
	150mg (15ml vial)	£7.49	
	450mg (45ml vial)	£20.39	
	600mg (60ml vial)	£27.89	

Agent	Size	Cost	Source
Alectinib	224 cap pack (150mg)	£5,032.00	MIMS, accessed 19/06/2017
Docetaxel	20mg (1ml vial)	£3.85	eMit, accessed 10/07/2017
	80mg (4ml vial)	£12.39	
	140 mg (7ml vial)	£20.62	
	160mg (8ml vial)	£20.44	
Gemcitabine	200mg	£2.76	
	1000mg	£7.96	
	2000mg	£20.57	
Paclitaxel	30mg (5ml)	£3.70	
	100mg (16.7ml)	£9.84	
	150mg (25ml)	£12.55	
	300mg (50ml)	£34.33	
Vinorelbine	10mg (1ml)	£43.47	
	50mg (5ml)	£178.96	

Abbreviations: eMit, electronic market information tool; MIMS, Monthly Index of Medical Specialities.

Table 57: Administration costs of subsequent therapies

Treatment	Setting	Cost code	Description	Unit cost
Pemetrexed	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Ceritinib	N/A	N/A	Dispensing cost (12 minutes pharmacist time) (assumed equal to crizotinib)	£14.59
Cisplatin	Day case and regular day/night	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£406.63
Carboplatin	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Alectinib	N/A	N/A	Dispensing cost (12 minutes pharmacist time) (assumed equal to crizotinib)	£14.59
Docetaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Gemcitabine	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Paclitaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Vinorelbine	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30

Abbreviations: N/A, not applicable.

The unit drug and administration costs were used to calculate the total per model cycle cost for each subsequent therapy before being applied to the proportion of patients receiving each subsequent therapy for each treatment arm. The per model drug and administration cycle costs for the basket of therapies are presented in Table 58 and Table 59, respectively. The subsequent therapies were applied in the model for 4 cycles, based on the average time on subsequent therapy in PROFILE 1014.

Table 58: Basket of subsequent therapies - total drug costs per model cycle

Model cycle	Crizotinib arm	Pemetrexed plus platinum arm
1	£2,034.95	£1,148.70
2	£1,607.20	£1,067.57
3	£2,032.83	£1,148.27
4	£1,609.32	£1,068.01

Table 59: Basket of subsequent therapies - total administration costs per model cycle

Model cycle	Crizotinib arm	Pemetrexed plus platinum arm
1	£608.94	£145.24
2	£345.27	£81.03
3	£575.17	£138.24
4	£379.04	£88.03

Subsequent Line

It is assumed that all patients go on to receive best supportive care following subsequent line treatment with either crizotinib or docetaxel.

B.3.6 Summary of base-case analysis inputs

A summary of key model parameters is provided in Table 60. A full summary of model parameters is provided in Appendix L.

Table 60: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Model controls			
Time horizon	20	None	B.3.2.2
Discount rate for costs	3.50%	1.5%-3.5% tested in OWSA, not varied in PSA	B.3.2.2
Discount rate for QALYs	3.50%		B.3.2.2
Discount rate for LYs	0.00%	None	B.3.2.2
Proportion of patients receiving carboplatin in combination with pemetrexed	46.15%	Beta (38.71%, 53.68%)	B.3.2.2
Patient characteristics at baseline			

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
BSA (PROFILE 1001)	1.80	Normal (1.75, 1.85)	B.3.3.1
Height (TA406)	164.08	Normal (163.17, 164.99)	B.3.3.1
Weight (TA406)	65.80	Log normal (12.90, 335.75)	B.3.3.1
BSA (TA422)	1.80	Normal (1.45, 2.15)	B.3.3.1
Treatment costs			
Drug cost: crizotinib 60-tab pack (200mg)	£4,689.00	None	B.3.5.1
Drug cost: crizotinib 60-tab pack (250mg)	£4,689.00	None	B.3.5.1
Drug cost: pemetrexed 100mg	£160.00	None	B.3.5.1
Drug cost: pemetrexed 500mg	£800.00	None	B.3.5.1
Drug cost: carboplatin 50mg (5ml vial)	£3.25	Normal (£3.24, £3.26)	B.3.5.1
Drug cost: carboplatin 150mg (15ml vial)	£7.49	Normal (£7.44, £7.54)	B.3.5.1
Drug cost: carboplatin 450mg (45ml vial)	£20.39	Normal (£20.22, £20.56)	B.3.5.1
Drug cost: carboplatin 600mg (65ml vial)	£27.89	Normal (£27.66, £28.12)	B.3.5.1
Drug cost: cisplatin 10mg (10ml vial)	£1.99	Normal (£1.96, £2.02)	B.3.5.1
Drug cost: cisplatin 50mg (50ml vial)	£6.48	Normal (£6.45, £6.51)	B.3.5.1
Drug cost: cisplatin 100mg (100ml vial)	£8.45	Normal (£8.40, £8.50)	B.3.5.1
Drug cost: docetaxel 20mg (20mg/ml, 1ml Vial)	£3.85	Normal (£3.82, £3.88)	B.3.5.1
Drug cost: docetaxel 80mg (20mg/ml, 4ml Vial)	£12.38	Normal (£12.05, £12.71)	B.3.5.1
Drug cost: docetaxel 140mg (20mg/ml, 7ml Vial)	£20.62	Normal (£20.29, £20.95)	B.3.5.1
Drug cost: docetaxel 160mg (20mg/ml, 8ml Vial)	£20.44	Normal (£19.77, £21.11)	B.3.5.1
Treatment administration costs			
Administration cost: Crizotinib (TA406)	£14.40	Normal (£11.58, £17.22)	B.3.5.1
Administration cost: SB14Z outpatient cost	£304.30	Normal (£244.65, £363.94)	B.3.5.1
Administration cost: SB14Z day case and regular day/night cost	£406.63	Normal (£326.93, £486.33)	B.3.5.1
ROS1 testing costs			
Cost per IHC test	£50.00	Normal (£40.20, £59.80)	B.3.5.4
Cost per FISH test	£120.00	Normal (£96.48, £143.52)	B.3.5.4
ROS1 ICH specificity	83.00%	Beta (63.95%, 95.72%)	B.3.5.4
ROS1 incidence in adenocarcinoma patients	1.80%	Beta (1.46%, 2.17%)	B.3.5.4
Stage III/IV NSCLC patients who are non-squamous histological subtype	67.64%	Beta (53.74%, 80.11%)	B.3.5.4

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Stage III/IV NSCLC patients who are adenocarcinoma histological subtype	63.47	Beta (50.63%, 75.41%)	B.3.5.4
Utilities			
Utility: progression free on crizotinib	0.81	Beta (0.79, 0.85)	B.3.4.5
Utility: progression free on peckish/carb	0.72	Beta (0.70, 0.74)	B.3.4.5
Utility: progressed on docetaxel	0.66	Beta (0.58, 0.74)	B.3.4.5
2nd line utility: progression free on crizotinib	0.81	Beta (0.79, 0.85)	B.3.4.5
2nd line utility: progression free on docetaxel	0.66	Beta (0.58, 0.74)	B.3.4.5
2nd line utility: progressive disease: 3rd line treatment with BSC	0.47	Beta (0.38, 0.56)	B.3.4.5
Survival and progression - 1st line (PROFILE 1001 analysis)			
Crizotinib vs. Pemetrexed+cis/carb for PFS (HR)	0.45	Log normal (0.35, 0.60)	B.3.3.4
Crizotinib vs. Pemetrexed+cis/carb for OS (HR) - Adjusted: Wilcoxon (new data cut)	[redacted]	[redacted]	B.3.3.4
Survival and progression - 2nd line (PROFILE 1001 analysis)			
Crizotinib vs. docetaxel for PFS (HR) - chemotherapy	0.49	Log normal (0.37, 0.64)	B.3.3.4
Crizotinib vs. docetaxel for OS (HR) - Adjusted (chemotherapy): RPSFTM - Log-rank	0.38	Log normal (0.04, 0.99)	B.3.3.4
Curve fit parameters (OS) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter OS: Rate	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (PFS) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter PFS: Rate	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (TTF) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter TTF: Rate	[redacted]	Multinormal distribution	B.3.3.4
Survival and progression - 2nd line (ALK-POSITIVE accepted HR; base case)			
Crizotinib vs. docetaxel for OS (HR) - TA422 ALK-POSITIVE crizotinib	0.49	Log normal (0.37, 0.64)	B.3.3.4
Curve fit parameters (OS) – Exponential - Crizotinib 1L ALK-POSITIVE curve – Adjusted: Wilcoxon (updated PROFILE 1014 data cut) (base case)			
Curve fit parameter OS: Rate - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	B.3.3.4

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter OS: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (OS) - Exponential - Pemetrexed 1L ALK-POSITIVE curve – Adjusted: Wilcoxon (updated PROFILE 1014 data cut) (base case)			
Curve fit parameter OS: Rate - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Ecog=2) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (PFS) – Log-normal - Crizotinib 1L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Mean log-criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: SD log - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (PFS) - Gamma - Pem 1L ALK-POSITIVE curve (base case)			

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter PFS: Mu - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: Sigma - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: Q - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Ecog=2) -pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (TTD) - Exponential - Crizotinib 1L ALK-POSITIVE curve (base case)			
Curve fit parameter TTD: Rate - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (TTD) - Gompertz - Pem 1L ALK-POSITIVE curve (base case)			
Curve fit parameter TTD: Shape -pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: Rate - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	B.3.3.4

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter TTD: covariate (Ecog=2) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (OS) - Exponential - 2L ALK-POSITIVE curve (base case)			
Curve fit parameter OS: Rate	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (PFS) - Weibull - Crizotinib 2L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: ln p	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (PFS) - Log-normal - Crizotinib 2L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: sigma	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (TTD) - Weibull - Crizotinib 2L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: ln p	[redacted]	Multinormal distribution	B.3.3.4

Abbreviation: BSA, body surface area; carb, carboplatin; CI, confidence interval; cis, cisplatin; FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, ImmunoHistoChemistry, LYs, life years; NSCLC, non-small cell lung cancer; OS, overall survival; OWSA, one-way sensitivity analysis; pem + c/c; pemetrexed + cisplatin or carboplatin; PFS, progression free survival; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; RPSFTM, Rank Preserving Structural Failure Time Models; TA, Technology appraisal; TTF, time to treatment failure.

B.3.6.1 Assumptions

A summary of key assumptions is provided in Table 61.

Table 61: Summary of assumptions applied in the economic model

Assumptions	Assumption description	Justification
Time horizon	Lifetime (20 years)	The economic model runs for 20 years to reflect the extrapolated life expectancy of the full crizotinib cohort. The impact of varying time horizon on the results is tested in sensitivity analysis.
Target dose for carboplatin is 500mg	TA181[6] and TA406[5] estimated that a target AUC of 5 would result in a dose of 500mg, and TA347 estimated that a target AUC of 5 would result in a dose of 750 mg. In both base case analyses, the target dose was assumed to be 500mg.	The dose of 500 mg was selected in both base case analyses as a conservative assumption as this results in the lower cost for carboplatin.
Chemotherapy administration setting	Cisplatin-containing regimens were assumed to incur a day case appointment, whereas carboplatin-containing regimens were assumed to incur an outpatient appointment.	This is based on assumptions made in a previous NICE technology appraisal (TA181) for pemetrexed, due to the more complex administration required for cisplatin.[6]
Cisplatin/ carboplatin mix in pemetrexed regimen	The proportion of patients receiving pemetrexed plus cisplatin or pemetrexed plus carboplatin in the PROFILE 1014 trial is reflective of current practice.	The efficacy data for pemetrexed is based on the pooled combination with cisplatin and carboplatin. The proportion with which these two regimens are used in the model (and the resulting impact on average therapy cost) is that which was observed in the PROFILE 1014 trial. A sensitivity analysis is presented in the results whereby proportionate use favours the cheaper carboplatin over cisplatin (25% cisplatin, 75% carboplatin). The pemetrexed survival has been modelled using the pooled pemetrexed treatment arm with pooled efficacy outcomes as the difference in efficacy between cisplatin and carboplatin is assumed negligible.
Number of pemetrexed treatment cycles	The number of pemetrexed treatment cycles is assumed to be 6 (PROFILE 1001 analysis).	This is based on the median number of cycles of pemetrexed plus platinum therapy received in the PROFILE 1014 trial where up to 6 cycles were allowed. A sensitivity analysis is presented assuming 4 cycles in line with expected clinical practice.
Resource utilisation	Resource utilisation is expected to be the same for patients receiving first- and second-line treatment for NSCLC.	This assumption was confirmed by clinical experts in TA406.
Treatment beyond progression	Treatment with crizotinib beyond progression is modelled based on time on treatment curves for crizotinib.	The PROFILE 1001, PROFILE 1007 and PROFILE 1014 trials allowed treatment beyond progression with crizotinib at the investigator's discretion.

Assumptions	Assumption description	Justification
ROS1-testing	The cost of ROS1-testing is applied for the crizotinib arm. The modelled method of testing is IHC followed by confirmatory FISH.	Crizotinib is only licensed for use in ROS1- or ALK-positive patients so the testing cost is not included for standard of care comparators. The modelled method of testing of IHC followed by confirmatory FISH test is derived from ESMO guidelines which state this is a "cost-effective" approach to testing.[62]
Fully stratified survival models	In the base case first-line model, separate survival curves were fitted to the crizotinib and pemetrexed plus platinum therapy arms. These curves were taken from TA406 for PFS and TTF and from an updated data cut of PROFILE 1014 for OS.	This is in line with the committee preferred base case for the survival models from the appraisal for crizotinib in untreated ALK-positive NSCLC (TA406).
Crossover method (base case analysis)	RPSFTM- Wilcoxon was used for crossover adjustment for PROFILE 1014	The Wilcoxon method was selected as it gives the most conservative results of the ones tested
OS curve (base case analysis)	The exponential curve from the updated data cut of PROFILE 1014 was used in the base case for crizotinib and pemetrexed plus platinum therapy.	The exponential curves were selected based on visual inspection and clinical plausibility and AIC/BIC results.
PFS curve (base case analysis)	In the base case, the log-normal and gamma curves (accepted in TA406) were used for crizotinib and pemetrexed, respectively	These are the curve that were accepted by the committee in the appraisal of crizotinib in untreated ALK- positive NSCLC (TA406)
Time on treatment curve (base case analysis)	In the base case, the exponential and gompertz curves (accepted in TA406) were used for crizotinib and pemetrexed, respectively	These are the curve that were accepted by the committee in the appraisal of crizotinib in untreated ALK-positive NSCLC (TA406)
Proportional hazards (PROFILE 1001 analysis)	A proportional treatment effect is assumed for both PFS and OS (applicable for PROFILE 1001 analysis only)	If we do not assume proportional hazards this would lead to fitting separate survival curves to the comparator arms of PROFILE 1014 and 1007 respectively and if these are directly representative of ROS1-positive patients receiving the comparator treatments. We considered that the assumption of proportional hazards was preferable to naively comparing survival curves in the absence of sufficient data to support an MAIC approach.
PFS curve (PROFILE 1001 analysis)	The exponential curve was selected as the base case curve for PFS (applicable for PROFILE 1001 analysis only)	The exponential curve was selected for the base case as it had a similar statistical fit to the observed data compared with other curves (based on the AIC, BIC) and provided a plausible extrapolation; other curves predict longer, more unrealistic PFS times.

Assumptions	Assumption description	Justification
OS curve (PROFILE 1001 analysis)	The exponential curve was selected as the base case curve for OS (applicable for PROFILE 1001 analysis only)	The exponential curve had a similar statistical fit to the observed data compared with other curves (based on the AIC, BIC) and provided the most plausible extrapolation (and other curves predict longer, more unrealistic OS times), and this curve was therefore selected in the PROFILE 1001 analysis
Utility values in *progression-free*	Utility values were assumed to vary by treatment in the *progression-free* health state.	Differences in HRQoL were observed between the treatment arms in the PROFILE 1014 and PROFILE 1007 trial.
No additional quantified disutility due to adverse events	It was assumed that there would be no explicit decrements of disutility associated with adverse events, beyond existing on-treatment EQ-5D utility	The utility estimates included in the economic model for the crizotinib, pemetrexed plus platinum therapy and docetaxel arms are taken directly from patients on treatment in the PROFILE 1014 and PROFILE 1007 trials, and hence this HRQoL reporting is expected to already reflect the negative changes in utility incurred through the adverse event profiles of the treatments. The impact of including a disutility due to adverse events could be deemed 'double-counting'. This assumption was accepted in TA406.
HRQoL is assumed constant over time in each state	It was assumed that HRQoL in each disease state is constant irrespective of time spent in that state, once a patient has transitioned into this states after the first cycle.	Symptoms that impact HRQoL are directly related to the progression of disease, whilst a patient is in the progression free health state they would not be expected to experience a worsening of symptoms and hence there is no expected change in HRQoL.
ALK-positive data is a suitable proxy for ROS-positive	Base case: ALK- positive NSCLC data used as proxy for ROS1-positive patients PROFILE 1001 analysis: published HRs from PROFILE 1014 and PROFILE 1007 used to estimated comparative efficacy versus pemetrexed plus platinum and docetaxel, respectively	ALK-positive and ROS1-positive NSCLC have extensive homology. With the lack of comparative efficacy data in ROS1-positive patients this assumption was consider the next best estimate. Due to the small sample size and uncertainty associated with the PROFILE 1001, in the base case we use OS and PFS curves as proxy for ROS1-positive patients.[8] Clinical experts at an ad board stated that ALK-positive data would be a suitable proxy for ROS1-positive NSCLC.
Pooled chemotherapy is an appropriate proxy for docetaxel monotherapy	As no crossover adjusted HR is available for crizotinib versus docetaxel monotherapy, pooled chemo therapy is used as proxy	This is a conservative assumption as pooled chemotherapy would be expected to have better survival estimates than docetaxel alone. This assumption was made in TA422 and accepted by the committee.[8]

Abbreviation: AIC, Akaike information criterion; ALK, Anaplastic lymphoma kinase; AUC, area under the curve; BIC, Bayesian information criterion; ESMO, European Society for Medical Oncology; EQ-5D, EuroQol five dimensions questionnaire; FISH, fluorescence in situ hybridization; HRQoL, health-related quality of life; IHC, Immunohistochemistry, MAIC, matching adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life years; TA, technology appraisal; TTF, time to treatment failure.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The model results are presented below for both the base case (where ALK-positive curves for crizotinib and comparators from TA406 [alongside an updated data cut for OS from PROFILE 1014] and TA422 were used as a proxy for ROS1-positive NSCLC) and the PROFILE 1001 analysis, where survival curves were fit to OS and PFS in ROS1-positive patients from PROFILE 1001 and ALK-positive HRs were applied to estimate comparative efficacy.

Deterministic results are presented in Section B.3.7.1 whilst sensitivity analysis for both the base case and PROFILE 1001 analysis are presented in Section 0. The results are presented with a [redacted] PAS applied to crizotinib; the results without PAS are reported in Appendix N.

First-line

The deterministic results, with a [redacted] PAS applied to crizotinib, are presented in Table 60 for the base case for the first-line model and in Table 63 for the first-line PROFILE 1001 analysis.

The results show that the base case ICER is [redacted] versus pemetrexed plus platinum therapy. The results indicate that crizotinib is a cost-effective treatment option at a willingness to pay threshold of £50,000 at end of life when it is provided with a PAS. These results are not directly comparable with those from TA406 (crizotinib for the treatment of first-line ALK-positive NSCLC) as an earlier, less mature, data cut of the PROFILE 1014 trial was used in TA406.

Table 62: Base case results: crizotinib with PAS versus pemetrexed plus platinum therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

The ICER produced in the PROFILE 1001 analysis is [redacted] versus pemetrexed plus platinum. The difference between this and the base case ICER of [redacted] is caused by the different survival modelling approaches undertaken. Despite taking a conservative approach in using the PROFILE 1001 first- and second-line data as an 'all lines' approach, (as discussed in section B.3.3.4), extrapolation of the PFS, TTF and OS data from PROFILE 1001 over estimates these outcomes which results in clinically implausible curves. This is due to the small patient numbers and immaturity of the clinical data in this trial. This also explains the large difference seen between the costs and clinical outcomes for the PROFILE 1001 and base case analyses. The base case analysis uses mature OS data from the latest PROFILE 1014 data cut and previously accepted PFS and time on treatment curves from TA406 and so provides more robust and clinically plausible outcomes.

Table 63: PROFILE 1001 analysis: crizotinib with PAS versus pemetrexed plus platinum therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£22,570	2.15	1.29				
Crizotinib	[redacted]	5.75	3.25	[redacted]	3.60	1.95	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Subsequent-line

The subsequent-line deterministic results with a [redacted] PAS for crizotinib are presented in Table 64 for the base case and in Table 65 for the PROFILE 1001 analysis. The results show that the base case ICER is [redacted] versus docetaxel. The results indicate that crizotinib is a cost-effective treatment option at a willingness to pay threshold of £50,000 at end of life when it is provided with a PAS. The results are similar to the final with-PAS ICER of [redacted] which was approved by the committee in previously-treated ALK-positive NSCLC (TA422) because similar data have been used for extrapolation of PFS, OS and time on treatment as were accepted in TA422.

Table 64: Base case results: crizotinib with PAS versus docetaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£11,076	1.39	0.71				
Crizotinib	[redacted]	2.75	1.63	[redacted]	1.36	0.93	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

The results of the PROFILE 1001 analysis produce an ICER of [redacted] versus docetaxel. As discussed in section B.3.3.4, extrapolation of the PFS, TTF and OS data from PROFILE 1001 over estimates these outcomes and results in clinically implausible curves due to the small patient numbers and immaturity of the clinical data in this trial. This explains the large difference seen between the outcomes for the PROFILE 1001 and base case analyses. The total costs of docetaxel in the PROFILE 1001 analysis however remain close to the base case as docetaxel, in line with TA422, is costed based on a fixed number of cycles in both analyses.

Table 65: PROFILE 1001 analysis: crizotinib with PAS versus docetaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£12,706	2.32	1.29				
Crizotinib	[redacted]	5.75	3.24	[redacted]	3.43	1.95	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

10,000 probabilistic iterations were run for first-line crizotinib and pemetrexed plus platinum therapy, and for subsequent-line crizotinib and docetaxel monotherapy and the total costs, life years and QALYs obtained from each simulation were recorded and averaged.

First-line

The incremental results from the first-line probabilistic analyses for the base case are presented in

Table 66 and for the PROFILE 1001 analysis in Table 67. The results show that the probabilistic ICER is [redacted] in the base case analysis versus pemetrexed plus platinum therapy. The results of the probabilistic analysis are similar to the deterministic base case results in the base case analysis (ICERs of [redacted]).

Table 66: Probabilistic results (base case): crizotinib with PAS versus pemetrexed plus platinum therapy (deterministic ICER [redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life year

The probabilistic ICER produced for the PROFILE 1001 analysis is [redacted] versus pemetrexed plus platinum therapy. The results of the probabilistic PROFILE 1001 analysis differ from the deterministic results (ICERs of [redacted]). This is largely due to the uncertainty around the parametric survival curves for crizotinib modelled from the PROFILE 1001 data. As the curves are based upon data from only 53 patients from the PROFILE 1001 trial, there is a large amount of uncertainty surrounding the estimated survival outcomes in the PROFILE 1001 analysis.

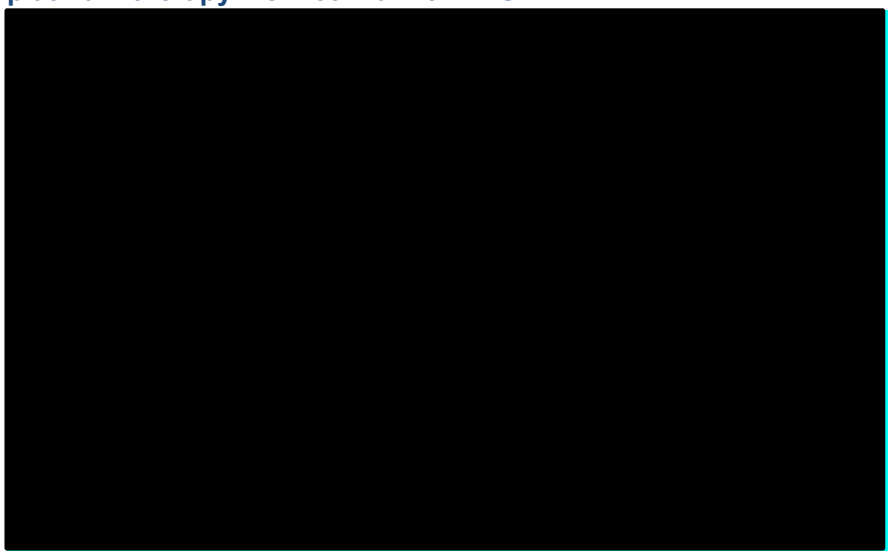
Table 67: Probabilistic results (PROFILE 1001 analysis): crizotinib with PAS versus pemetrexed plus platinum therapy (deterministic ICER [redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£22,913	2.41	1.39				
Crizotinib	[redacted]	5.82	3.34	[redacted]	3.42	1.95	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life year

Figure 32 shows the scatter plot of incremental costs and QALYs for crizotinib vs. pemetrexed plus platinum therapy from 10,000 probabilistic simulations when crizotinib is provided with a PAS in the base case. All iterations show crizotinib results in higher costs and higher QALYs compared with pemetrexed plus platinum therapy.

Figure 32: Base case: Cost-effectiveness plane: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS



Abbreviation: PSA, probabilistic sensitivity analysis; QALYs: quality-adjusted life year.

Figure 33 shows the cost-effectiveness acceptability curve (CEAC) for crizotinib vs. pemetrexed plus platinum therapy on the incremental net monetary benefit (NMB) at a range of willingness to pay thresholds to a maximum of £100,000 per QALY when crizotinib is provided with the PAS, for the base case. The CEAC demonstrates crizotinib has a [redacted] probability of being cost-effective at a willingness to pay threshold of £50,000.

Figure 33: Base case: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS

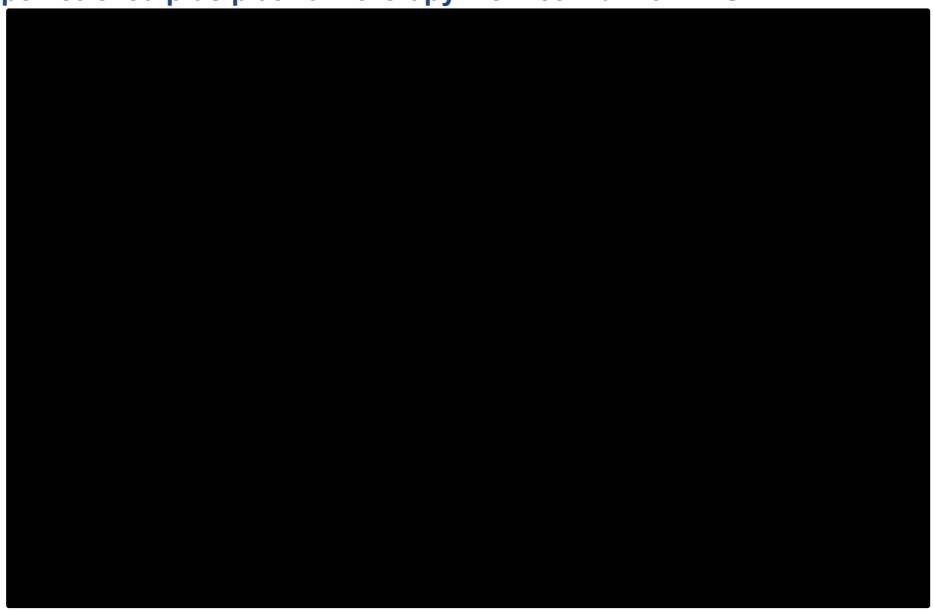
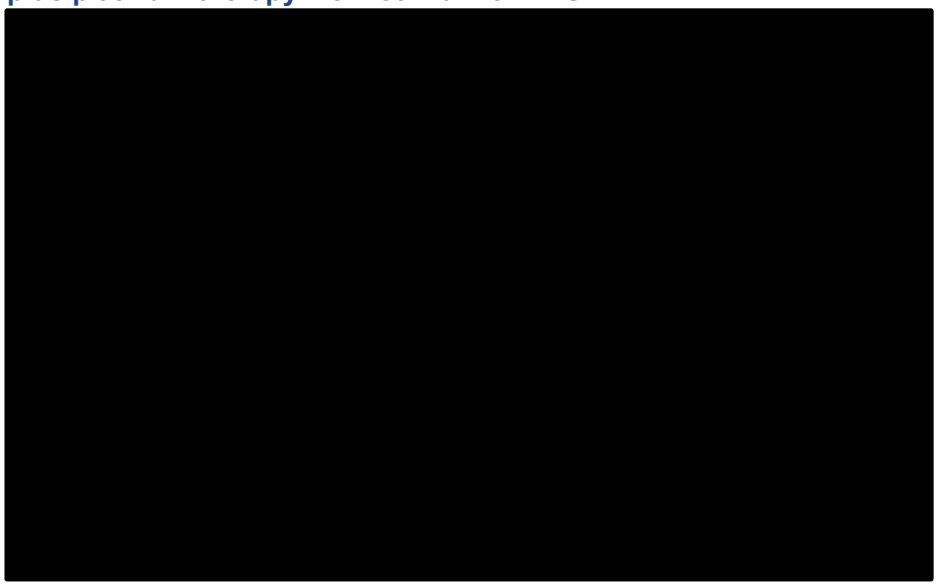


Figure 34 shows the scatter plot of incremental costs and QALYs for crizotinib vs. pemetrexed plus platinum therapy from 10,000 probabilistic simulations when crizotinib is provided with a PAS in the PROFILE 1001 analysis. All iterations show crizotinib results in higher costs and higher QALYs compared with pemetrexed plus platinum therapy, in the PROFILE 1001 analysis.

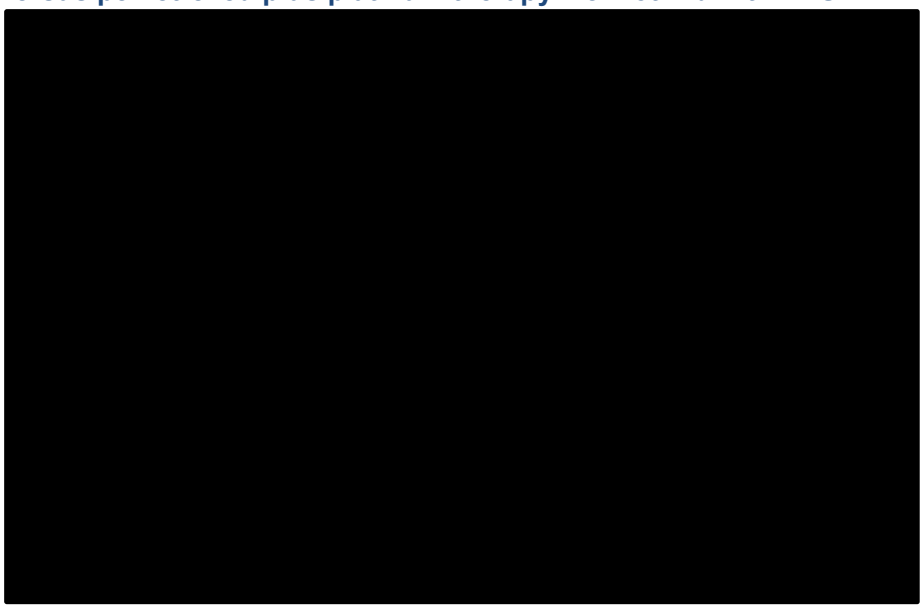
Figure 34: PROFILE 1001 analysis: Cost-effectiveness plane: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS



Abbreviations: PSA, probabilistic sensitivity analysis; QALYs: quality-adjusted life year.

Figure 35 shows the CEAC for crizotinib vs. pemetrexed plus platinum therapy on the incremental NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY when crizotinib is provided with the PAS for the PROFILE 1001 analysis. The CEAC demonstrates crizotinib has an [redacted] chance of being cost-effective versus pemetrexed plus platinum therapy at a willingness to pay threshold of £50,000, when provided with its PAS, for the PROFILE 1001 analysis.

Figure 35: PROFILE 1001 analysis: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS



Subsequent-line

The incremental results from the subsequent-line base case probabilistic analyses are presented in Table 68 for crizotinib with a PAS applied. Table 69 provides the mean probabilistic results for crizotinib (with PAS) versus docetaxel for the PROFILE 1001 analysis. The results indicate the probabilistic ICER produced versus docetaxel is [redacted] in the base case probabilistic analysis. The probabilistic results are very similar to the deterministic base case results in the base case analysis (ICERs of [redacted]).

Table 68: Probabilistic results (base case): crizotinib with PAS versus docetaxel (deterministic ICER [redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£11,092	1.40	0.71				
Crizotinib	[redacted]	2.76	1.63	[redacted]	1.37	0.92	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

In the PROFILE 1001 probabilistic analysis, the ICER is [redacted] versus docetaxel. In the PROFILE 1001 analysis the results of the probabilistic analysis differ from the deterministic (ICERs of [redacted]). This is largely due to the uncertainty around the parametric survival curves for crizotinib modelled from the PROFILE 1001 data. As the curves are based upon data from 53 patients from the PROFILE 1001 trial, there is a large amount of uncertainty surrounding the estimated survival outcomes in the PROFILE 1001 analysis. For example, when the time on treatment curve used in the PROFILE 1001 analysis for crizotinib is sampled at its lower bound values, the resultant curve has a long tail meaning in some iterations patients are being treated with crizotinib for their lifetime, leading to increased total costs in the crizotinib arm. As such, owing to the close structural homology between the ATP-binding kinase domains and the similarity of behaviour between ROS1- and ALK-positive NSCLC, the clinical plausibility of using the more robust PROFILE 1007 data, as presented in the base case of this submission, for the purposes of decision making for the reimbursement of crizotinib in ROS1 NSCLC is well supported.

Table 69: Probabilistic results (PROFILE 1001 analysis): crizotinib with PAS versus docetaxel (deterministic ICER [redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£13,378	2.83	1.47				
Crizotinib	[redacted]	5.82	3.33	[redacted]	2.99	1.86	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Figure 36 shows the scatter plot of incremental costs and QALYs for crizotinib vs. docetaxel from 10,000 probabilistic simulations when crizotinib is provided with the PAS for the base case. All of the iterations demonstrate crizotinib results in higher costs and higher QALYs compared with docetaxel, for the base case.

Figure 36: Base case: Cost-effectiveness plane: crizotinib versus docetaxel – crizotinib with PAS

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs: quality-adjusted life year.

Figure 37 show the CEAC for crizotinib vs. docetaxel on the incremental NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY when crizotinib is provided with its PAS, for the base case. The CEAC demonstrates crizotinib has a [redacted] probability of being cost-effective at a willingness to pay threshold of £50,000, with its PAS applied, for the base case.

Figure 37: Base case: Cost-effectiveness acceptability curve: crizotinib versus docetaxel – crizotinib with PAS

Figure 38 shows the scatter plot of incremental costs and QALYs for crizotinib vs. docetaxel from 10,000 probabilistic simulations when crizotinib is provided with the PAS, for the PROFILE 1001 analysis. The majority of the iterations demonstrate crizotinib results in higher costs and higher QALYs compared with docetaxel, for the PROFILE 1001 analysis.

Figure 38: PROFILE 1001 analysis: Cost-effectiveness plane: crizotinib versus docetaxel – crizotinib with PAS

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs: quality-adjusted life year.

Figure 39 shows the CEAC for crizotinib vs. docetaxel on the incremental NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY when crizotinib is provided with the PAS for the PROFILE 1001 analysis. The CEAC demonstrates crizotinib has a [redacted] probability of being cost-effective at a willingness to pay threshold of £50,000, with its PAS applied, for the PROFILE 1001 analysis.

Figure 39: PROFILE 1001 analysis: Cost-effectiveness acceptability curve: crizotinib versus docetaxel – crizotinib with PAS

B.3.8.2 Deterministic sensitivity analysis

First-line

The tornado diagrams showing the key drivers of cost-effectiveness in the first-line comparison of crizotinib and pemetrexed plus platinum therapy, for the base case, are presented in Figure 40 when crizotinib is provided with its PAS.

The tornado diagram shows that the key drivers of the model are the covariates for the OS curve from the new data cut of PROFILE 1014. It is unsurprising that these parameters are the most influential as they drive the incremental differences in OS between the two treatment arms, and therefore affect the overall QALYs and costs attributed to each treatment arm.

Figure 41 shows the tornado diagram presenting the key drivers of cost-effectiveness in the first-line comparison of crizotinib (with PAS) and pemetrexed plus platinum therapy, for the PROFILE 1001 analysis.

The tornado diagram shows that the key driver of the model is the HR of crizotinib versus pemetrexed plus platinum therapy for OS, in the PROFILE 1001 analysis. It is unsurprising that this parameter is the most influential as it drives the incremental difference in OS between the two treatment arms, and therefore affects the overall QALYs and costs attributed to each treatment arm. The following three key drivers are the statistical parameters for survival modelling (OS, PFS and time on treatment), It is again unsurprising that these parameters are associated with a larger amount of uncertainty as the parametric survival curves are fit to data from only 53 patients.

Figure 40: Base case tornado diagram: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS ([redacted])

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; TSA, Two-stage adjustment A; TTD, time to treatment discontinuation.

Figure 41: PROFILE 1001 analysis tornado diagram: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS (PROFILE 1001 [redacted])

Abbreviations: BSC, best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Subsequent-line

The tornado diagram showing the key drivers of cost-effectiveness in the subsequent-line comparison of crizotinib (with PAS) and docetaxel in the base case are presented in Figure 42.

The tornado diagram shows that the key driver of the model in the base case is the HR of crizotinib versus docetaxel for OS (taken from TA422). It is unsurprising that this parameter is the most influential as it drives the incremental difference in OS between the two treatment arms, and therefore affects the overall QALYs and costs attributed to each treatment arm. The following two key drivers are statistical parameters for survival modelling (OS and PFS). The key drivers seen here are consistent with those observed in TA422.

Figure 43 shows the tornado diagram presenting the key drivers of cost-effectiveness in the subsequent-line comparison of crizotinib (with PAS) and docetaxel in the PROFILE 1001 analysis.

The tornado diagram shows that the key driver of the model for the PROFILE 1001 analysis is the HR of crizotinib versus docetaxel for OS. It is unsurprising that this parameter is the most influential as it drives the incremental difference in OS between the two treatment arms, and therefore affects the overall QALYs and costs attributed to each treatment arm. The following three key drivers are the statistical parameters for survival modelling (OS, PFS and time on treatment), it is again unsurprising that these three parameters are associated with a larger amount of uncertainty as the parametric survival curves are fit to data from only 53 patients.

Figure 42: Base case: Tornado diagram: crizotinib versus docetaxel – crizotinib with PAS (base case [redacted])

Abbreviations: BSC, best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; RPSFTM, Rank Preserving Structural Failure Time Model; TTF, time to treatment failure.

Figure 43: PROFILE 1001 analysis: Tornado diagram: crizotinib versus docetaxel – crizotinib with PAS (PROFILE 1001 [redacted]

Abbreviations: BSC, Best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; RPSFTM, Rank Preserving Structural Failure Time Model; TA, Technology appraisal; TTF, time to treatment failure.

B.3.8.3 Scenario analysis

Base case

The full list of scenarios for the base case is presented in Table 70. The results of the scenario analysis are presented in Table 71 for both the first-line and subsequent-line models for crizotinib with PAS. In the first-line model, no scenarios on the base case analysis led to a result that was not cost-effective at a willingness to pay threshold of £50,000. The only scenario that produced a result which was not cost-effective, with a willingness to pay threshold of £50,000, in the subsequent-line analyses was reducing the time horizon to 5-years. 5 years is not considered to be a sufficiently long time horizon to appropriately capture all costs and benefits associated with treatments for ROS1-positive NSCLC.

Table 70: Scenarios tested on base case

No.	Scenario setting	Base case
1	Time horizon equal to 5 years	20-year time horizon
2	Time horizon equal to 10 years	
3	Time horizon equal to 15 years	
4	Excluding wastage	Include wastage
5	Sequential testing for ROS1	Upfront testing for ROS1
8	25% of patients receive carboplatin	46% of patients receive carboplatin in line with PROFILE 1014
7	Crossover adjustment method: Log-rank	Crossover adjustment method: Wilcoxon
8	Weibull OS models	Exponential OS models
9	Gamma OS models	
10	Log normal OS models	
11	Log logistic OS models	
12	Gompertz OS models	
13	Include a basket of subsequent therapies based on PROFILE 1014	Patients receive docetaxel monotherapy as subsequent treatment

Table 71: Results of scenario analysis on base case - crizotinib with PAS

Scenario No.	Scenario setting	ICER: crizotinib versus pemetrexed plus platinum therapy (first-line)	ICER: crizotinib versus docetaxel monotherapy (subsequent-line)
Base case		[redacted]	[redacted]
1	Time horizon equal to 5 years	[redacted]	[redacted]
2	Time horizon equal to 10 years	[redacted]	[redacted]
3	Time horizon equal to 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	Sequential testing for ROS1	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	N/A
7	Crossover adjustment method: Log-rank	[redacted]	N/A

Scenario No.	Scenario setting	ICER: crizotinib versus pemetrexed plus platinum therapy (first-line)	ICER: crizotinib versus docetaxel monotherapy (subsequent-line)
8	Weibull OS models	[redacted]	N/A
9	Gamma OS models	[redacted]	N/A
10	Log normal OS models	[redacted]	N/A
11	Log logistic OS models	[redacted]	N/A
12	Gompertz OS models	[redacted]	N/A
13	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

Abbreviation: ICER, incremental cost-effectiveness ratio; NA., not applicable; PAS, patient access scheme.

PROFILE 1001 analysis

The full list of scenarios for the PROFILE 1001 analysis is presented in Table 72. The results of the scenario analysis are presented for both the first-line and subsequent-line models with a [redacted] PAS applied to crizotinib in Table 73. In the first-line, only the scenario where the time horizon is reduced to 5 years produces a result that is not cost-effective, with PAS, when considering a willingness to pay threshold of £50,000. In the subsequent-line analysis the scenarios which produce the highest ICERs are reducing the time horizon to 5 or 10 years. However, all other scenarios in the subsequent-line, with PAS, provide results that are cost-effective when considering a willingness to pay threshold of £50,000. 5 or 10 years are not considered to be sufficiently long time horizons to appropriately capture all costs and benefits associated with treatments for ROS1-positive NSCLC.

Table 72: Scenarios tested

No.	Scenario setting	Base case
1	Time horizon equal to 5 years	20-year time horizon
2	Time horizon equal to 10 years	
3	Time horizon equal to 15 years	
4	Excluding wastage	Include wastage
5	Sequential testing for ROS1	Upfront testing for ROS1
6	25% of patients receive carboplatin	46% of patients receive carboplatin in line with PROFILE 1014
7	Maximum of 4 pemetrexed cycles	Maximum 6 pemetrexed cycles
8	Include covariate for line of treatment for crizotinib	Model crizotinib using ‘all lines’ approach
9	Weibull OS model	Exponential OS model
10	Weibull PFS model	Exponential PFS model
11	Weibull TTF model	Exponential TTF model
12	Weibull OS, PFS, TTF model	Exponential models
13	OS HR (1st line): RPSFTM Log-rank (new data cut)	OS HR (1st line): Wilcoxon (new data cut)
14	OS HR (Subsequent-line): RPSFTM Wilcoxon	OS HR (Subsequent-line): RPSFTM Log rank

No.	Scenario setting	Base case
15	OS HR (Subsequent-line): RPSFTM Cox	
16	PFS HR (2nd line): crizotinib versus docetaxel	PFS HR (2nd line): crizotinib versus combined chemotherapy
17	Include a basket of subsequent therapies based on PROFILE 1014	Patients receive docetaxel monotherapy as subsequent treatment

Abbreviations: ERG, evidence review group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RPSFTM, Rank Preserving Structural Failure Time Model; TTF, time to treatment failure

Table 73: Results of scenario analysis - crizotinib with PAS

Scenario No.	Scenario	ICER: crizotinib versus pemetrexed plus platinum therapy (first-line)	ICER: crizotinib versus docetaxel (subsequent-line)
Base case		[redacted]	[redacted]
1	Time horizon equal to 5 years	[redacted]	[redacted]
2	Time horizon equal to 10 years	[redacted]	[redacted]
3	Time horizon equal to 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	Sequential testing for ROS1	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	[redacted]
7	Maximum of 4 pemetrexed cycles	[redacted]	[redacted]
8	Include covariate for line of treatment for crizotinib	[redacted]	[redacted]
9	Weibull OS model	[redacted]	[redacted]
10	Weibull PFS model	[redacted]	[redacted]
11	Weibull TTF model	[redacted]	[redacted]
12	Weibull OS, PFS, TTF model	[redacted]	[redacted]
13	OS HR (1st line): RPSFTM Log-rank (new data cut)	[redacted]	N/A
14	OS HR (Subsequent-line): RPSFTM Wilcoxon	N/A	[redacted]
15	OS HR (Subsequent-line): RPSFTM Cox	N/A	[redacted]
16	PFS HR (Subsequent-line): crizotinib versus docetaxel	N/A	[redacted]
17	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

Abbreviations: ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NA., not applicable; OS, overall survival; PFS, progression-free survival; RPSFTM, Rank Preserving Structural Failure Time Model; TTF, time to treatment failure

B.3.8.4 Summary of sensitivity analyses results

Base case analysis

- The ICER for crizotinib (with PAS) versus pemetrexed plus platinum therapy at first-line is lower than the £50,000 willingness to pay threshold for end of life.

- The ICER for crizotinib (with PAS) versus docetaxel at subsequent-line is lower than the £50,000 willingness to pay threshold for end of life.
- The key drivers of the model were similar to those observed in TA406 and TA422.
- In the first-line base case analysis, crizotinib remained cost-effective (at a £50,000 willingness to pay threshold for end of life) versus pemetrexed plus platinum therapy in all scenarios explored.
- In the subsequent-line base case analysis, crizotinib remained cost-effective versus docetaxel in all scenarios explored except for when the time horizon was reduced to 5 years, when considering a willingness to pay threshold of £50,000.
- In the first- and subsequent-line analyses, the ICER remained relatively consistent across the majority of scenarios explored.
- The results of the subsequent-line analysis ([redacted]) are similar to the final ICER of [redacted], with PAS, approved by the committee in previously-treated ALK-positive NSCLC (TA422).
- The results of the first-line base case analysis are not directly comparable to those approved by the committee in first-line ALK-positive NSCLC (TA406) as an earlier, less mature data cut of the PROFILE 1014 trial was used to inform TA406

PROFILE 1001 analysis.

- The ICER for crizotinib (with PAS) versus pemetrexed plus platinum therapy at first-line is lower than the £50,000 willingness to pay threshold for end of life.
- The ICER for crizotinib versus docetaxel at subsequent-line is lower than the £50,000 willingness to pay threshold for end of life. when provided with a PAS in the PROFILE 1001 analysis.
- There is some uncertainty associated with the parametric survival modelling of 53 patients using immature data in the PSA, in the PROFILE 1001 analysis.
- In the PROFILE 1001 analysis, one-way sensitivity analysis indicated that the key drivers of the model are the HRs attributed to the calculation of OS in the comparator arms and the parameters for fitting survival curves for OS, PFS and TTF.
- In the first-line PROFILE 1001 analysis, crizotinib remained cost-effective versus pemetrexed plus platinum therapy in all but one scenario (reducing the time horizon to 5 years) at a willingness to pay threshold of £50,000 considered for end of life.
- In the subsequent-line PROFILE 1001 analysis, crizotinib remained cost-effective at a willingness to pay threshold of £50,000 considered for end of life in the majority of scenarios tested.
- In the first- and subsequent-line analyses, the ICER remained relatively consistent across most of the scenarios explored.
- Despite taking a conservative approach in using the PROFILE 1001 first- and second-line data as an ‘all lines’ approach, the results of the PROFILE 1001 analysis are not comparable to the base case analysis as the extrapolation of the PFS, TTF and OS data from PROFILE 1001 over estimates these outcomes and results in clinically implausible curves due to the small patient numbers and immaturity of the clinical data in this trial. The base case analysis uses previously accepted OS, PFS and time on treatment curves from ALK-positive NSCLC

submissions which are based on more mature data from a larger sample of patients and so is considered more robust.

B.3.9 Subgroup analysis

No subgroup analyses are presented as part of this submission; other than the pre-specified separate populations in both the base case analysis and PROFILE 1001 analysis (see Section B.3.2.1) consisting of first-line and subsequent-line ROS1-positive NSCLC patients.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Consistency with previous appraisals and trial or literature outcomes

First-line

Previous trial and literature PFS outcomes are presented alongside the model's PFS and OS in Table 109 for crizotinib and Table 110 or pemetrexed plus platinum therapy, in Appendix J.

Base case model results are similar to those from PROFILE 1014. The crizotinib median PFS estimates from the model and PROFILE 1014, which represents a patient population receiving crizotinib in the first line setting, are far lower than observed in PROFILE 1001, which includes patients treated across different lines of therapy. This suggests that using the ALK-positive data as a proxy provides a conservative estimate of PFS outcomes compared to what is seen in ROS1-positive patients. This is supported by recent data collected for patients with ROS1-positive advanced NSCLC treated with crizotinib in the EUCROSS study (N=30, median PFS [redacted]) and from the real-world audit data collected by [redacted], median PFS [redacted]).

In the PROFILE 1001 analysis, the economic model appears to overestimate PFS outcomes for all treatments; this is likely due to the uncertainty surrounding parametric survival modelling using 53 patients and immature survival data. Therefore, as discussed in Section B.3.3.4, given the extensive homology between ROS1-positive and ALK-positive NSCLC patients, and the much larger evidence base available for patients with ALK-positive NSCLC, the survival data estimated in a previous appraisal for crizotinib (TA406) and subsequent new PROFILE 1014 data is considered a more robust source and considered as an appropriate proxy for ROS1-positive patients in the base case.[5, 96] This was supported by 12 clinical experts at an advisory board held in July 2017.[3]

No previous appraisals were identified for patients with ROS1-positive NSCLC, therefore a comparison with prior appraisals in this population is limited. Due to the extensive homology between ROS1- and ALK-positive NSCLC consistent modelling assumptions have been made to those in a previous technology appraisal in previously-treated ALK-positive NSCLC (TA406). The cost-effectiveness results of the first-line base case analysis are however not directly comparable to those approved by the committee in first-line ALK-positive NSCLC (TA406) as an earlier, less mature data cut of the PROFILE 1014 trial was used to inform TA406.

Subsequent-line

Previous trial and literature PFS outcomes are presented alongside the model's PFS and OS in Table 111 for crizotinib and Table 112 for pemetrexed plus platinum based chemotherapy (cisplatin/carboplatin), in Appendix J.

In the PROFILE 1001 analysis, the economic model appears to overestimate outcomes; this is likely due to the uncertainty surrounding parametric survival modelling using 53 patients from PROFILE 1001. Therefore, as discussed in Section B.3.3.4, given the extensive homology between ROS1-positive and ALK-positive NSCLC patients highlighted, and the much larger evidence base available for patients with ALK-positive NSCLC, the survival data estimated in previous appraisals for crizotinib (TA406 and TA422), along with the updated PROFILE 1014 data is considered more robust as a proxy for ROS1-positive patients in the base case. As noted previously, model results for the base case are similar to those from PROFILE 1007. Also, the crizotinib median PFS estimates in the base case and PROFILE 1007, are lower than observed in PROFILE 1001. This suggests that using the ALK-positive data as a proxy provides a conservative estimate of PFS outcomes for crizotinib compared to those observed in ROS1-positive patients.

No previous appraisals were identified for patients with ROS1-positive NSCLC, therefore a comparison with prior appraisals in this population is limited. Due to the extensive homology between ROS1- and ALK-positive NSCLC comparisons have been made to previous technology appraisal in previously-treated ALK-positive NSCLC (TA422). In the base case, where final accepted ALK-POSITIVE survival curves are used as a proxy for ROS1-positive patients, total outcomes are similar showing consistency between appraisals. The resulting ICERs are also very similar [redacted]. The resulting ICERs between the base case ([redacted]) and previously accepted TA422 ([redacted]) are also very similar.

Clinical expert validation

The projected OS curves based on PROFILE 1001 for crizotinib, and the application of published HRs for pemetrexed plus platinum therapy and docetaxel monotherapy (PROFILE 1001 analysis) were shown to clinical experts at an advisory board meeting held in July 2017. In general, the clinicians were in agreement that the ROS1-positive extrapolated curves for crizotinib from PROFILE 1001 were predicting higher survival estimates in the long-term than they would expect to see in clinical practice. The exponential curve was considered to be the only curve with a potentially clinically plausible extrapolation, but this was still considered likely to be overly optimistic. Clinicians further agreed that the resulting median OS estimates for pemetrexed plus platinum therapy ([redacted]) derived from the application of the published ALK-positive HRs to the extrapolated ROS1-postive data for crizotinib was higher than would be expected in clinical practice (<24 months). The resulting estimates for docetaxel using the same methodology were also considered to be higher than those expected in clinical practice. The base analysis provides more clinical plausible and robust predicted outcomes.

Clinical experts also stated ROS1-postive and ALK-positive NSCLC exhibit extensive homology and therefore believe data in ALK-positive patients would be a suitable proxy for ROS1-positive patients.

Quality control

Internal quality control of the economic model was undertaken by the developers of the model on behalf of the manufacturer.

B.3.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

To our knowledge this is the first economic evaluation comparing crizotinib with pemetrexed plus platinum therapy (first-line) and docetaxel monotherapy (subsequent-line) in patients with ROS1-positive NSCLC.

Relevance of the economic evaluation to all patients who could potentially use the technology as identified in the decision problem

This evaluation considers all patients identified in the decision problem.

Generalisability of the analysis

The analysis is relevant and generalisable to clinical practice in the UK. PROFILE 1014 and PROFILE 1007, also used in this submission as proxy for comparative efficacy of crizotinib versus pemetrexed plus platinum and docetaxel monotherapy were deemed generalisable by NICE committee in TA406 and TA422, respectively.[5, 8] Clinical experts confirmed that the data from PROFILE 1001 is aligned with what they would expect to see in UK clinical practice and thus it can be concluded that the data is generalisable to the UK population. The crizotinib median PFS estimates from the model and PROFILE 1014, which represents a patient population receiving crizotinib in the first line setting, are far lower than observed in PROFILE 1001, which includes patients treated across different lines of therapy. This suggests that using the ALK-positive data as a proxy provides a conservative estimate of PFS outcomes compared to what in seen in ROS1-positive patients. This is supported by recent data collected for patients with ROS1-positive advanced NSCLC treated with crizotinib in the EUCROSS study (N=30, median PFS [redacted]) and from the real-world audit data collected by the [redacted]

The model was developed using the NHS Reference costs and costs from previous technology appraisals presented to NICE as a source of cost inputs. These cost inputs are considered most appropriate to model the cost-effectiveness of crizotinib in the UK population, as they have been previously validated by UK clinicians.

In summary, all steps have been taken to produce a robust and conservative estimate of the clinical and cost-effectiveness of crizotinib reflective of UK clinical practice.

Strengths of the economic evaluation

The economic analysis optimises the use of available data in this patient population, while fully accounting for the clinically and economically relevant parameters in the decision problem.

The model structure and key assumptions are based on those previously accepted by NICE in TA406 and TA422, and result in similar outcomes. Uncertainty has been explored extensively in sensitivity analysis and a large number of alternative assumptions have been presented. In the majority of alternative scenarios presented, crizotinib, when provided with the agreed PAS,

remains cost-effective compared with pemetrexed plus cisplatin/carboplatin in the first-line setting and compared with docetaxel in the subsequent-line setting, at a willingness to pay threshold of £50,000 per QALY gained at the end of life.

Limitations of the economic evaluation

A key limitation of the analysis were the small patient numbers and lack of comparator data available in the ROS1-positive NSCLC population. This meant that, due to the extensive homology between ROS1-positive and ALK-positive NSCLC, ALK-positive data were considered an appropriate proxy to estimate comparative efficacy in the absence of comparative evidence in a ROS1-positive population.

Further to this, the immature data, small number of patients and associated events in PROFILE 1001 (even when first-line and subsequent-line data was pooled) lead to extrapolations of PFS and OS that did not exhibit a good fit to the observed data and that may not be clinically plausible in the PROFILE 1001 analyses. Subsequently, when the HRs used to estimate comparative efficacy are applied to these curves, the resulting PFS and OS estimates for the comparator arms are considered clinically implausible, predicting much higher estimates than would be seen in clinical practice based on opinion by 12 experts at a recent advisory board

Due to these limitations, in the base case ALK-positive data has been used as a proxy for ROS1-positive NSCLC. The data and assumptions used have been previously accepted by NICE in TA422 and TA406. These data are based on more mature RCT evidence with much larger sample sizes and so is considered a more robust approach. Further to this, the PFS data and earlier data cut of the OS data has already been appraised and accepted by NICE. The ALK-positive crizotinib median PFS from PROFILE 1014 and PROFILE 1007 are lower than the median PFS observed in the PROFILE 1001 and so using ALK-positive NSCLC data as a proxy for ROS1-positive NSCLC could be considered conservative.

No utilities have been collected within ROS1-positive NSCLC patients and so utilities in ALK-positive NSCLC patients have been used as an estimate for these. Further to this, no trial-based utilities were available for patients receiving third-line best-supportive care. Therefore, utilities from the literature which have been used and accepted in previous technology appraisals for NSCLC were used within the model for best supportive care. This has been previously accepted in TA406 and TA422.

Further analyses

Longer-term, comparative data in a larger number of patients with ROS1-positive NSCLC would improve the robustness of the economic evaluation presented here; however, it is recognised that there are ethical constraints which may prevent future comparative analyses being conducted in a rare patient population such as this.

The ROS1 arm of PROFILE 1001 is closed to recruitment and no further analyses are planned to examine efficacy. There are, however, ongoing clinical studies identified in Section B.2.11 which in the future will add further information regarding the clinical outcomes for patients with ROS1 positive advanced NSCLC.

Conclusions

Crizotinib is an efficacious treatment for patients ROS1-positive NSCLC with a good safety profile and is expected to result in improved outcomes compared with treatment with pemetrexed plus platinum therapy (first-line) and docetaxel monotherapy (subsequent-line).

The base case results, using ALK-positive data as a proxy for ROS1-positive NSCLC, show crizotinib to be cost-effective in both the first-line and subsequent line, when considering a willingness to pay threshold of £50,000 for end of life and a PAS is applied.

The results show that at first-line the base case ICER is [redacted] versus pemetrexed plus platinum therapy. At subsequent-line, the results show that the base case ICER is [redacted] versus docetaxel. This therefore shows crizotinib to be a viable cost-effective use of NHS resources. When considering the PROFILE 1001 analysis, which is based on less robust data, the first-line and subsequent-line ICER still fall below the £50,000 willingness to pay threshold for end of life.

The crizotinib median PFS estimates from the model and PROFILE 1014 and PROFILE 1007, are far lower than observed in PROFILE 1001. Therefore, using the ALK-positive data as a proxy provides a conservative estimate of PFS outcomes compared to what in seen in ROS1-positive patients. Considering this and the previous, recent positive recommendations for ALK-positive patients at first-line and subsequent-lines and the extensive homology between ROS1-positive and ALK-positive NSCLC, this positive recommendation should be extended to the small number of ROS1-postive NSCLC patients with a high unmet need, who currently do not have access to a targeted treatment for this end of life condition.

B.4 References

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Single technology appraisal

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

Dear Pfizer,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 12 September 2017 from Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 19 October 2017**.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Abi Senthinathan, Technical Lead (Abitha.senthinanathan@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.yates@nice.org.uk)

Yours sincerely

Frances Sutcliffe
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **Priority request**. Throughout the clinical effectiveness section of the company submission (CS), the company states that the clinical similarities between ROS1 positive non-small cell lung cancer (NSCLC) and ALK positive NSCLC and the generalisability of ALK positive data to the patient population with ROS1 positive is supported by 12 clinical experts in the UK (CS, pages 9, 11, 16, 85). Please provide an unredacted version of the supporting evidence for these statements as cited in the CS, i.e. Pfizer Ltd. Data on file – clinical advisory board with 12 leading UK clinical experts. 5th July 2017.

A2. **Priority request**. Table 15 (page 57) of the CS provides a comparison of the key outcomes of the PROFILE 1001 study and the PROFILE 1007 and PROFILE 1014 trials. Median progression-free survival (PFS) in the PROFILE 1001 study (19.3 months) is considerably longer than for patients treated with crizotinib in the PROFILE 1007 and PROFILE 1014 (7.7 months and 10.9 months) trials. It is noted that the confidence intervals (CI) associated with the PROFILE 1001 study account for the small study size; however, there is no overlap between the median PFS CIs for the PROFILE 1001 study compared with the CIs for the PROFILE 1007 and PROFILE 1014 trials. Please explain why, despite these important differences in median PFS, the company consider evidence from the patient population with ALK positive NSCLC to be an appropriate proxy for the patient population with ROS1 positive NSCLC.

A3. **Priority request**. Please provide the statistical analysis plans and protocols for the PROFILE 1001 study and the PROFILE 1007 and PROFILE 1014 trials.

A4. **Priority request**. The reference packs supplied with the CS did not include all of the articles referenced in the CS. Please provide the following references: 12, 23, 27-29, 31, 44, 45, 64, 65, 87, 91, 92, 97, 101-105, 108-110, 112-120, 124,129.

A5. Please list the prior systemic treatments received by patients in the PROFILE 1001 study.

A6. Please list the prior systemic treatments received by patients in the PROFILE 1007 trial. Please provide the information for patients in the crizotinib treatment arm and in the comparator treatment arm for patients who received treatment with i) pemetrexed and ii) docetaxel.

A7. On page 85 of the CS, it is stated that: “At the time of the PFS analysis, overall survival (OS) data for PROFILE 1001 was immature with only 30% of patients having

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died at the latest cut-off date…..No follow-up OS analysis is planned." Please explain why no follow-up OS analysis is planned for the PROFILE 1001 study.

A8. Please provide the key results for the PROFILE 1007 trial stratified by type of chemotherapy administered in the comparator treatment arm, i.e., for each of the outcomes presented in Table 15 of the CS, please provide results for patients who received treatment with docetaxel and the results for patients who received treatment with pemetrexed separately.

A9. On page 69 of the CS, it is stated that: "The results of any MAIC analysis would apply to the patient population in the target studies. For the two scenarios described here, MAIC would provide the relative effects (HRs) of crizotinib compared to pemetrexed plus platinum in patients with ALK positive NSCLC at first-line and for crizotinib compared to chemotherapy in patients with ALK positive NSCLC at subsequent-line". Please clarify why it would not be possible to have the population with ROS1 positive NSCLC as the target population, if IPD is available for both patient populations. It should be possible to map from either population to the other.

A10. In Appendix D of the CS, Table 5, reference is made to an updated analysis of the EUCROSS trial: "Updated results: Pfizer data on file (EUCROSS analysis)". Please provide the results of updated analyses of the EUCROSS trial, including Kaplan-Meier (K-M) data for time-to-event outcomes if available.

A11. In the CSR for the PROFILE 1007 trial (e.g. page 40) it is reported that the preliminary CSR contains the final results for PFS, objective response rate (ORR), disease control rate (DCR) at 6 and 12 weeks, duration of response (DR), time to tumour response (TTR), safety, and patient-reported outcomes (PROs). None of these results are reported in the final CSR. Please provide the preliminary CSR for the PROFILE 1007 trial.

Section B: Clarification on cost-effectiveness data

B1. **Priority request.** Please provide the K-M analyses listed in a) to d) and to the following specifications:

- Study data set: PROFILE 1001 study, November 2014 data cut (or more recent if available).
- Format: Please present analysis outputs using the format of the sample table provided (to include censoring times).
- Population: Intention-to-treat (ITT) population including all patients who were lost to follow-up or withdrawing from the trial.

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- Cohort: population with ROS1 positive NSCLC (n=50) and patients with ALK negative NSCLC who were retrospectively identified as having ROS1 positive NSCLC (n=3). Please indicate the patients who were retrospectively determined as having ROS1 positive NSCLC.

a) Time to death from any cause (OS). K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

b) Progression-free survival. K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

c) Post-progression survival. K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

d) Time to study treatment discontinuation. K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

B2. **Priority request.** Please provide the K-M analysis listed in a) to d) to the following specifications:

- Trial data set: PROFILE 1007 trial.
- Population: ITT population including all patients who were lost to follow-up or withdrawing from the trial.
- Format: Please present analysis outputs using the format of the sample table provided (to include censoring times).
- Time to death from any cause (OS) K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

a. Time to death from any cause (OS). K-M analysis for all patients, stratified by treatment.

b. Progression-free survival. K-M analysis for all patients, stratified by treatment.

c. Post-progression survival. K-M analysis for all patients, stratified by treatment.

d. Time to study treatment discontinuation. K-M analysis for all patients, stratified by treatment.

B3. Priority request. Please provide the K-M analyses listed in a) to h) to the following specifications:

- Trial data set: PROFILE 1014 trial.

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- Format: Please present analysis outputs using the format of the sample table provided (to include censoring times).
- Population: ITT population including all patients lost to follow-up or withdrawing from the trial.

a. Time to death from any cause (OS) K-M analysis for all patients, stratified by treatment.

b. Time to death from any cause (OS) K-M analysis for all patients, stratified by treatment and adjusted for crossover using the rank preserved structural failure time (RPSFT) Wilcoxon method.

c. Time to death from any cause (OS) K-M analysis for all patients, stratified by treatment and adjusted for crossover using the RPSFT log rank method.

d. Progression-free survival. K-M analysis for all patients, stratified by treatment.

e. Post-progression survival. K-M analysis for all patients, stratified by treatment.

f. Post-progression survival. K-M analysis for all patients, stratified by treatment and adjusted for crossover using the RPSFT Wilcoxon method.

g. Post-progression survival. K-M analysis for all patients, stratified by treatment and adjusted for crossover using the RPSFT log rank method.

h. Time to study treatment discontinuation. K-M analysis for all patients, stratified by treatment.

B4. Priority request: Utility data. Please complete the table below using EQ-5D data collected during the PROFILE 1007 trial valued using the UK time trade-off (TTO) value set stratified by:

a) All patients.

b) European patients only.

Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Baseline						
Cycle 4						
.						
.						
Exit						

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B5. Priority request: Utility data. Please complete the table below using EQ-5D data collected during the PROFILE 1014 trial valued using the UK TTO value set stratified by:

a) All patients.

b) European patients only.

Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Baseline						
Cycle x						
.						
.						
Exit						

B6. Please explain the process by which patients in the PROFILE 1001 trial were tested for ALK and ROS1 rearrangements. This should include the tests received and the order in which they were given. The purpose of this question is to help our understanding how and why some patients were wrongly identified as having ALK positive NSCLC or ROS1 positive NSCLC and then retrospectively identified as having a different rearrangement.

Section C: Textual clarifications and additional points

C1. Figure 3 in the CS is a waterfall plot to illustrate the objective responses of individual participants recruited to the PROFILE 1001 study. The final 8 bars in Figure 3 all indicate a 100% decrease in tumour size from baseline. However, only 5 of the 8 bars are labelled as a complete response, with the other 3 bars labelled as a partial response. Please clarify.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58

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8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

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Single technology appraisal

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

Dear Pfizer,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 12 September 2017 from Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 19 October 2017**.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted]
Any procedural questions should be addressed to [redacted]

Yours sincerely

[redacted] – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

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A1. **Priority request**. Throughout the clinical effectiveness section of the company submission (CS), the company states that the clinical similarities between ROS1 positive non-small cell lung cancer (NSCLC) and ALK positive NSCLC and the generalisability of ALK positive data to the patient population with ROS1 positive is supported by 12 clinical experts in the UK (CS, pages 9, 11, 16, 85). Please provide an unredacted version of the supporting evidence for these statements as cited in the CS, i.e. Pfizer Ltd. Data on file – clinical advisory board with 12 leading UK clinical experts. 5th July 2017.

As discussed during the clarification call with the ERG and NICE on the 9th October, the advisory board discussions covered many topics, and those not relevant to the current submission have been redacted. The relevant information in the advisory board report relating to ROS1-positive NSCLC is not redacted and therefore available to the ERG.

As part of this response to clarification questions, Pfizer have re-sought expert opinion with a leading targeted mutation specialist clinician, Dr Alastair Greystoke, Senior Lecturer and Honorary Consultant in Medical Oncology University of Newcastle upon Tyne, who confirmed the similarities between ROS1-positive and ALK-positive NSCLC, and the generalisability of ALK-positive data to the ROS1-positive patient population.

A2. **Priority request**. Table 15 (page 57) of the CS provides a comparison of the key outcomes of the PROFILE 1001 study and the PROFILE 1007 and PROFILE 1014 trials. Median progression-free survival (PFS) in the PROFILE 1001 study (19.3 months) is considerably longer than for patients treated with crizotinib in the PROFILE 1007 and PROFILE 1014 (7.7 months and 10.9 months) trials. It is noted that the confidence intervals (CI) associated with the PROFILE 1001 study account for the small study size; however, there is no overlap between the median PFS CIs for the PROFILE 1001 study compared with the CIs for the PROFILE 1007 and PROFILE 1014 trials. Please explain why, despite these important differences in median PFS, the company consider evidence from the patient population with ALK positive NSCLC to be an appropriate proxy for the patient population with ROS1 positive NSCLC.

The analysis with ALK data as a proxy for ROS1-positive patients is presented in the current submission as the base case due to the larger sample size, maturity of data and availability of head-to-head outcomes from PROFILE 1014 and PROFILE 1007 (data from which have previously been accepted in TA406 and TA422).

PROFILE 1001 was not used in the base case as it is a very small single-arm study, with only 53 patients enrolled due to the ultra-orphan nature of the indication, which

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could lead to selection bias. Instead these data are used in an alternative analysis ("PROFILE 1001 analysis"), also presented as part of the submission. Similarly, because of the small sample size and the possible selection bias in PROFILE 1001, a comparison of the CIs from PROFILE 1001 with CIs from other trials may be misleading.

The evidence from the patient population with ALK-positive NSCLC is considered to be an appropriate and relevant proxy for the patient population with ROS1-positive NSCLC, supported by the following:

- The biological and clinical characteristics of ROS1-positive and ALK-positive lung cancer are highly similar (Table 11 in Section B.2.3.3 of CS).
- [redacted] (Table 1).

Table 1: Comparison of probability of survival at 12 months

Outcome	PROFILE 1001 (N=53)	PROFILE 1007 (N=173)	PROFILE 1014 (N=172)
Probability of survival at 12 months for crizotinib-treated patients, % (95% CI)	79.0%(65.3–87.8)	[redacted]	[redacted]

Abbreviations: CI, confidence interval
Source: PROFILE 1001[1, 2]; PROFILE 1007[3]; PROFILE 1014[4]

- Consulted UK clinical expert opinion is unanimous in that ALK and ROS1-positive patients are highly similar in their characteristics and response to treatment.[5] The experts consider the results from the PROFILE 1001 study to be more favourable for crizotinib than what is expected to be seen in clinical practice, due to the inherent uncertainty within this very small study.
- Real world evidence for crizotinib-treated ROS1-positive NSCLC patients in the UK from a national audit coordinated by the [redacted] shows PFS outcomes for these patients to be in line with the PFS seen in the ALK trials: in the real-world audit the preliminary median PFS was [redacted] months for patients treated by pemetrexed plus platinum and maintenance pemetrexed in the first-line setting, and [redacted] months with crizotinib in the first-line and subsequent-line settings. This compares to PFS of 7.7 (6.0–8.8) months and 10.9 (8.3–13.9) months observed in PROFILE 1007 (subsequent-line) and PROFILE 1014 (first-line), respectively.
- The EUCROSS study is a single-arm Pfizer sponsored study of crizotinib in ROS1-positive NSCLC patients (N=30) from Europe, and therefore it provides additional supportive evidence to PROFILE 1001 in the current submission.[6] The

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95% CIs for the PFS for crizotinib from EUCROSS overlap with those from PROFILE 1014:

- EUCROSS median PFS for crizotinib in ROS1 patients (local data): [redacted][6]
- PROFILE 1014 median PFS for crizotinib in first-line ALK patients: 10.9 months (95% CI: 8.3–13.9)

- Based on the similarities between ROS1- and ALK-positive NSCLC, the generalisability of data from ALK-positive patients to ROS1-positive patients has been recognised by the European Medicines Agency (EMA) in their market authorisation of crizotinib.[1]

If it is believed that there are differences in the PFS for ROS1- and ALK-positive NSCLC patients treated with crizotinib, then the results of PROFILE 1001 would indicate that the ALK data is actually a conservative estimate of the clinical benefits of crizotinib. We have provided analyses using ALK data in the base case (as a conservative proxy for the limited ROS1 data) as well as an alternative analysis that uses the available data from ROS1-positive patients from PROFILE 1001. These analyses, by demonstrating that crizotinib is a cost-effective use of resources in both cases, utilise all available data, present a conservative base case, and thus limit the uncertainty in decision making as far as possible.

A3. **Priority request**. Please provide the statistical analysis plans and protocols for the PROFILE 1001 study and the PROFILE 1007 and PROFILE 1014 trials.

Please find these in the Reference Pack submitted with this response.

A4. **Priority request**. The reference packs supplied with the CS did not include all of the articles referenced in the CS. Please provide the following references: 12, 23, 27-29, 31, 44, 45, 64, 65, 87, 91, 92, 97, 101-105, 108-110, 112-120, 124,129.

These references have already been shared with NICE, as part of post-submission communications.

A5. Please list the prior systemic treatments received by patients in the PROFILE 1001 study.

Please find below a summary of the prior pemetrexed use from PROFILE 1001 (Table 2). Please also find academic in confidential data on file on the types of prior systematic treatment received by patients in the PROFILE 1001 study in the Reference Pack submitted with this response.

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Table 2: Prior pemetrexed use in PROFILE 1001

Number (%) of Subjects	PROFILE 1001 (N=53)
Number of subjects with first-line metastatic therapy with pemetrexed	[redacted]
Number of subjects with second-line metastatic therapy with pemetrexed	[redacted]
Number of subjects with any line of metastatic treatments with pemetrexed	[redacted]

Source: PROFILE 1001 Clinical Study Report, Table 14.4.2.2.2.ros

A6. Please list the prior systemic treatments received by patients in the PROFILE 1007 trial. Please provide the information for patients in the crizotinib treatment arm and in the comparator treatment arm for patients who received treatment with i) pemetrexed and ii) docetaxel.

Please find this commercial in confidential data on file in the Reference Pack submitted with this response.

A7. On page 85 of the CS, it is stated that: "At the time of the PFS analysis, overall survival (OS) data for PROFILE 1001 was immature with only 30% of patients having died at the latest cut-off date. No follow-up OS analysis is planned." Please explain why no follow-up OS analysis is planned for the PROFILE 1001 study.

[redacted]

A8. Please provide the key results for the PROFILE 1007 trial stratified by type of chemotherapy administered in the comparator treatment arm, i.e., for each of the outcomes presented in Table 15 of the CS, please provide results for patients who received treatment with docetaxel and the results for patients who received treatment with pemetrexed separately.

Table 3 provides the ORR, PFS and OS analysis results from PROFILE 1007 broken down by whether patients in the chemotherapy arm received pemetrexed or docetaxel. It is important to note that these two groups were not randomised groups within the control arm and therefore the docetaxel-treated patients and the pemetrexed-treated patients cannot be considered to be equivalent. Hence the outcomes stratified by docetaxel and pemetrexed may be biased. For patients randomized to the chemotherapy arm, the first choice for patient treatment was pemetrexed. This was due to the docetaxel restrictive labelling for liver function test elevations and peripheral neuropathy. There were however two exceptions to this rule: patients who have had pemetrexed as part of their prior chemotherapy regimen

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or patients who had received pemetrexed as maintenance therapy were to be assigned to docetaxel.[7]

The ORR of patients treated by docetaxel was lower ([redacted]) than the ORR of patients treated by pemetrexed ([redacted]), suggesting that patients treated with pemetrexed responded better compared to patients treated by docetaxel (Table 3). Patients treated with crizotinib responded significantly better than patients treated by either pemetrexed or docetaxel (Table 3). The results also indicate that patients treated with crizotinib had a significantly longer PFS than those treated with either pemetrexed or docetaxel, with patients treated by docetaxel having a numerically shorter PFS than patients treated by pemetrexed (Table 3).

As patients were not randomised to the choice of chemotherapy within the control arm, crossover adjusted HRs for OS for crizotinib versus docetaxel and for crizotinib versus pemetrexed alone are not available from the mature PROFILE 1007 analyses; therefore, the crossover-adjusted HR for the pooled chemotherapy arm from PROFILE 1007 is used and assumed to be representative of docetaxel monotherapy for OS. Given that patients in PROFILE 1007 performed better on pemetrexed than docetaxel (Table 3),[8] the use of results from the pooled chemotherapy arm in the model is a conservative assumption with respect to crizotinib, as it overestimates the treatment effect of docetaxel monotherapy on OS. This assumption was accepted in the previous appraisal for crizotinib in previously treated ALK-positive NSCLC patients (TA422), where it formed part of the committee's preferred ICER.

Table 3: Overview of key clinical efficacy results from PROFILE 1007

Outcome	Crizotinib (N=172)	Pemetrexed (N=99)	Docetaxel (N=72)
Tumour response, overall response rate (ORR)			
No. of patients (%) [95% CI]	[redacted]	[redacted]	[redacted]
RR, crizotinib vs comparator (95% CI; p-value)		[redacted]	[redacted]
Progression-free survival (PFS)			
PFS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR, crizotinib vs comparato		0.59 (0.43–0.80; p<0.001)[8]	0.30 (0.21–0.43; p<0.001)[8]

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r (95% CI; p-value)			
Overall survival (OS)			
OS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR (not adjusted for crossover), crizotinib vs comparator (95% CI; p-value)		[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival
Source: Data on file, unless stated

A9. On page 69 of the CS, it is stated that: "The results of any MAIC analysis would apply to the patient population in the target studies. For the two scenarios described here, MAIC would provide the relative effects (HRs) of crizotinib compared to pemetrexed plus platinum in patients with ALK positive NSCLC at first-line and for crizotinib compared to chemotherapy in patients with ALK positive NSCLC at subsequent-line". Please clarify why it would not be possible to have the population with ROS1 positive NSCLC as the target population, if IPD is available for both patient populations. It should be possible to map from either population to the other.

In principle, MAICs could be constructed as a comparison of individual patient data (IPD) for pemetrexed plus platinum in ALK-positive patients versus crizotinib treated ROS1-positive patients and similarly for chemotherapy compared to crizotinib. This would indeed give a result that applies to the ROS1 population in the PROFILE 1001 study. However, this would not overcome the inherent limitations of a MAIC given these data. MAICs assume that all known effect modifiers and prognostic variables are known and were included in the matching (NICE DSU TSD 18).

Since IPD were available from all three studies, we did consider the possibility of using covariate adjusted regression models to estimate the clinical endpoints from the IPD. However, this analysis would still be limited by the small sample size in the PROFILE 1001 study; the results would be driven primarily by the larger PROFILE 1014 and 1007 data sets. Only a small number of variables could be included in the model due to the limited patient numbers in the PROFILE 1001 study (N=53) and therefore the results would still be subject to confounding by those variables not included in the model.

As stated on page 69 of the CS:

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"*Estimates of these same hazard ratios could be obtained directly from the respective RCTs in ALK-positive patients (PROFILE 1014 and PROFILE 1007). Given the structural similarities between the ALK and ROS1 rearrangements and the comparable patients characteristics between ALK-positive and ROS1-positive NSCLC patients (as discussed in Section B.1.3.1), we preferred to use these HRs directly rather than attempt to estimate the same result based on complex methods with limited data*."

A10. In Appendix D of the CS, Table 5, reference is made to an updated analysis of the EUCROSS trial: "Updated results: Pfizer data on file (EUCROSS analysis)". Please provide the results of updated analyses of the EUCROSS trial, including Kaplan-Meier (K-M) data for time-to-event outcomes if available.

The EUCROSS study is a single-arm Pfizer sponsored study of crizotinib in ROS1-positive NSCLC patients (N=30) from Europe, and therefore it provides additional supportive evidence to PROFILE 1001 in the current submission. The updated results of the EUCROSS study were not published at the time of the SLR. Nevertheless, the results from EUCROSS study, which became available after the SLR, were included in the submission due to its relevance to the UK population, as stated in the text above Table 5 in Appendix D:

"With the completion of the OX-ONC study on 30th July 2016 and the EUCROSS study in August 2017, the updated results from these studies have been included in the tables below alongside the interim data identified from the SLR search. The updated outcomes from the OX-ONC study and the EUCROSS study have not been included in the PRISMA diagram below, as these updates were not identified from the SLR search and as these updates have not been published."

The updated ORR, PFS and survival results from EUCROSS are presented as academic in confidence in Table 8 in Appendix D. The Kaplan Meier plots for PFS and OS are presented below in Figure 1 and Figure 2, respectively.

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Figure 1. Kaplan Meier plot for progression free survival – updated results for ROS1-positive NSCLC patients treated with crizotinib from EUCROSS

Figure 2. Kaplan Meier plot for overall survival – updated results for ROS1-positive NSCLC patients treated with crizotinib from EUCROSS

A11. In the CSR for the PROFILE 1007 trial (e.g. page 40) it is reported that the preliminary CSR contains the final results for PFS, objective response rate (ORR), disease control rate (DCR) at 6 and 12 weeks, duration of response (DR), time to

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tumour response (TTR), safety, and patient-reported outcomes (PROs). None of these results are reported in the final CSR. Please provide the preliminary CSR for the PROFILE 1007 trial.

Please find these in the Reference Pack submitted with this response. Further EQ-5D data are also provided as part of the response to B4 (see below).

Section B: Clarification on cost-effectiveness data

B1. **Priority request.** Please provide the K-M analyses listed in a) to d) and to the following specifications:

- Study data set: PROFILE 1001 study, November 2014 data cut (or more recent if available).
- Format: Please present analysis outputs using the format of the sample table provided (to include censoring times).
- Population: Intention-to-treat (ITT) population including all patients who were lost to follow-up or withdrawing from the trial.
- Cohort: population with ROS1 positive NSCLC (n=50) and patients with ALK negative NSCLC who were retrospectively identified as having ROS1 positive NSCLC (n=3). Please indicate the patients who were retrospectively determined as having ROS1 positive NSCLC.

Survival analysis was conducted in R using flexsurv rather than SAS therefore the output format differs slightly from that indicated in the template however the same information is reported. The column “treatment.line” indicates patients who were treatment naïve (treatment.line=1) and pre-treated (treatment.line=2) respectively. The population column indicates the three patients that were retrospectively classified as having ROS1 positive NSCLC. These three patients are labelled ALK since they were initially classified as having ALK positive NSCLC then retrospectively reclassified as having ROS1 positive NSCLC.

a) Time to death from any cause (OS). K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

Please see these data in the Excel file labelled as Question B1.

b) Progression-free survival. K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

Please see these data in the Excel file labelled as QuestionB1.

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c) Post-progression survival. K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

Please see these data in the Excel file labelled as QuestionB1.

d) Time to study treatment discontinuation. K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

Please see these data in the Excel file labelled as QuestionB1.

B2. **Priority request.** Please provide the K-M analysis listed in a) to d) to the following specifications:

- Trial data set: PROFILE 1007 trial.
- Population: ITT population including all patients who were lost to follow-up or withdrawing from the trial.
- Format: Please present analysis outputs using the format of the sample table provided (to include censoring times).
- Time to death from any cause (OS) K-M analysis for the ROS1 positive cohort treated with crizotinib, stratified by treatment naïve and pre-treated patients.

To confirm, time to death from any cause (OS) K-M analysis data (fourth bullet point above) is provided for the ALK-positive cohort treated with crizotinib from the PROFILE 1007 trial as discussed during our clarification questions telecom (identification of typo in the fourth bullet point).

Survival analysis was conducted in R using flexsurv rather than SAS therefore the output format differs slightly from that indicated in the template however the same information is reported. For each endpoint the treatment received is indicated by the treatment column. There were three patients randomised to the chemotherapy arm who did not receive treatment. These patients could not be classified as either pemetrexed or docetaxel therefore these three patients are listed separately as 'chemotherapy'.

a. Time to death from any cause (OS). K-M analysis for all patients, stratified by treatment.

Please see these data in the Excel file labelled as QuestionB2.

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b. Progression-free survival. K-M analysis for all patients, stratified by treatment.

Please see these data in the Excel file labelled as QuestionB2.

c. Post-progression survival. K-M analysis for all patients, stratified by treatment.

Please see these data in the Excel file labelled as QuestionB2.

d. Time to study treatment discontinuation. K-M analysis for all patients, stratified by treatment.

Please see these data in the Excel file labelled as QuestionB2.

B3. Priority request. Please provide the K-M analyses listed in a) to h) to the following specifications:

- Trial data set: PROFILE 1014 trial.
- Format: Please present analysis outputs using the format of the sample table provided (to include censoring times).
- Population: ITT population including all patients lost to follow-up or withdrawing from the trial.

Survival analysis was conducted in R using flexsurv rather than SAS therefore the output format differs slightly from that indicated in the template however the same information is reported. In the study dataset the treatment arms were designated ARM A and ARM B. ARM A = crizotinib, ARM B = pemetrexed plus platinum.

a. Time to death from any cause (OS) K-M analysis for all patients, stratified by treatment.

Please see these data in the Excel file labelled as QuestionB3.

b. Time to death from any cause (OS) K-M analysis for all patients, stratified by treatment and adjusted for crossover using the rank preserved structural failure time (RPSFT) Wilcoxon method.

Please see these data in the Excel file labelled as QuestionB3.

c. Time to death from any cause (OS) K-M analysis for all patients, stratified by treatment and adjusted for crossover using the RPSFT log rank method.

Please see these data in the Excel file labelled as QuestionB3.

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d. Progression-free survival. K-M analysis for all patients, stratified by treatment.

Please see these data in the Excel file labelled as QuestionB3.

e. Post-progression survival. K-M analysis for all patients, stratified by treatment.

Calculation of PPS as:
PPS = RPSFT adjusted OS – observed PFS resulted in some patients with negative PPS values, i.e. PPS <0. These patients were excluded from the analysis. There were 6 crizotinib patients and 15 pemetrexed plus platinum patients.

Please see these data in the Excel file labelled as QuestionB3.

f. Post-progression survival. K-M analysis for all patients, stratified by treatment and adjusted for crossover using the RPSFT Wilcoxon method.

Calculation of PPS as:
PPS = RPSFT adjusted OS – observed PFS resulted in some patients with negative PPS values, i.e. PPS <0. These patients were excluded from the analysis. There were 6 crizotinib patients and 12 pemetrexed plus platinum patients.

Please see these data in the Excel file labelled as QuestionB3.

g. Post-progression survival. K-M analysis for all patients, stratified by treatment and adjusted for crossover using the RPSFT log rank method.

Please see these data in the Excel file labelled as QuestionB3.

h. Time to study treatment discontinuation. K-M analysis for all patients, stratified by treatment.

Please see these data in the Excel file labelled as QuestionB3.

B4. Priority request: Utility data. Please complete the table below using EQ-5D data collected during the PROFILE 1007 trial valued using the UK time trade-off (TTO) value set stratified by:

a) All patients.

Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Cycle 3	[redacted]					
Cycle 4						
Cycle 5						
Cycle 6						
Cycle 7						
Cycle 8						
Cycle 9						
Cycle 10						
Cycle 11						
Cycle 12						
Cycle 13						
Cycle 14						
Cycle 15						
Cycle 16						
Cycle 17						
Cycle 18						
Cycle 19						
Cycle 20						
Cycle 21						
Cycle 22						
Cycle 23						
Cycle 24						
Cycle 25						
Cycle 26						
Cycle 27						
Cycle 28						
Cycle 29						
Cycle 30						
Cycle 31						
Cycle 32						
Cycle 33						

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Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Cycle 34	[redacted]	[redacted]				
Cycle 35	[redacted]	[redacted]				
Cycle 36	[redacted]	[redacted]				
Cycle 37	[redacted]	[redacted]				
Exit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) European patients only.

Please note that the stratification of patients by region breaks the randomisation and therefore the results stratified by region may be biased (as patients stratified by region cannot be considered to be equivalent).

Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Cycle 19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20	[redacted]	[redacted]				
Cycle 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24	[redacted]	[redacted]				
Cycle 25	[redacted]	[redacted]				
Cycle 26	[redacted]	[redacted]				
Cycle 27	[redacted]	[redacted]				
Exit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B5. Priority request: Utility data. Please complete the table below using EQ-5D data collected during the PROFILE 1014 trial valued using the UK TTO value set stratified by:

a) All patients.

Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]				
Cycle 8	[redacted]	[redacted]				
Cycle 9	[redacted]	[redacted]				
Cycle 10	[redacted]	[redacted]				
Cycle 11	[redacted]	[redacted]				
Cycle 12	[redacted]	[redacted]				
Cycle 13	[redacted]	[redacted]				
Cycle 14	[redacted]	[redacted]				
Cycle 15	[redacted]	[redacted]				

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Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Cycle 16	[redacted]	[redacted]				
Cycle 17	[redacted]	[redacted]				
Cycle 18	[redacted]	[redacted]				
Cycle 19	[redacted]	[redacted]				
Cycle 20	[redacted]	[redacted]				
Cycle 21	[redacted]	[redacted]				
Cycle 22	[redacted]	[redacted]				
Cycle 23	[redacted]	[redacted]				
Cycle 24	[redacted]	[redacted]				
Cycle 25	[redacted]	[redacted]				
Cycle 26	[redacted]	[redacted]				
Cycle 27	[redacted]	[redacted]				
Cycle 28	[redacted]	[redacted]				
Cycle 29	[redacted]	[redacted]				
Cycle 30	[redacted]	[redacted]				
Cycle 31	[redacted]	[redacted]				
Cycle 32	[redacted]	[redacted]				
Cycle 33	[redacted]	[redacted]				
Cycle 34	[redacted]	[redacted]				
Cycle 35	[redacted]	[redacted]				
Cycle 36	[redacted]	[redacted]				
Cycle 37	[redacted]	[redacted]				
Cycle 38	[redacted]	[redacted]				
Cycle 39	[redacted]	[redacted]				
Cycle 40	[redacted]	[redacted]				
Cycle 41	[redacted]	[redacted]				
Cycle 42	[redacted]	[redacted]				
Cycle 43	[redacted]	[redacted]				
Cycle 44	[redacted]	[redacted]				
Cycle 45	[redacted]	[redacted]				
Cycle 46	[redacted]	[redacted]				

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Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Cycle 47	[redacted]	[redacted]				
Cycle 48	[redacted]	[redacted]				
Cycle 49	[redacted]	[redacted]				
Cycle 50	[redacted]	[redacted]				
Exit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) European patients only.

Please note that the stratification of patients by region breaks the randomisation and therefore the results stratified by region may be biased (as patients stratified by region cannot be considered to be equivalent).

Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]				
Cycle 8	[redacted]	[redacted]				
Cycle 9	[redacted]	[redacted]				
Cycle 10	[redacted]	[redacted]				
Cycle 11	[redacted]	[redacted]				
Cycle 12	[redacted]	[redacted]				
Cycle 13	[redacted]	[redacted]				
Cycle 14	[redacted]	[redacted]				
Cycle 15	[redacted]	[redacted]				
Cycle 16	[redacted]	[redacted]				
Cycle 17	[redacted]	[redacted]				
Cycle 18	[redacted]	[redacted]				
Cycle 19	[redacted]	[redacted]				

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Time point	Crizotinib		Chemotherapy		Difference	
	n	Mean (sd)	n	Mean (sd)	Mean (sd)	p-value
Cycle 20	[redacted]	[redacted]				
Cycle 21	[redacted]	[redacted]				
Cycle 22	[redacted]	[redacted]				
Cycle 23	[redacted]	[redacted]				
Cycle 24	[redacted]	[redacted]				
Cycle 25	[redacted]	[redacted]				
Cycle 26	[redacted]	[redacted]				
Cycle 27	[redacted]	[redacted]				
Cycle 28	[redacted]	[redacted]				
Cycle 29	[redacted]	[redacted]				
Cycle 30	[redacted]	[redacted]				
Cycle 31	[redacted]	[redacted]				
Cycle 32	[redacted]	[redacted]				
Cycle 33	[redacted]	[redacted]				
Cycle 34	[redacted]	[redacted]				
Cycle 35	[redacted]	[redacted]				
Cycle 36	[redacted]	[redacted]				
Cycle 37	[redacted]	[redacted]				
Cycle 38	[redacted]	[redacted]				
Cycle 39	[redacted]	[redacted]				
Cycle 40	[redacted]	[redacted]				
Cycle 41	[redacted]	[redacted]				
Cycle 42	[redacted]	[redacted]				
Cycle 43	[redacted]	[redacted]				
Cycle 44	[redacted]	[redacted]				
Cycle 45	[redacted]	[redacted]				
Cycle 46	[redacted]	[redacted]				
Exit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B6. Please explain the process by which patients in the PROFILE 1001 trial were tested for ALK and ROS1 rearrangements. This should include the tests received and the order in which they were given. The purpose of this question is to help our understanding how and

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why some patients were wrongly identified as having ALK positive NSCLC or ROS1 positive NSCLC and then retrospectively identified as having a different rearrangement.

PROFILE 1001 included a dose escalation component and enriched populations of patients with disease that is molecularly defined, including the following cohorts: (1) patients having NSCLC tumours that are positive for ALK chromosomal translocations, inversions, or gene amplification, (2) patients having NSCLC tumours positive for c-MET amplification, (3) patients having NSCLC tumours that are positive for ROS1 chromosomal translocations, and (4) patients having tumours positive for ALK, c-MET or ROS1 that confer sensitivity to crizotinib other than those already indicated in Cohorts 1-3.

[redacted] PROFILE 1001 required patients to be identified through the use of ROS1 fluorescence in situ hybridization (FISH) tests.

[redacted]

Available tissue samples (n=37 from 36 patients) were retrospectively tested for ALK gene rearrangement. Following further testing, two patients treated with crizotinib were found to be ROS1-negative on testing with next generation sequencing (NGS):[1]

One patient with a ROS1 rearrangement identified by FISH testing at MGH, showed an atypical hybridization pattern (isolated 5′ green signal), and NGS subsequently revealed normal, non-rearranged ROS1.[1]
[redacted]

In a second patient the tumour was found to be positive for both ROS1 and ALK rearrangement based on FISH, but NGS revealed only an EML4-ALK fusion and no ROS1 rearrangement.[1]
[redacted]

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[redacted]

The testing algorithms employed to screen for patients with ROS1-positive advanced NSCLC have developed since the design of the PROFILE 1001 trial, as is the case for ALK-positive advanced NSCLC. Current clinical expert opinion and clinical guidelines recognise immunohistochemistry (IHC) to be a robust screening tool for the detection of ROS1-rearranged lung tumours, offers a rapid turnaround time and low cost upfront testing relative to FISH-based methods.[10-12] For these reasons, consulted clinical experts in the UK have recommended ROS1 IHC screening to be considered as routine practice at the point of access to ROS1-targeted therapies. There is additional recommendation for orthogonal testing after patients are found to be ROS1-positive by IHC,[10-12] which consulted experts and clinical guidelines have suggested should be FISH.[11] This approach has been adopted in the NICE submission to reflect the recommended approach to patient screening in the UK.

Section C: Textual clarifications and additional points

C1. Figure 3 in the CS is a waterfall plot to illustrate the objective responses of individual participants recruited to the PROFILE 1001 study. The final 8 bars in Figure 3 all indicate a 100% decrease in tumour size from baseline. However, only 5 of the 8 bars are labelled as a complete response, with the other 3 bars labelled as a partial response. Please clarify.

The waterfall plot in Document B, Figure 3 shows the best percentage change in target lesions from baseline. Therefore, the final 8 bars represent patients who experienced a 100% reduction in at least one target lesion. However, only 5 of these 8 patients experienced a complete response, which based on the RECIST definition is a disappearance of all target lesions.[13]

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60

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3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

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12. IASLC ATLAS OF ALK AND ROS1 TESTING IN LUNG CANCER. International Association for the Study of Lung Cancer (IASLC). Accessed on October 19th, 2017. *[available at:* https://www.iaslc.org/sites/default/files/wysiwyg-assets/alk-ros1_atlas_low-res.pdf *]*
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Response to clarification follow-up

Q1. At the clarification TC on 9 October 2017 it was confirmed that all the information included in Pfizer's submission relating to the advisory board meeting was included in the redacted versions of the documents. However it is unclear how some of the conclusions in the company submission are supported by the redacted versions of these documents. For specific examples please see the table in this link:
https://appraisals.nice.org.uk/request/36259

We have revisited the advisory board minutes to check that all relevant information is unredacted. Please find attached a version of the advisory board minutes with updated redactions. Please also see detailed responses to each of the conclusions highlighted in the table below.

Page in CS	Text	Verified in redacted advisory board document?	Response
26	Clinical experts have suggested that approximately 15% of patients with advanced NSCLC would be eligible for pemetrexed maintenance after platinum doublet first-line chemotherapy, based on fitness. In the real world, only the fittest patients, (Eastern Cooperative Oncology Group [ECOG] performance status 0–1) who achieve disease control with four cycles of induction therapy would be considered for treatment with pemetrexed maintenance, as per NICE recommendation.[59]	No	The figure of approximately 15% of patients eligible for pemetrexed maintenance was from previous discussions with clinical experts, and therefore the ROS1-positive advisory board was not referenced here. This figure was accepted by NICE in the submission for crizotinib for untreated ALK-positive advanced NSCLC patients. The reference used here is the NICE TA402 submission. In addition, the advisory board for ALK-positive NSCLC provides supportive evidence the discussion with clinical experts about 15% of patients eligible for pemetrexed maintenance. The minutes from the ALK advisory board have been included in the reference pack submitted with this response, for your reference.
29	Given the efficacy of crizotinib in ROS1-positive patients demonstrated in PROFILE 1001, clinical experts consider it unethical to conduct further comparative trials due to the lack of clinical equipoise	No	Whether it was ethical to conduct further comparative trials was from previous discussions with clinical experts and therefore the advisory board was not referenced here. No reference has been given for this statement.

31	Given the efficacy of crizotinib in ROS1 patients as demonstrated in the phase I single-arm PROFILE 1001 trial, clinical experts consider it unethical to conduct further comparative trials due to the lack of clinical equipoise. This trial has been validated by clinicians as generalisable to the UK population.3	No	Whether it was ethical to conduct further comparative trials was from previous discussions with clinical experts and therefore the advisory board was not referenced here. No reference has been given for this statement. The reference given is to support the statement that data from the PROFILE 1001 trial are representative of UK patients (see response to query from CS page 53 below).
53	PROFILE 1001 was a single arm, non-comparative study and therefore the discussion of bias is not relevant here. UK clinical experts confirmed that the baseline characteristics in PROFILE 1001 are representative of patients encountered in UK clinical practice,3 and as such selection bias is unlikely to be a concern.	No	In the advisory board, the experts were asked to comment on whether the datasets presented were relevant to their experience of the diagnosis and management of patients with ROS1-positive advanced NSCLC. The data presented included PROFILE 1001. The advisors agreed that the data presented from the trials of patients with ROS1-positive NSCLC were believable. Additionally, real world data from the [redacted] audit presented for discussion at the advisory board is similar in relation to age and histology. Complete smoking data was not presented at the advisory board. To supplement the advisory report, the confirmation that baseline characteristics from PROFILE 1001 are representative of patients encountered in the UK is supported by discussions with clinical experts.
83	The safety profile of crizotinib observed in PROFILE 1001 was consistent with that reported across four crizotinib trials (1,669 patients), including PROFILE 1007 and PROFILE 1014, as detailed in the pooled analysis presented in Section B.2.10. As noted by UK clinical experts consulted at an advisory board for ALK-positive NSCLC,5 the majority of AEs known to be associated with crizotinib can be managed by dose reductions or dose delay as recommended in the	No	The advisory board referred to here was a previous advisory board for crizotinib in ALK-positive NSCLC, which was accepted as part of the NICE TA406 submission (reference 5). Therefore, this information is not contained within the ROS1-positive redacted advisory board and the ROS1-positive advisory board was not referenced.

	SmPC, thus allowing overall continuation of crizotinib		The minutes from the ALK advisory board have been included in the reference pack submitted with this response, for your reference.
114	For all curves, the AIC and BIC points were within 5 points which indicated that there is no substantial difference between curves in terms of statistical fit to the data. There was however large variation in the long-term OS predicted by the curves. The curves were then examined for clinical plausibility. Only the exponential curve appeared potentially clinically plausible, while all other curves examined predict longer, more unrealistic OS estimates over the long-term than can be substantiated. Clinical experts, at an advisory board held in July 2017, stated that exponential was the most, potentially, clinical plausible, but is still considered to predict optimistic survival estimates. Despite this, visual inspection suggests that the exponential curve does not fit the data well and therefore it could be argued that none of the curves fit to the PROFILE 1001 data to provide a plausible estimation of the OS for crizotinib in ROS1-positive patients. Considering the information and limitations of the three assessment techniques, and that it predicted the most conservative survival estimates, the exponential curve was ultimately selected for the “PROFILE 1001” analysis. The Weibull parametric curve fit was tested in a scenario analysis (B.3.8.3). In summary, the results of the PROFILE 1001 analysis should be treated with caution.	No	The advisors were asked which of the PROFILE 1001 extrapolation curves presented was most clinically plausible. They commented that the exponential curve was the most believable, although this was still considered to be more optimistic than expected: advisors agreed that all OS curves should be moved to the left. This is included in the advisory board report. A version of the advisory board report which this section unredacted is attached.
178	The analysis is relevant and generalisable to clinical practice in the UK. PROFILE 1014 and PROFILE 1007, also used in this submission as proxy for comparative efficacy of crizotinib versus pemetrexed plus platinum and docetaxel monotherapy were deemed generalisable by NICE committee in TA406 and TA422, respectively.5, 8 Clinical experts confirmed that the data from PROFILE 1001 is aligned with what they would expect to see in UK clinical practice and thus it can be concluded that the data is generalisable to the UK population.	No	The PROFILE 1007 and PROFILE 1014 data used in the current submission were real-world adjusted based on the baseline characteristics of a retrospective cohort study conducted by Davis et al. (2015) to adjust the data to be more representative of the UK population. The same real-world adjustment was also applied and accepted in the previous crizotinib submissions in ALK-positive NSCLC (TA406 and TA422), see Section B.2.13.1. Clinical experts at the ROS1 advisory board and further

			discussions with clinical experts following the advisory board, confirm the data from PROFILE 1001 to be representative of UK patients (see response to query from CS page 53 above).
179	Further to this, the immature data, small number of patients and associated events in PROFILE 1001 (even when first-line and subsequent-line data was pooled) lead to extrapolations of PFS and OS that did not exhibit a good fit to the observed data and that may not be clinically plausible in the PROFILE 1001 analyses. Subsequently, when the HRs used to estimate comparative efficacy are applied to these curves, the resulting PFS and OS estimates for the comparator arms are considered clinically implausible, predicting much higher estimates than would be seen in clinical practice based on opinion by 12 experts at a recent advisory board	No	The advisors were asked which of the PROFILE 1001 extrapolation curves presented was most clinically plausible. They commented that the exponential curve was the most believable, although this was still considered to be more optimistic than expected: advisors agreed that all OS curves should be moved to the left. Furthermore, the advisors did not think that the simulated PROFILE 1001 PFS curves were believable and questioned the model used to create the curves. These discussions are included in the advisory board report. A version of the advisory board report which this section unredacted is attached.

Q2. Please could you provide the baseline characteristics for participants in the EUROCROSS study?

Please find the baseline characteristics of participants in the EUCROSS study attached.

Q3. Please could you provide details on how many patients in the PROFILE 1007 trial were treated with pemetrexed+platinum as their first-line treatment?

Please find the patient numbers from PROFILE 1007 who were treated with pemetrexed+platinum as their first-line treatment attached.

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

Dear [redacted],

Thank you for providing unredacted versions of the company submissions for previous related technology appraisal (TA296, TA406 and TA422).

We would like to request further details about the rationale for including specific data in the company's model. These explanations should refer to reasons **other** than being accepted in a previous TA and should include reference to the evidence base for ROS-1 non-small-cell lung cancer and relevance to NHS clinical practice.

Therefore we request the following:

1. Please complete tables 1 and 2 (for untreated and previously treated populations) attached

2. Please provide the password for the locked worksheets in the company model for TA406 to allow the ERG to provide a full critique.

3. Please provide instructions on how to remove the baseline characteristic adjustment from PFS and TTD in the first-line model.

Please return your responses by **4pm on Friday 10 November 2017**

Many thanks

Table 1. Rationale for clinical and cost effectiveness data for <u>untreated</u> ROS-1 NSCLC population

	Parameter/input in company base case	Details of values used in company model	Rationale (explanations should explore reasons <u>other</u> than being accepted in a previous TA and should include relevance to the clinical evidence base for ROS1 NSCLC and NHS clinical practice)	Do assumptions differ from TA406? If so, please state reasons
Extrapolation of clinical data (please include curve and statistical distribution)	Extrapolation PFS	Crizotinib: Log-normal (fully stratified) Pemetrexed + platinum: Generalised Gamma (fully stratified)	ALK+ data is considered to be an appropriate proxy for ROS1 due to the following: • ROS1 and ALK receptor tyrosine kinases (RTKs) are both part of the insulin-receptor family and share close structural homology between the adenosine triphosphate (ATP)-binding kinase domains, to which crizotinib binds with high affinity in both ROS1 and ALK RTKs. • Secondly, the clinical demographics are similar between patients with ALK- and ROS1-positive advanced NSCLC (usually non-smokers or light smokers, predominantly adenocarcinoma histology and younger in age compared to unselected NSCLC). • Thirdly, ALK- and ROS1-positive advanced NSCLC both show similar clinical activity in response to treatment with crizotinib. The generalisability of ALK data to the ROS1-positive population is supported and validated by 12 clinical experts in the UK, which included one expert from Scotland. Furthermore, the EMA also concluded in their authorisation of crizotinib that: *"Based on the pre-clinical and anti-tumour similarities between ALK-positive*	No

			and ROS1-positive NSCLC the EMA concluded there was no concern regarding the efficacy of crizotinib in the first-line treatment of patients with ROS1-positive NSCLC." The log-normal and generalised gamma curves, adjusted for patient's characteristics from RWE, was considered to provide more clinically plausible predictions of PFS in ALK+ patients, than the alternative extrapolation options tested. As ALK+ data is considered an appropriate proxy for ROS1 data, then it is concluded that the generalised gamma curve is also the most clinically plausible for ROS1 patients. A PROFILE1001 analysis has been presented in this submission which presents extrapolated PFS data for the only ROS1. However, there is a large amount of uncertainty associated with the parametric survival modelling based on these data. This is primarily due to the small sample size of the combined first-line and subsequent-line populations (n=53 patients), an artefact of the rarity of ROS1 NSCLC as a disease. Further to this, the immaturity of the PROFILE 1001 (only 30% of patients had died at completion) contributes to the uncertainty. The PROFILE 1001 dataset included only 7 first line patients of which only 3 experienced an event. Fitting parametric survival models to these 7 patients was considered implausible.	

	Extrapolation time on treatment	Crizotinib: Exponential Pemetrexed + platinum: Gompertz	These curves were chosen by the ERG and determined to be the best fit and therefore most appropriate. Regarding the pemetrexed arm, treatment is capped at 6-cycles of therapy therefore exptrapolation beyond these cycles is not required. Hence, the use of curves is to act as a best fit, not necessarily to extrapolate. The Gompertz curve was in the model accepted by NICE, but choice of curve resulted in minimal impact to the modelled outcomes.	No
Health related quality of life (please include values and a source)	Utility	Crizotinib: 0.81 (patients on crizotinib), PROFILE1014 Pemetrexed + platinum: 0.72 (Patients progression free and on pemetrexed + platinum), PROFILE1014	The rationale for choosing 0.81 for crizotinib and 0.72 for chemotherapy was that these are the EQ-5D derived estimates on treatment in the PROFILE 1014 trial. Crizotinib received its marketing authorisation for ROS1-positive patients based on evidence from a Phase I, safety, pharmacokinetic and pharmacodynamic study designed for regulatory purposes. Therefore, the clinical trial evidence base does not contain HRQoL data. ALK data is considered an appropriate proxy for ROS1 (clinical rationale provided earlier in table). Therefore in the absence of ROS1 specific utilities, utilities from ALK+ patients was considered the next best option.	In TA406, the utility for patients on crizotinib was applied until progression. After TA406, it came to light that the utility (0.81) was actually based on treatment duration, not progression status and so was applied based on time on treatment in this model. In TA406, Pfizer believed the basecase estimate for pemetrexed plus platinum should reflect the clinical trial, 0.72. In response to critique in the ACD, Pfizer revised this estimate to 0.75 for patients who had completed pemetrexed

				treatment but were still pre-progression. The committee preferred this revision in the FAD.
	Exclusion of disutilities from AEs	Excluded in base case	As the HRQoL estimates included in the PROFILE1014 trial are estimates taken from patients whilst on treatment, they thus reflect the health status of the patients, including the effects on HRQoL of the adverse event profiles associated with crizotinib and pemetrexed plus cisplatin/carboplatin	No

Table 2. Rationale for clinical and cost effectiveness data for previously treated ROS-1 NSCLC population

	Parameter/input in company base case	Details of values used in company model	Rationale (explanations should explore reasons other than being accepted in a previous TA and should include relevance to the clinical evidence base for ROS1 NSCLC and NHS clinical practice)	Do assumptions differ from TA422? If so, please state reasons
Extrapolation of clinical data (please include curve and statistical distribution)	Extrapolation OS	Crizotinib: Exponential (via application of HR) Docetaxel: Exponential	ALK+ data is considered to an appropriate proxy for ROS1 due to the following: • ROS1 and ALK receptor tyrosine kinases (RTKs) are both part of the insulin-receptor family and share close structural homology between the adenosine triphosphate (ATP)-binding kinase domains, to which crizotinib binds with high affinity in both ROS1 and ALK RTKs. • Secondly, the clinical demographics are similar between patients with ALK- and ROS1-positive advanced NSCLC (usually non-smokers or light smokers, predominantly adenocarcinoma histology and younger in age compared to unselected NSCLC). • Thirdly, ALK- and ROS1-positive advanced NSCLC both show similar clinical activity in response	No

			to treatment with crizotinib. The generalisability of ALK data to the ROS1-positive population is supported and validated by 12 clinical experts in the UK, which included one expert from Scotland. Furthermore, the EMA also concluded in their authorisation of crizotinib that: *"Based on the pre-clinical and anti-tumour similarities between ALK-positive and ROS1-positive NSCLC the EMA concluded there was no concern regarding the efficacy of crizotinib in the first-line treatment of patients with ROS1-positive NSCLC."* The exponential curve, was considered to be the most appropriate as it is the statistically best fitting curve which also provided clinically plausible predictions of OS in ALK+ patients, than the alternative extrapolation options tested. On page 21 of the 2016 resubmission we stated: The exponential has the lowest cumulative AIC and BIC that produces estimates of survival with face validity for both arms (see Section **Error! Reference source not found.** for validation), and fit in **Error! Reference source not found.**. As ALK+ data is considered an appropriate proxy for ROS1 data, then is	

			concluded that the selected curve is also the most clinically plausible for ROS1 patients. A PROFILE1001 analysis has been presented in this submission which presents extrapolated OS data for the only ROS1. However, there is a large amount of uncertainty associated with the parametric survival modelling based on these data. This is primarily due to the small sample size of the combined first-line and subsequent-line populations (n=53 patients), an artefact of the rarity of ROS1 NSCLC as a disease. Further to this, the immaturity of the PROFILE 1001 (only 30% of patients had died at completion) contributes to the uncertainty. The PROFILE 1001 dataset included only 7 first line patients of which only 2 experienced an event. Fitting parametric survival models to these 7 patients was considered implausible.	
	Extrapolation PFS	Crizotinib: Weibull Docetaxel: Log-Normal	For the reasons stated above ALK data is considered an appropriate proxy for ROS1. The selected curves, were considered to be the best fit to the PROFILE1007 data, rather than the alternative curves. Weibull had the lowest AIC/BIC figures and	No

			provided a good fit for the data visually with a clinically plausible long-term survival estimate, and so was chosen as base case. The log normal model was chosen as the best fit, as it provided the lowest AIC/BIC figures and showed a good visual fit to the Kaplan-Meier data As ALK+ data is considered an appropriate proxy for ROS1 data, then it is concluded that the selected curve is also the most appropriate for ROS1 patients. A PROFILE1001 analysis has been presented in this submission which presents extrapolated PFS data for the only ROS1. However, there is a large amount of uncertainty associated with the parametric survival modelling based on these data. This is primarily due to the small sample size of the combined first-line and subsequent-line populations (n=53 patients), an artefact of the rarity of ROS1 NSCLC as a disease. Further to this, the immaturity of the PROFILE 1001 (only 30% of patients had died at completion) contributes to the uncertainty.	

	Extrapolation time on treatment	Crizotinib: Weibull Docetaxel: N/A – fixed number of cycles	For the reasons stated above ALK data is considered an appropriate proxy for ROS1. The selected curve, was considered to the best fit to the PROFILE1007 data, compared to the alternative curves As ALK+ data is considered an appropriate proxy for ROS1 data, then is concluded that the selected curve is also the most appropriate for ROS1 patients. A PROFILE1001 analysis has been presented in this submission which presents extrapolated PFS data for the only ROS1. However, there is a large amount of uncertainty associated with the parametric survival modelling based on these data. This is primarily due to the small sample size of the combined first-line and subsequent-line populations (n=53 patients), an artefact of the rarity of ROS1 NSCLC as a disease. Further to this, the immaturity of the PROFILE 1001 (only 30% of patients had died at completion) contributes to the uncertainty.	No
Health related quality of life (please include	Utility	Crizotinib: 0.81 (patients on crizotinib), PROFILE1014	Crizotinib received its marketing authorisation for ROS1-positive patients based on evidence from a Phase I, safety, pharmacokinetic and pharmacodynamic	In TA422 a utility of 0.82 was used for patients on crizotinib.

values and a source)		Docetaxel: 0.66 (Patients progression free and on docetaxel), PROFILE1007	study designed for regulatory purposes. Therefore, the clinical trial evidence base does not contain HRQoL data. ALK data is considered an appropriate proxy for ROS1 (clinical rationale provided earlier in table). Therefore, in the absence of ROS1 specific utilities, utilities from ALK+ patients were considered the next best option.	For consistency, a conservative assumption was made so that the lower utility was applied to both arms
	Exclusion of disutilities from AEs	Excluded	As the HRQoL estimates included in the PROFILE1014 and PROFILE1007 trial are estimates taken from patients whilst on treatment, they thus reflect the health status of the patients, including the effects on HRQoL of the adverse event profiles associated with crizotinib and docetaxel	No

Dear Stephanie,

With reference to: Response submitted - Lung cancer (non-small-cell, advanced, untreated, ROS1-positive) - crizotinib Appraisal 1098

While completing the ERG's request of the 8th November for further rationale for data included in the cost-effectiveness model, Pfizer noticed that two of the survival functions were misplaced in the model (first-line PFS crizotinib should be informed by the "Log-normal" function and first-line TTF crizotinib should be informed by the "Exponential" function). Below is a summary of the functions being replaced and the affected tab/sheet within the model:

- **Crizotinib PFS**: Sheet 'ALK+ 1L PFS' - Rows 21 – 47. The first-line PFS for crizotinib is now informed by Log-normal parameters and variance-covariance (replacing the Generalised Gamma model that was previously there for crizotinib). These parameters feed through the 'Lists' sheet (Rows 97 – 100), which in turn feed through to the '1L ALK+ survival (TA406)' changing the PFS curve to a log-normal distribution (Column G).

- **Crizotinib TTD**: Sheet 'ALK+ 1L TTD' – Rows 21-42. The first-line TTD for crizotinib is now informed by Exponential parameters and variance-covariance (replacing the Gompertz model that was previously there for crizotinib). These parameters feed through the 'Lists' sheet (Rows 108-110), which in turn feed through to the '1L ALK+ survival (TA406)' changing the TTD curve to an exponential distribution (Column H)

Please note that the impact of this on the first-line base case ICER is £1,316, which is considered to be minimal.

Following your request (email dated 16th November) to submit an addendum with the correct values alongside the ERG response, Pfizer have attached this document for your reference.

Best wishes,

[redacted]

[redacted]

[redacted]

[redacted]

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

Addendum to Document B and appendices document

Contents

Document A, Table 4: Overview of key clinical efficacy results from PROFILE 1001, 1007 and 1014

Outcome	PROFILE 1001 (N=53)	PROFILE 1007 (N=347)	PROFILE 1014 (N=343)
Median progression-free survival (PFS)			
Crizotinib, months (95% CI)	19.3 (14.8–NR)	7.7 (6.0–8.8)	10.9 (8.3–13.9)
Chemotherapy	NA	3.0 (2.6–4.3)	7.0 (6.8–8.2)
HR, (95% CI; p-value)	NA	0.487 (0.371–0.638; p<0.0001)	0.45 (0.35–0.60; p<0.001)[a]
% of patients who crossed-over			
Crizotinib	NA	65/173 (37.6%)	33/172 (19.2%)
Chemotherapy	NA	154/174 (88.5%)	144/171 (84.2%)
Tumour response, overall response rate (ORR)[b]			
Crizotinib, no. of patients (%) [95% CI][c]	37 (69.8) [55.7–81.7]	112 (65.3) [57.7–72.4]	128 (74.4) [67.2– 80.8)
Chemotherapy	NA	34 (19.5) [13.9–26.2]	77 (45) [37–53]
Median overall survival (OS)			
Crizotinib, months	NR	21.7 (18.9–30.5)	[redacted]
Chemotherapy	NA	21.9 (16.8–26.0)	[redacted]
HR, (95% CI, p-value)	NA	Unadjusted: 0.854 (0.66–1.10; p=0.11)	Unadjusted: [redacted]
		Crossover adjusted: 0.383 (0.283, 0.518)	Crossover adjusted: [redacted] See Document B, **Error! Reference source not found.** and Section B.3.3.4 for details

[a]For between-group comparisons (crizotinib vs. chemotherapy), two-sided log-rank test stratified according to baseline stratification factors were used; stratified Cox regression models were applied to estimate HRs. [b]Tumour response was assessed using RECIST (v1.0 for ROS1 patients in PROFILE 1001, v1.1 for PROFILE 1007, 1014 and three patients from ALK-negative cohort respectively determined to be ROS1-positve in PROFILE 1001) and were confirmed by IRR. [c]P<0.001 for between-group comparison.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria on Solid Tumours.
Source: PROFILE 1001: EPAR Xalkori/crizotinib 21st July 2016[7]; PROFILE 1007: Shaw et al. 2013[71], CSR[70]; Shaw et al. 2016[47]; PROFILE 1014: Solomon et al. 2014[73], CSR[72], updated CSR[96], Mok et al. 2017 ESMO Presentation

Document B, Table 15: Overview of key clinical efficacy results from PROFILE 1001, 1007 and 1014

Outcome	PROFILE 1001 (N=53)	PROFILE 1007 (N=347)	PROFILE 1014 (N=343)
Median progression-free survival (PFS)			
Crizotinib, months (95% CI)	19.3 (14.8–NR)	7.7 (6.0–8.8)	10.9 (8.3–13.9)
Chemotherapy	NA	3.0 (2.6–4.3)	7.0 (6.8–8.2)
HR, (95% CI; p-value)	NA	0.487 (0.371–0.638; p<0.0001)	0.45 (0.35–0.60; p<0.001)[a]
% of patients who crossed-over			
Crizotinib	NA	65/173 (37.6%)	33/172 (19.2%)
Chemotherapy	NA	154/174 (88.5%)	144/171 (84.2%)
Tumour response, overall response rate (ORR)[b]			
Crizotinib, no. of patients (%) [95% CI][c]	37 (69.8) [55.7–81.7]	112 (65.3) [57.7–72.4]	128 (74.4) [67.2– 80.8)
Chemotherapy	NA	34 (19.5) [13.9–26.2]	77 (45) [37–53]
Median overall survival (OS)			
Crizotinib, months	NR	21.7 (18.9–30.5)	[redacted]
Chemotherapy	NA	21.9 (16.8–26.0)	[redacted]
HR, (95% CI, p-value)	NA	Unadjusted: 0.854 (0.66–1.10; p=0.11)	Unadjusted: [redacted]
		Crossover adjusted: 0.383 (0.283, 0.518)	Crossover adjusted: [redacted] See **Error! Reference source not found.** and Section B.3.3.4 for details

[a]For between-group comparisons (crizotinib vs. chemotherapy), two-sided log-rank test stratified according to baseline stratification factors were used; stratified Cox regression models were applied to estimate HRs. [b]Tumour response was assessed using RECIST (v1.0 for ROS1 patients in PROFILE 1001, v1.1 for PROFILE 1007, 1014 and three patients from ALK-negative cohort respectively determined to be ROS1-positve in PROFILE 1001) and were confirmed by IRR. [c]P<0.001 for between-group comparison.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria on Solid Tumours.
Source: PROFILE 1001: EPAR Xalkori/crizotinib 21st July 2016[7]; PROFILE 1007: Shaw et al. 2013[71], CSR[70]; Shaw et al. 2016[47]; PROFILE 1014: Solomon et al. 2014[73], CSR[72], updated CSR[96], Mok et al. 2017 ESMO Presentation

Appendix J, Table 49: Clinical outcomes (in months) from the model versus published first-line studies – crizotinib

Outcome	Model result Base case (ALK-positive data as a proxy)	Model result PROFILE 1001 analysis (ROS1-positive data)	PROFILE 1001 Shaw *et al.* (2014)	PROFILE 1014
Median PFS (months)	8.9	23.7	19.2	10.9
Median OS (months)	32.5	49.3	Not reached	[redacted]
Median PPS (months)	23.7	25.6	Not estimable	[redacted]

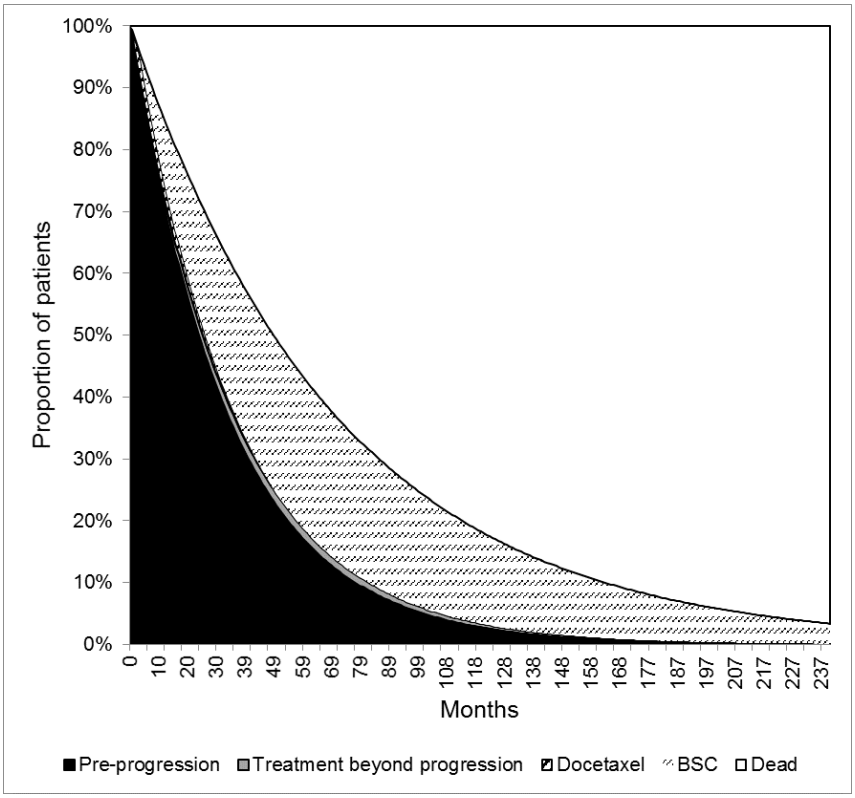
Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

Appendix J, Table 50: Clinical outcomes (in months) from the model versus published first-line studies – pemetrexed plus platinum therapy

Outcome	Model result Base case (ALK-positive data as a proxy)	Model result PROFILE 1001 analysis (ROS1-positive data)	PROFILE 1014 (cross-over adjusted)
Median PFS (months)	6.9	11.8	7.0
Median OS (months)	12.8	17.7	[redacted]
Median PPS (months)	5.9	5.9	[redacted]

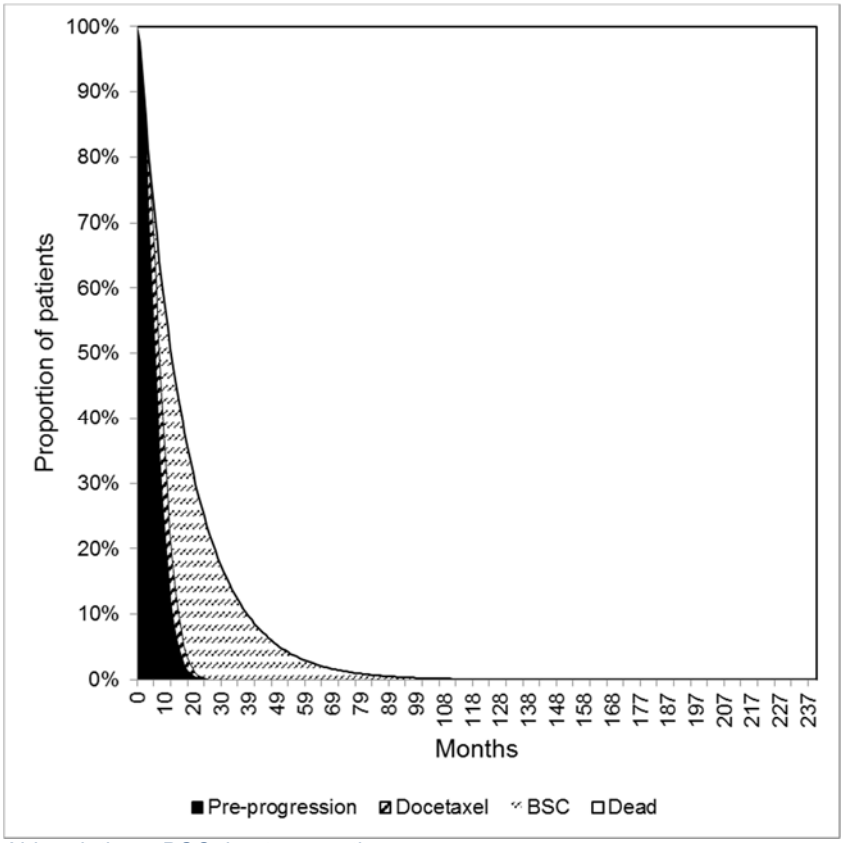
Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

Figure 9: Markov trace - crizotinib, PROFILE 1001 analysis (first-line)



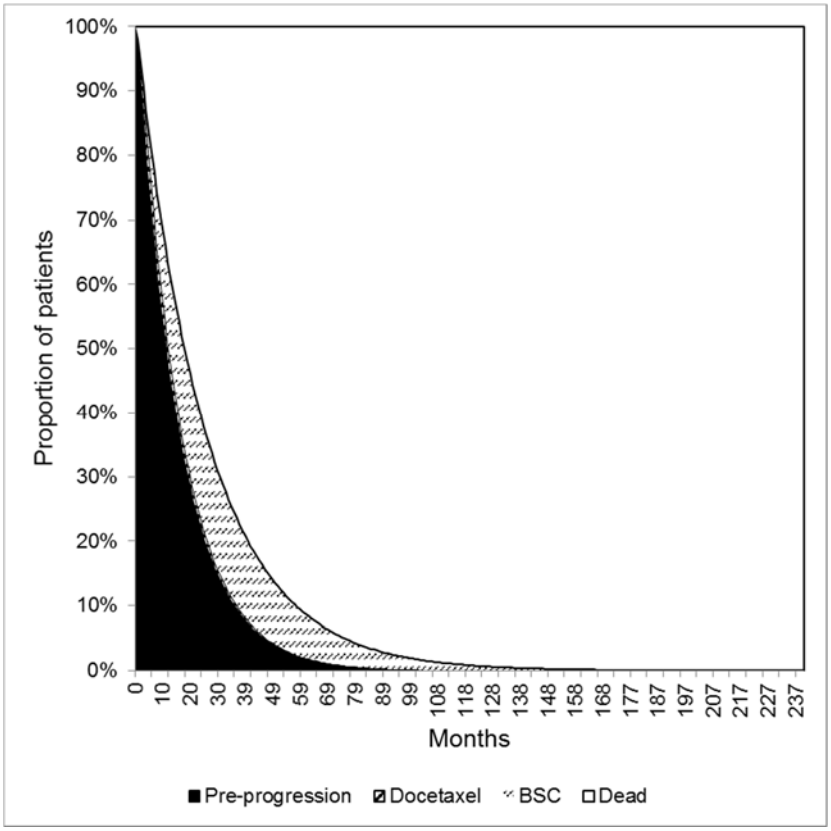
Abbreviations: BSC, best supportive care.

Figure 10: Markov trace - pemetrexed plus platinum therapy, base case (first-line)



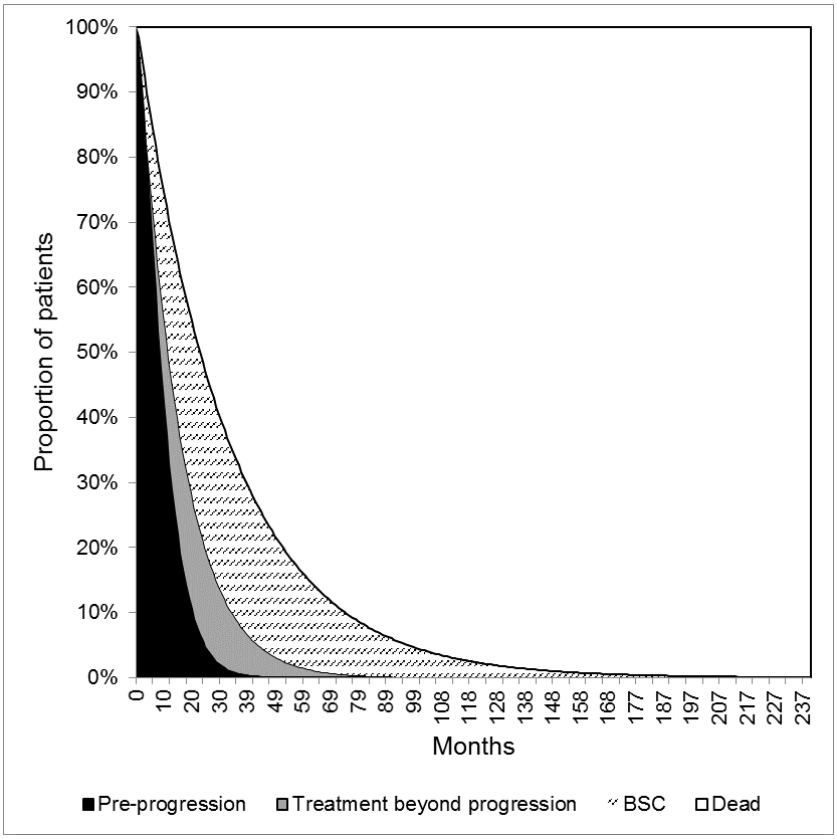
Abbreviations: BSC, best supportive care.

Figure 11: Markov trace - pemetrexed plus platinum therapy, PROFILE 1001 analysis (first-line)



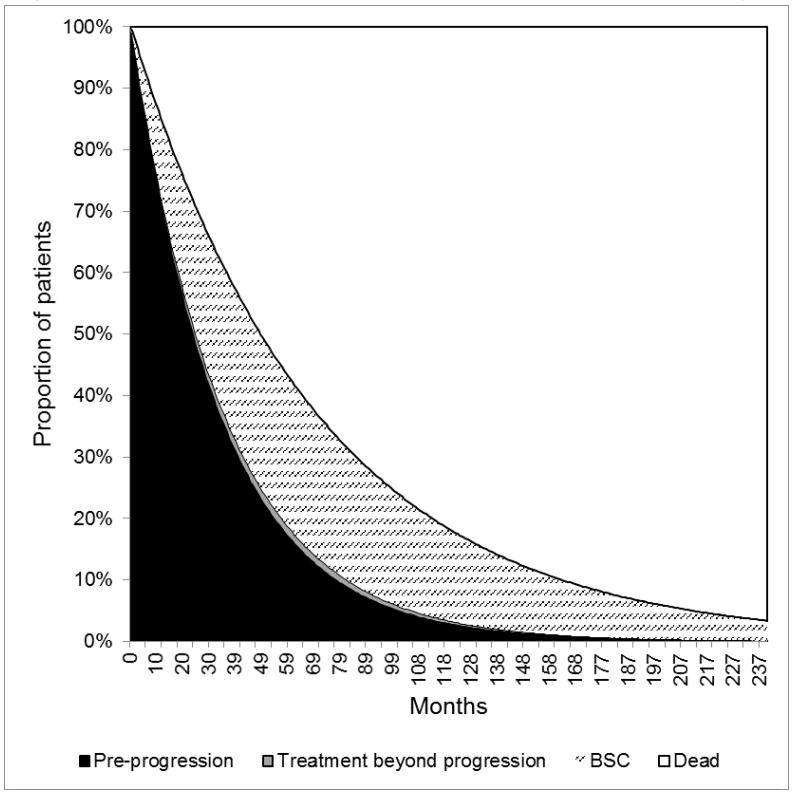
Abbreviations: BSC, best supportive care.

Figure 12: Markov trace, crizotinib, base case (subsequent-line)



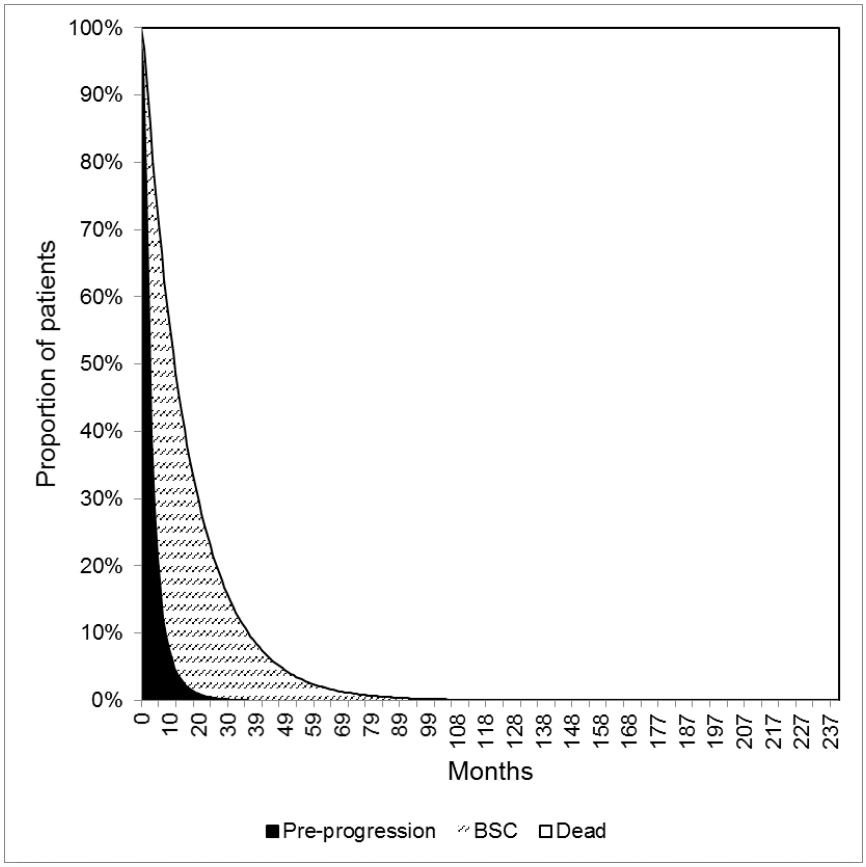
Abbreviations: BSC, best supportive care.

Figure 13: Markov trace - crizotinib, PROFILE 1001 analysis (subsequent-line)



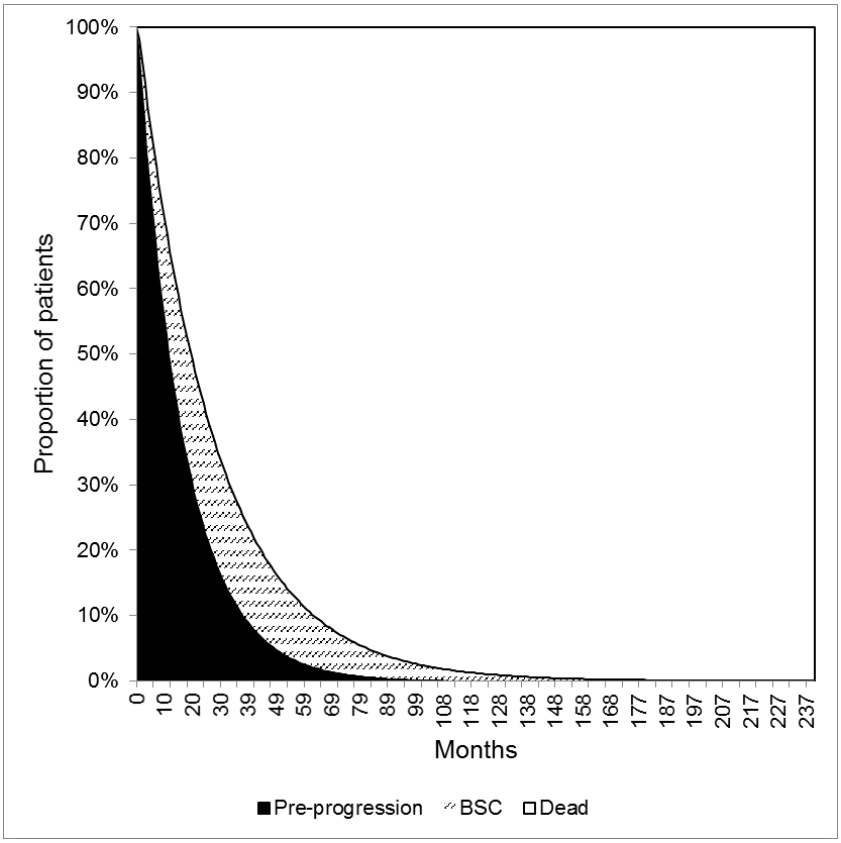
Abbreviations: BSC, best supportive care.

Figure 14: Markov trace - docetaxel, base case (subsequent-line)



Abbreviations: BSC, best supportive care.

Figure 15: Markov trace - docetaxel, PROFILE 1001 analysis (subsequent-line)



Abbreviations: BSC, best supportive care.

Text Body Corrections

Document and Section	Description
Document B, Section B.3.10.1 (page 176)	PFS from EUCROSS to be corrected to "[redacted])" as reported in the summary box for Section B.2 and in Section B.2.6.2
Document B and Document A, throughout	[redacted] and [redacted] to be highlighted as AiC.
Appendices Document, Appendix O (page 201–207)	All mention of ICER values to be marked as CiC, as in Table 79 to Table 86 in the Appendices Document

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

Addendum to Document B and appendices document

Contents

Base case results (first-line, base case). Document A; Section A.13; page 21

Table 1: Base-case results: crizotinib with PAS versus pemetrexed plus platinum therapy (deterministic) – Document B, B.3.7.1, Table 62 (page 157)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Pemetrexed plus platinum therapy	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year

Probabilistic results (first-line, base case). Document A; Section A.14; page 22

Table 2: Base-case results: crizotinib with PAS versus pemetrexed plus platinum therapy (probabilistic) – Document B, B.3.8.1, Table 66 (page 160)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Pemetrexed plus platinum therapy	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 1: Base case cost-effectiveness plane: crizotinib versus pemetrexed plus platinum therapy (crizotinib with PAS) – Document B, B.3.8.1, Figure 32 (page 161)

Abbreviation: PSA, probabilistic sensitivity analysis; QALYs: quality-adjusted life year.

One-way sensitivity analysis (first-line, base case). Document A; Section A.15; page 26

Figure 2: Base case tornado diagram: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS [redacted] [Document B, B.3.8.2, Figure 41 (page 168)]

Abbreviation: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; TSA, Two-stage adjustment A; TTF, time to treatment failure.

Scenario analysis (first-line, base case). Document A; Section A.15; page 28

Table 3: Key scenario analyses to base case and resulting ICERs with PAS

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (versus pemetrexed plus platinum)	Impact on base-case ICER (versus docetaxel)
Base case			[redacted]	[redacted]
Time horizon equal to 5 years	N/A	The time horizon has an impact of the total costs and total QALYs	[redacted]	[redacted]
Time horizon equal to 10 years	N/A	The time horizon has an impact of the total costs and total QALYs	[redacted]	[redacted]
Sequential testing for ROS1	ROS1 testing is offered to EGFR- and ALK-negative non-squamous NSCLC patients	Sequential testing would reduce the number of patients who would be tested, and hence reduce the total cost of testing	[redacted]	[redacted]
Log normal OS models	N/A	As the new data cut for PROFILE 1014 OS has not previously been appraised, the impact of alternative models is explored	[redacted]	N/A
Log logistic OS models	N/A	As the new data cut for PROFILE 1014 OS has not previously been appraised, the impact of alternative models is explored	[redacted]	N/A
Gompertz OS models	N/A	As the new data cut for PROFILE 1014 OS has not previously been appraised, the impact of alternative models is explored	[redacted]	N/A

Abbreviation: ICER, incremental cost-effectiveness ratio; N/A., not applicable; NSCLC, non-small-cell lung cancer; OS, overall survival; QALYs, Quality-adjusted life-years.

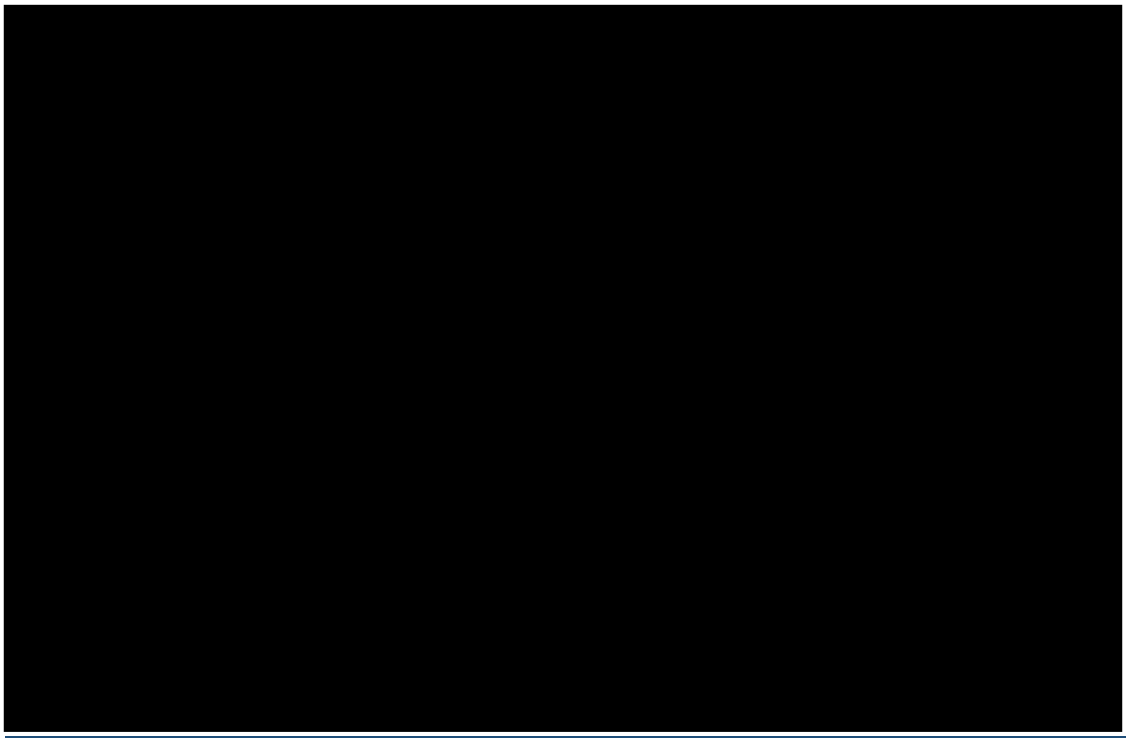
Progression-free survival. Document B; Section B.3.3.4; Page 107

Progression Free Survival

First line

The PROFILE 1014 PFS data and extrapolations have already been appraised and accepted by NICE in TA406.[5] Therefore, only the final accepted curves have been modelled for crizotinib and pemetrexed + platinum therapy. Fully stratified log-normal and generalised gamma curves (for crizotinib and pemetrexed + platinum therapy, respectively) which independently adjusted for covariates (and therefore did not assume proportional hazards between treatment groups) were used in this base case analysis which best reflected the committee's preferences. The curves, which used data from PROFILE 1014, were adjusted to reflect the characteristics of patients in England, using data from a retrospective cohort study in the US and Canada.[127] These curves are shown in Figure 3.

Figure 3: Final accepted PFS curves for crizotinib and pemetrexed plus platinum therapy from TA406



Abbreviations: PFS, progression-free survival; TA, technology appraisal
Source: NICE TA406[5]

Time on treatment curves. Document B; Section B.3.3.4; Page 109

Time on Treatment

First-line

The PROFILE 1014 time on treatment data and extrapolations have already been appraised and accepted by NICE in TA406.5 Therefore, only the final accepted curves have been modelled for crizotinib and pemetrexed plus platinum therapy. In the committee's preferred base case, fully stratified (independent) exponential and gompertz curves (for crizotinib and pemetrexed + platinum therapy, respectively) which were adjusted to reflect the population in England were used to estimate time on treatment.127 These curves, along with the final accepted OS and PFS curves are shown in Figure 4 and **Error! Reference source not found.**, respectively.

Figure 4: Updated PROFILE 1014 OS and final accepted PFS and TTD curves for crizotinib from TA406

Abbreviations: OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TTD, time to treatment discontinuation
Source: NICE TA406[5]

Model parameters. Document B; Section B.3.6. page 147

Table 4: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Model controls			
Time horizon	20	None	**Error! Reference source not found.**
Discount rate for costs	3.50%	1.5%-3.5% tested in OWSA, not varied in PSA	**Error! Reference source not found.**
Discount rate for QALYs	3.50%		**Error! Reference source not found.**
Discount rate for LYs	0.00%	None	**Error! Reference source not found.**
Proportion of patients receiving carboplatin in combination with pemetrexed	46.15%	Beta (38.71%, 53.68%)	**Error! Reference source not found.**
Patient characteristics at baseline			
BSA (PROFILE 1001)	1.80	Normal (1.75, 1.85)	**Error! Reference source not found.**
Height (TA406)	164.08	Normal (163.17, 164.99)	**Error! Reference source not found.**
Weight (TA406)	65.80	Log normal (12.90, 335.75)	**Error! Reference source not found.**
BSA (TA422)	1.80	Normal (1.45, 2.15)	**Error! Reference source not found.**
Treatment costs			
Drug cost: crizotinib 60-tab pack (200mg)	£4,689.00	None	**Error! Reference source not found.**
Drug cost: crizotinib 60-tab pack (250mg)	£4,689.00	None	**Error! Reference source not found.**

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Drug cost: pemetrexed 100mg	£160.00	None	**Error! Reference source not found.**
Drug cost: pemetrexed 500mg	£800.00	None	**Error! Reference source not found.**
Drug cost: carboplatin 50mg (5ml vial)	£3.25	Normal (£3.24, £3.26)	**Error! Reference source not found.**
Drug cost: carboplatin 150mg (15ml vial)	£7.49	Normal (£7.44, £7.54)	**Error! Reference source not found.**
Drug cost: carboplatin 450mg (45ml vial)	£20.39	Normal (£20.22, £20.56)	**Error! Reference source not found.**
Drug cost: carboplatin 600mg (65ml vial)	£27.89	Normal (£27.66, £28.12)	**Error! Reference source not found.**
Drug cost: cisplatin 10mg (10ml vial)	£1.99	Normal (£1.96, £2.02)	**Error! Reference source not found.**
Drug cost: cisplatin 50mg (50ml vial)	£6.48	Normal (£6.45, £6.51)	**Error! Reference source not found.**
Drug cost: cisplatin 100mg (100ml vial)	£8.45	Normal (£8.40, £8.50)	**Error! Reference source not found.**
Drug cost: docetaxel 20mg (20mg/ml, 1ml Vial)	£3.85	Normal (£3.82, £3.88)	**Error! Reference source not found.**
Drug cost: docetaxel 80mg (20mg/ml, 4ml Vial)	£12.38	Normal (£12.05, £12.71)	**Error! Reference source not found.**
Drug cost: docetaxel 140mg (20mg/ml, 7ml Vial)	£20.62	Normal (£20.29, £20.95)	**Error! Reference source not found.**
Drug cost: docetaxel 160mg (20mg/ml, 8ml Vial)	£20.44	Normal (£19.77, £21.11)	**Error! Reference source not found.**
Treatment administration costs			
Administration cost: Crizotinib (TA406)	£14.40	Normal (£11.58, £17.22)	**Error! Reference source not found.**

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Administration cost: SB14Z outpatient cost	£304.30	Normal (£244.65, £363.94)	**Error! Reference source not found.**
Administration cost: SB14Z day case and regular day/night cost	£406.63	Normal (£326.93, £486.33)	**Error! Reference source not found.**
ROS1 testing costs			
Cost per IHC test	£50.00	Normal (£40.20, £59.80)	**Error! Reference source not found.**
Cost per FISH test	£120.00	Normal (£96.48, £143.52)	**Error! Reference source not found.**
ROS1 ICH specificity	83.00%	Beta (63.95%, 95.72%)	**Error! Reference source not found.**
ROS1 incidence in adenocarcinoma patients	1.80%	Beta (1.46%, 2.17%)	**Error! Reference source not found.**
Stage III/IV NSCLC patients who are non-squamous histological subtype	67.64%	Beta (53.74%, 80.11%)	**Error! Reference source not found.**
Stage III/IV NSCLC patients who are adenocarcinoma histological subtype	63.47	Beta (50.63%, 75.41%)	**Error! Reference source not found.**
Utilities			
Utility: progression free on crizotinib	0.81	Beta (0.79, 0.85)	**Error! Reference source not found.**
Utility: progression free on peckish/carb	0.72	Beta (0.70, 0.74)	**Error! Reference source not found.**
Utility: progressed on docetaxel	0.66	Beta (0.58, 0.74)	**Error! Reference source not found.**
2nd line utility: progression free on crizotinib	0.81	Beta (0.79, 0.85)	**Error! Reference source not found.**
2nd line utility: progression free on docetaxel	0.66	Beta (0.58, 0.74)	**Error! Reference source not found.**

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
2nd line utility: progressive disease: 3rd line treatment with BSC	0.47	Beta (0.38, 0.56)	**Error! Reference source not found.**
Survival and progression - 1st line (PROFILE 1001 analysis)			
Crizotinib vs. Pemetrexed+cis/carb for PFS (HR)	0.45	Log normal (0.35, 0.60)	**Error! Reference source not found.**
Crizotinib vs. Pemetrexed+cis/carb for OS (HR) - Adjusted: Wilcoxon (new data cut)	[redacted]	[redacted]	**Error! Reference source not found.**
Survival and progression - 2nd line (PROFILE 1001 analysis)			
Crizotinib vs. docetaxel for PFS (HR) - chemotherapy	0.49	Log normal (0.37, 0.64)	**Error! Reference source not found.**
Crizotinib vs. docetaxel for OS (HR) - Adjusted (chemotherapy): RPSFTM - Log-rank	0.38	Log normal (0.04, 0.99)	**Error! Reference source not found.**
Curve fit parameters (OS) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter OS: Rate	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameters (PFS) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter PFS: Rate	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameters (TTF) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter TTF: Rate	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Survival and progression - 2nd line (ALK-POSITIVE accepted HR; base case)			
Crizotinib vs. docetaxel for OS (HR) - TA422 ALK-POSITIVE crizotinib	0.49	Log normal (0.37, 0.64)	**Error! Reference source not found.**
Curve fit parameters (OS) – Exponential - Crizotinib 1L ALK-POSITIVE curve – Adjusted: Wilcoxon (updated PROFILE 1014 data cut) (base case)			
Curve fit parameter OS: Rate - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter OS: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameters (OS) - Exponential - Pemetrexed 1L ALK-POSITIVE curve – Adjusted: Wilcoxon (updated PROFILE 1014 data cut) (base case)			
Curve fit parameter OS: Rate - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Ecog=2) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter OS: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter OS: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameters (PFS) – Log-normal - Crizotinib 1L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Mean log- criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: SD log - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameters (PFS) - Gamma - Pem 1L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Mu - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: Sigma - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter PFS: Q - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Ecog=2) -pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter (TTD) - Exponential - Crizotinib 1L ALK-POSITIVE curve (base case)			
Curve fit parameter TTD: Rate - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter TTD: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter (TTD) - Gompertz - Pem 1L ALK-POSITIVE curve (base case)			
Curve fit parameter TTD: Shape -pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: Rate - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Ecog=2) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter TTD: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameters (OS) - Exponential - 2L ALK-POSITIVE curve (base case)			
Curve fit parameter OS: Rate	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter (PFS) - Weibull - Crizotinib 2L ALK-POSITIVE curve (base case)			

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: ln p	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter (PFS) - Log-normal - Crizotinib 2L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: sigma	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter (TTD) - Weibull - Crizotinib 2L ALK-POSITIVE curve (base case)			
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	**Error! Reference source not found.**
Curve fit parameter PFS: ln p	[redacted]	Multinormal distribution	**Error! Reference source not found.**

Abbreviation: BSA, body surface area; carb, carboplatin; CI, confidence interval; cis, cisplatin; FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, ImmunoHistoChemistry, LYs, life years; NSCLC, non-small cell lung cancer; OS, overall survival; OWSA, one-way sensitivity analysis; pem + c/c; pemetrexed + cisplatin or carboplatin; PFS, progression free survival; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; RPSFTM, Rank Preserving Structural Failure Time Models; TA, Technology appraisal; TTF, time to treatment failure.

Assumptions. Document B; Section B.3.6.1; page 153

Table 5: Summary of assumptions applied in the economic model

Assumptions	Assumption description	Justification
Time horizon	Lifetime (20 years)	The economic model runs for 20 years to reflect the extrapolated life expectancy of the full crizotinib cohort. The impact of varying time horizon on the results is tested in sensitivity analysis.

Assumptions	Assumption description	Justification
Target dose for carboplatin is 500mg	TA181[6] and TA406[5] estimated that a target AUC of 5 would result in a dose of 500mg, and TA347 estimated that a target AUC of 5 would result in a dose of 750 mg. In both base case analyses, the target dose was assumed to be 500mg.	The dose of 500 mg was selected in both base case analyses as a conservative assumption as this results in the lower cost for carboplatin.
Chemotherapy administration setting	Cisplatin-containing regimens were assumed to incur a day case appointment, whereas carboplatin-containing regimens were assumed to incur an outpatient appointment.	This is based on assumptions made in a previous NICE technology appraisal (TA181) for pemetrexed, due to the more complex administration required for cisplatin.[6]
Cisplatin/ carboplatin mix in pemetrexed regimen	The proportion of patients receiving pemetrexed plus cisplatin or pemetrexed plus carboplatin in the PROFILE 1014 trial is reflective of current practice.	The efficacy data for pemetrexed is based on the pooled combination with cisplatin and carboplatin. The proportion with which these two regimens are used in the model (and the resulting impact on average therapy cost) is that which was observed in the PROFILE 1014 trial. A sensitivity analysis is presented in the results whereby proportionate use favours the cheaper carboplatin over cisplatin (25% cisplatin, 75% carboplatin). The pemetrexed survival has been modelled using the pooled pemetrexed treatment arm with pooled efficacy outcomes as the difference in efficacy between cisplatin and carboplatin is assumed negligible.
Number of pemetrexed treatment cycles	The number of pemetrexed treatment cycles is assumed to be 6 (PROFILE 1001 analysis).	This is based on the median number of cycles of pemetrexed plus platinum therapy received in the PROFILE 1014 trial where up to 6 cycles were allowed. A sensitivity analysis is presented assuming 4 cycles in line with expected clinical practice.
Resource utilisation	Resource utilisation is expected to be the same for patients receiving first- and second-line treatment for NSCLC.	This assumption was confirmed by clinical experts in TA406.
Treatment beyond progression	Treatment with crizotinib beyond progression is modelled based on time on treatment curves for crizotinib.	The PROFILE 1001, PROFILE 1007 and PROFILE 1014 trials allowed treatment beyond progression with crizotinib at the investigator's discretion.
ROS1-testing	The cost of ROS1-testing is applied for the crizotinib arm. The modelled method of testing is IHC followed by confirmatory FISH.	Crizotinib is only licensed for use in ROS1- or ALK-positive patients so the testing cost is not included for standard of care comparators. The modelled method of testing of IHC followed by confirmatory FISH test is derived from ESMO guidelines which state this is a "cost-effective" approach to testing.[62]

Assumptions	Assumption description	Justification
Fully stratified survival models	In the base case first-line model, separate survival curves were fitted to the crizotinib and pemetrexed plus platinum therapy arms. These curves were taken from TA406 for PFS and TTF and from an updated data cut of PROFILE 1014 for OS.	This is in line with the committee preferred base case for the survival models from the appraisal for crizotinib in untreated ALK-positive NSCLC (TA406).
Crossover method (base case analysis)	RPSFTM- Wilcoxon was used for crossover adjustment for PROFILE 1014	The Wilcoxon method was selected as it gives the most conservative results of the ones tested
OS curve (base case analysis)	The exponential curve from the updated data cut of PROFILE 1014 was used in the base case for crizotinib and pemetrexed plus platinum therapy.	The exponential curves were selected based on visual inspection and clinical plausibility and AIC/BIC results.
PFS curve (base case analysis)	In the base case, the log-normal and gamma curves (accepted in TA406) were used for crizotinib and pemetrexed, respectively	These are the curve that were accepted by the committee in the appraisal of crizotinib in untreated ALK- positive NSCLC (TA406)
Time on treatment curve (base case analysis)	In the base case, the exponential and gompertz curves (accepted in TA406) were used for crizotinib and pemetrexed, respectively	These are the curve that were accepted by the committee in the appraisal of crizotinib in untreated ALK-positive NSCLC (TA406)
Proportional hazards (PROFILE 1001 analysis)	A proportional treatment effect is assumed for both PFS and OS (applicable for PROFILE 1001 analysis only)	If we do not assume proportional hazards this would lead to fitting separate survival curves to the comparator arms of PROFILE 1014 and 1007 respectively and if these are directly representative of ROS1-positive patients receiving the comparator treatments. We considered that the assumption of proportional hazards was preferable to naively comparing survival curves in the absence of sufficient data to support an MAIC approach.
PFS curve (PROFILE 1001 analysis)	The exponential curve was selected as the base case curve for PFS (applicable for PROFILE 1001 analysis only)	The exponential curve was selected for the base case as it had a similar statistical fit to the observed data compared with other curves (based on the AIC, BIC) and provided a plausible extrapolation; other curves predict longer, more unrealistic PFS times.
OS curve (PROFILE 1001 analysis)	The exponential curve was selected as the base case curve for OS (applicable for PROFILE 1001 analysis only)	The exponential curve had a similar statistical fit to the observed data compared with other curves (based on the AIC, BIC) and provided the most plausible extrapolation (and other curves predict longer, more unrealistic OS times), and this curve was therefore selected in the PROFILE 1001 analysis

Assumptions	Assumption description	Justification
Utility values in *progression-free*	Utility values were assumed to vary by treatment in the *progression-free* health state.	Differences in HRQoL were observed between the treatment arms in the PROFILE 1014 and PROFILE 1007 trial.
No additional quantified disutility due to adverse events	It was assumed that there would be no explicit decrements of disutility associated with adverse events, beyond existing on-treatment EQ-5D utility	The utility estimates included in the economic model for the crizotinib, pemetrexed plus platinum therapy and docetaxel arms are taken directly from patients on treatment in the PROFILE 1014 and PROFILE 1007 trials, and hence this HRQoL reporting is expected to already reflect the negative changes in utility incurred through the adverse event profiles of the treatments. The impact of including a disutility due to adverse events could be deemed 'double-counting'. This assumption was accepted in TA406.
HRQoL is assumed constant over time in each state	It was assumed that HRQoL in each disease state is constant irrespective of time spent in that state, once a patient has transitioned into this states after the first cycle.	Symptoms that impact HRQoL are directly related to the progression of disease, whilst a patient is in the progression free health state they would not be expected to experience a worsening of symptoms and hence there is no expected change in HRQoL.
ALK-positive data is a suitable proxy for ROS-positive	Base case: ALK- positive NSCLC data used as proxy for ROS1-positive patients PROFILE 1001 analysis: published HRs from PROFILE 1014 and PROFILE 1007 used to estimated comparative efficacy versus pemetrexed plus platinum and docetaxel, respectively	ALK-positive and ROS1-positive NSCLC have extensive homology. With the lack of comparative efficacy data in ROS1-positive patients this assumption was consider the next best estimate. Due to the small sample size and uncertainty associated with the PROFILE 1001, in the base case we use OS and PFS curves as proxy for ROS1-positive patients.[8] Clinical experts at an ad board stated that ALK-positive data would be a suitable proxy for ROS1-positive NSCLC.
Pooled chemotherapy is an appropriate proxy for docetaxel monotherapy	As no crossover adjusted HR is available for crizotinib versus docetaxel monotherapy, pooled chemo therapy is used as proxy	This is a conservative assumption as pooled chemotherapy would be expected to have better survival estimates than docetaxel alone. This assumption was made in TA422 and accepted by the committee.[8]

Abbreviation: AIC, Akaike information criterion; ALK, Anaplastic lymphoma kinase; AUC, area under the curve; BIC, Bayesian information criterion; ESMO, European Society for Medical Oncology; EQ-5D, EuroQol five dimensions questionnaire; FISH, fluorescence in situ hybridization; HRQoL, health-related quality of life; IHC, Immunohistochemistry, MAIC, matching adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life years; TA, technology appraisal; TTF, time to treatment failure.

Base case results (first- line). Document B; Section B.3.7.1; page 157

Table 6: Base case results: crizotinib with PAS versus pemetrexed plus platinum therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Probabilistic results (first line, base case). Document B; Section B.3.8.1; page 159.

The incremental results from the first-line probabilistic analyses for the base case are presented in

Table 7 and for the PROFILE 1001 analysis in **Error! Reference source not found.**. The results show that the probabilistic ICER is [redacted] in the base case analysis versus pemetrexed plus platinum therapy. The results of the probabilistic analysis are similar to the deterministic base case results in the base case analysis (ICERs of [redacted]).

Table 7: Probabilistic results (base case): crizotinib with PAS versus pemetrexed plus platinum therapy (deterministic ICER [redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]

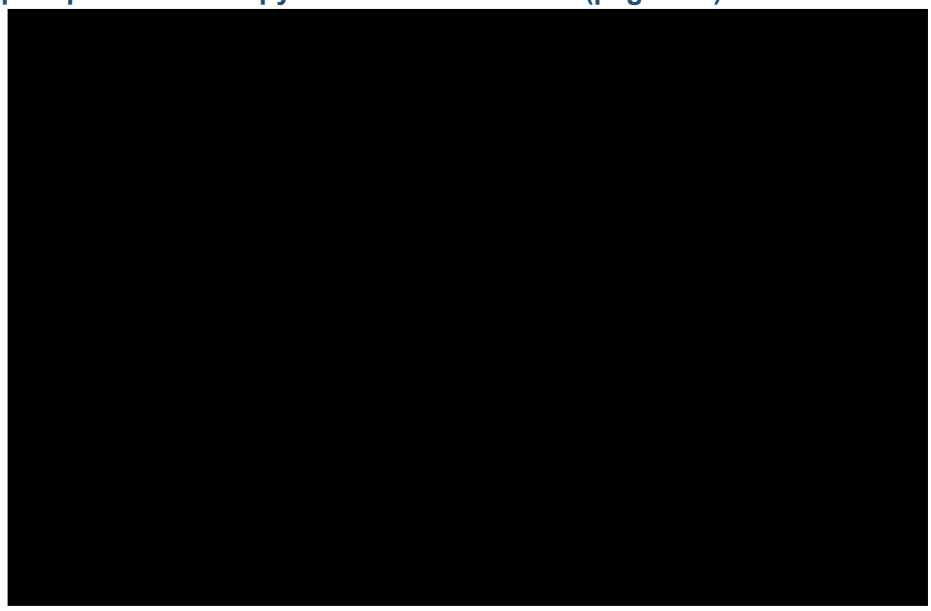
Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life year

Figure 5: Base case: Cost-effectiveness plane: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS (Page 161)

Abbreviation: PSA, probabilistic sensitivity analysis; QALYs: quality-adjusted life year.

The CEAC demonstrates crizotinib has a [redacted] probability of being cost-effective at a willingness to pay threshold of £50,000.

Figure 6: Base case: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS (page 161)



One-way sensitivity analysis (first-line, base case). Document B; Section B.3.8.2; Page 167

Figure 7: Base case tornado diagram: crizotinib versus pemetrexed plus platinum therapy – crizotinib with PAS ([redacted])

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; TSA, Two-stage adjustment A; TTD, time to treatment discontinuation.

Scenario analysis (first-line, base case). Document B; Section B.3.8.1; Page 172

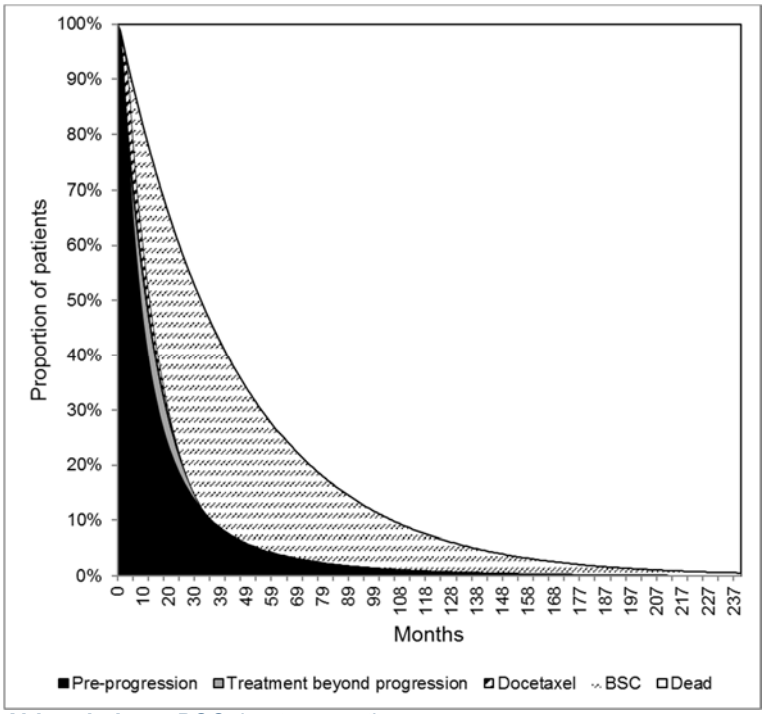
Table 8: Results of scenario analysis on base case - crizotinib with PAS

Scenario No.	Scenario setting	ICER: crizotinib versus pemetrexed plus platinum therapy (first-line)	ICER: crizotinib versus docetaxel monotherapy (subsequent-line)
Base case		[redacted]	[redacted]
1	Time horizon equal to 5 years	[redacted]	[redacted]
2	Time horizon equal to 10 years	[redacted]	[redacted]
3	Time horizon equal to 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	Sequential testing for ROS1	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	N/A
7	Crossover adjustment method: Log-rank	[redacted]	N/A
8	Weibull OS models	[redacted]	N/A
9	Gamma OS models	[redacted]	N/A
10	Log normal OS models	[redacted]	N/A
11	Log logistic OS models	[redacted]	N/A
12	Gompertz OS models	[redacted]	N/A
13	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

Abbreviation: ICER, incremental cost-effectiveness ratio; NA., not applicable; PAS, patient access scheme.

Markov Trace (first-line, base case). Appendix J.1; Page 154

Figure 8: Markov Trace, crizotinib, base case



Abbreviations: BSC, best supportive care.

Disaggregated Results (first-line, base case). Appendix J.2; page 160

Table 9: Summary of QALY gain by health state

Health state	QALY: crizotinib	QALY: pemetrexed plus platinum therapy	Increment	Absolute increment	% absolute increment
Pre-progression	1.071	0.435	0.636	0.636	49.62%
Post progression	1.054	0.409	0.645	0.645	50.38%
Total	2.125	0.844	1.281	1.281	100%

Abbreviations: QALY, quality-adjusted life year

Table 10: Summary of costs by health state – crizotinib list price

Health state	Cost: crizotinib	Cost: pemetrexed plus platinum therapy	Increment	Absolute increment	% absolute increment
Pre-progression	[redacted]	£13,794	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	£9,473	[redacted]	[redacted]	[redacted]
Total	[redacted]	£23,267	[redacted]	[redacted]	[redacted]

Table 11: Summary of costs by health state – crizotinib with PAS

Health state	Cost: crizotinib	Cost: pemetrexed plus platinum therapy	Increment	Absolute increment	% absolute increment
Pre-progression	[redacted]	£13,794	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	£9,473	[redacted]	[redacted]	[redacted]
Total	[redacted]	£23,267	[redacted]	[redacted]	[redacted]

Table 12: Summary of predicted resource use by category of cost – crizotinib list price

Item	Cost: crizotinib	Cost: pemetrexed plus platinum therapy	Increment	Absolute increment	% absolute increment
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.

Table 13: Summary of predicted resource use by category of cost – crizotinib with PAS

Item	Cost: crizotinib	Cost: pemetrexed plus platinum therapy	Increment	Absolute increment	% absolute increment
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.

Model Parameters. Appendix N; Page 185

Table 14: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Model controls			
Time horizon	20	None	B.3.2.2
Discount rate for costs	3.50%	1.5%-3.5% tested in OWSA, not varied in PSA	B.3.2.2
Discount rate for QALYs	3.50%		B.3.2.2
Discount rate for LYs	0.00%	None	B.3.2.2
Proportion of patients receiving carboplatin in combination with pemetrexed	46.15 %	Beta (38.71%, 53.68%)	B.3.5.1
Patient characteristics at baseline			
BSA (PROFILE 1001)	1.80	Normal (1.75, 1.85)	B.3.3.1
Height (TA406)	164.08	Normal (163.17, 164.99)	B.3.3.1
Weight (TA406)	65.80	Log normal (12.90, 335.75)	B.3.3.1
BSA (TA422)	1.80	Normal (1.45, 2.15)	B.3.3.1
Treatment costs			
Drug cost: crizotinib 60-tab pack (200mg)	£4,689 .00	None	B.3.5.1
Drug cost: crizotinib 60-tab pack (250mg)	£4,689 .00	None	B.3.5.1
Drug cost: pemetrexed 100mg	£160.0 0	None	B.3.5.1
Drug cost: pemetrexed 500mg	£800.0 0	None	B.3.5.1

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Drug cost: carboplatin 50mg (5ml vial)	£3.25	Normal (£3.24, £3.26)	B.3.5.1
Drug cost: carboplatin 150mg (15ml vial)	£7.49	Normal (£7.44, £7.54)	B.3.5.1
Drug cost: carboplatin 450mg (45ml vial)	£20.39	Normal (£20.22, £20.56)	B.3.5.1
Drug cost: carboplatin 600mg (65ml vial)	£27.89	Normal (£27.66, £28.12)	B.3.5.1
Drug cost: cisplatin 10mg (10ml vial)	£1.99	Normal (£1.96, £2.02)	B.3.5.1
Drug cost: cisplatin 50mg (50ml vial)	£6.48	Normal (£6.45, £6.51)	B.3.5.1
Drug cost: cisplatin 100mg (100ml vial)	£8.45	Normal (£8.40, £8.50)	**Error! Reference source not found.**
Drug cost: docetaxel 20mg (20mg/ml, 1ml Vial)	£3.85	Normal (£3.82, £3.88)	B.3.5.1
Drug cost: docetaxel 80mg (20mg/ml, 4ml Vial)	£12.38	Normal (£12.05, £12.71)	B.3.5.1
Drug cost: docetaxel 140mg (20mg/ml, 7ml Vial)	£20.62	Normal (£20.29, £20.95)	B.3.5.1
Drug cost: docetaxel 160mg (20mg/ml, 8ml Vial)	£20.44	Normal (£19.77, £21.11)	B.3.5.1
Treatment administration costs			
Administration cost: Crizotinib (TA406)	£14.40	Normal (£11.58, £17.22)	B.3.5.1
Administration cost: SB14Z outpatient cost	£304.30	Normal (£244.65, £363.94)	B.3.5.1
Administration cost: SB14Z day case and regular day/night cost	£406.63	Normal (£326.93, £486.33)	B.3.5.1

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
ROS1 testing costs			
Cost per IHC test	£50.00	Normal (£40.20, £59.80)	B.3.5.4
Cost per FISH test	£120.00	Normal (£96.48, £143.52)	B.3.5.4
ROS1 IHC specificity	83.00 %	Beta (63.95%, 95.72%)	B.3.5.4
ROS1 incidence in adenocarcinoma patients	1.80%	Beta (1.46%, 2.17%)	B.3.5.4
Stage III/IV NSCLC patients who are non-squamous histological subtype	67.64 %	Beta (53.74%, 80.11%)	B.3.5.4
Stage III/IV NSCLC patients who are adenocarcinoma histological subtype	63.47 %	Beta (50.63%, 75.41%)	B.3.5.4
Proportion NSCLC patients EGFR	16.60 %	Beta (13.48%, 19.98%)	B.3.5.4
Proportion ALK amongst NSCLC patients	3.40%	Beta (2.77%, 4.10%)	B.3.5.4
Proportion non-squamous patients ALK patients	94.00 %	Beta (65.87%, 100.00%)	B.3.5.4
Monitoring - patients on 1L and 2L treatment			
Monitoring - patients on 1L and 2L treatment: proportion of patients requiring an outpatient visit per month	75.00 %	Beta (58.99%, 88.09%)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: proportion of patients requiring a GP visit per month	10.00 %	Beta (8.13%, 12.04%)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: proportion of patients requiring a cancer nurse	20.00 %	Beta (16.23%, 24.06%)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: frequency of visits from a cancer nurse per month	1.00	Normal (0.59, 0.88)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: proportion of patients requiring a complete blood count per month	75.00 %	Beta (58.99%, 88.09%)	B.3.5.2

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Monitoring - patients on 1L and 2L treatment: proportion of patients requiring a biochemistry tests per month	75.00 %	Beta (58.99%, 88.09%)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: proportion of patients requiring a CT scan	30.00 %	Beta (24.29%, 36.04%)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: frequency of CT scans per month	0.75	Normal (0.59, 0.88)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: proportion of patients requiring an X-ray per month	75.00 %	Beta (58.99%, 88.09%)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: GP visit cost	£27.00	Normal (£21.71, £32.29)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: outpatient visit cost	£151.12	Normal (£121.50, £180.74)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: cancer nurse cost	£69.20	Normal (£55.64, £82.76)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: complete blood count cost	£3.10	Normal (£2.49, £3.71)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: biochemistry test cost	£1.18	Normal (£0.95, £1.41)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: CT scan cost	£132.19	Normal (£106.28, £158.10)	B.3.5.2
Monitoring - patients on 1L and 2L treatment: X-ray cost	£30.26	Normal (£24.33, £36.19)	B.3.5.2
Monitoring - patients on BSC			
Monitoring - patients on BSC: proportion of patients requiring an oncologist visit per month	100.00 %	Beta (100.00%, 100.00%)	B.3.5.2
Monitoring - patients on BSC: proportion of patients requiring a cancer nurse per month	10.00 %	Beta (8.13%, 12.04%)	B.3.5.2
Monitoring - patients on BSC: proportion of patients requiring a GP visit per month	28.00 %	Beta (22.68%, 33.64%)	B.3.5.2

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Monitoring - patients on BSC: proportion of patients requiring a complete blood count	100.00 %	Beta (100.00%, 100.00%)	B.3.5.2
Monitoring - patients on BSC: frequency of complete blood counts per month	1.00	Normal (0.80, 1.20)	B.3.5.2
Monitoring - patients on BSC: proportion of patients requiring biochemistry tests	100.00 %	Beta (100.00%, 100.00%)	B.3.5.2
Monitoring - patients on BSC: frequency of biochemistry tests per month	1.00	Normal (0.80, 1.20)	B.3.5.2
Monitoring - patients on BSC: proportion of patients requiring an CT scan	5.00%	Beta (4.07%, 6.02%)	B.3.5.2
Monitoring - patients on BSC: frequency of CT scans per month	0.75	Normal (0.60, 0.90)	B.3.5.2
Monitoring - patients on BSC: proportion of patients requiring an X-ray	30.00 %	Beta (24.29%, 36.04%)	B.3.5.2
Monitoring - patients on BSC: frequency of X-rays per month	0.75	Normal (0.60, 0.90)	B.3.5.2
Monitoring - patients on BSC: GP visit cost	£27.00	Normal (£21.71, £32.29)	B.3.5.2
Monitoring - patients on BSC: oncologist visit cost	£151.12	Normal (£121.50, £180.74)	B.3.5.2
Monitoring - patients on BSC: cancer nurse cost	£69.20	Normal (£55.64, £82.76)	B.3.5.2
Monitoring - patients on BSC: complete blood count cost	£3.10	Normal (£2.49, £3.71)	B.3.5.2
Monitoring - patients on BSC: biochemistry cost	£1.18	Normal (£0.95, £1.41)	B.3.5.2
Monitoring - patients on BSC: CT scan cost	£132.19	Normal (£106.28, £158.10)	B.3.5.2
Monitoring - patients on BSC: X-ray cost	£30.26	Normal (£24.33, £36.19)	B.3.5.2
AE costs			
% In PROFILE 1014 (Cruz) experiencing elevated transaminases	14.04 %	Beta (9.26%, 19.61%)	B.3.5.3

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
% In PROFILE 1014 (Criz) experiencing neutropenia	11.11 %	Beta (6.86%, 16.22%)	B.3.5.3
% In PROFILE 1014 (Criz) experiencing anaemia	0.00%	Beta (0.00%, 0.00%)	B.3.5.3
% In PROFILE 1014 (Criz) experiencing leukopenia	1.75%	Beta (0.37%, 4.19%)	B.3.5.3
% In PROFILE 1014 (Criz) experiencing thrombocytopenia	0.00%	Beta (0.00%, 0.00%)	B.3.5.3
% In PROFILE 1014 (Criz) experiencing pulmonary embolism	6.43%	Beta (3.27%, 10.55%)	B.3.5.3
% In PROFILE 1014 (Pem+c/c) experiencing elevated transaminases	2.37%	Beta (0.65%, 5.13%)	B.3.5.3
% In PROFILE 1014 (Pem+c/c) experiencing neutropenia	15.38 %	Beta (10.37%, 21.18%)	B.3.5.3
% In PROFILE 1014 (Pem+c/c) experiencing anaemia	8.88%	Beta (5.08%, 13.59%)	B.3.5.3
% In PROFILE 1014 (Pem+c/c) experiencing leukopenia	5.33%	Beta (2.48%, 9.17%)	B.3.5.3
% In PROFILE 1014 (Pem+c/c) experiencing thrombocytopenia	6.51%	Beta (3.31%, 10.67%)	B.3.5.3
% In PROFILE 1014 (Pem+c/c) experiencing pulmonary embolism	6.51%	Beta (3.31%, 10.67%)	B.3.5.3
% In PROFILE 1014 (Criz 2L) experiencing elevated transaminases	15.70 %	Beta (10.67%, 21.48%)	B.3.5.3
% In PROFILE 1014 (Criz 2L) experiencing neutropenia	13.37 %	Beta (8.72%, 18.83%)	B.3.5.3
% In PROFILE 1014 (Criz 2L) experiencing anaemia	2.33%	Beta (0.64%, 5.04%)	B.3.5.3
% In PROFILE 1014 (Criz 2L) experiencing leukopenia	1.16%	Beta (0.14%, 3.22%)	B.3.5.3
% In PROFILE 1014 (Criz 2L) experiencing thrombocytopenia	0.00%	Beta (0.00%, 0.00%)	B.3.5.3
% In PROFILE 1014 (Criz 2L) experiencing pulmonary embolism	5.23%	Beta (2.43%, 9.01%)	B.3.5.3
% In PROFILE 1014 (Docetax) experiencing elevated transaminases	2.34%	Beta (0.64%, 5.07%)	B.3.5.3

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
% In PROFILE 1014 (Docetax) experiencing neutropenia	19.30 %	Beta (13.75%, 25.52%)	B.3.5.3
% In PROFILE 1014 (Docetax) experiencing anaemia	5.26%	Beta (2.45%, 9.06%)	B.3.5.3
% In PROFILE 1014 (Docetax) experiencing leukopenia	4.68%	Beta (2.05%, 8.30%)	B.3.5.3
% In PROFILE 1014 (Docetax) experiencing thrombocytopenia	0.00%	Beta (0.00%, 0.00%)	B.3.5.3
% In PROFILE 1014 (Docetax) experiencing pulmonary embolism	1.75%	Beta (0.37%, 4.19%)	B.3.5.3
Cost per treatment of elevated transaminases	£0.00	Normal (£0.00, £.00)	B.3.5.3
Number of hospitalisation days required to treat anaemia	1.70	Normal (1.37, 2.03)	B.3.5.3
Cost per anaemia hospitalisation day	£335.57	Normal (£269.80, £401.34)	B.3.5.3
Number of hospitalisation days required to treat thrombocytopenia	2.00	Normal (1.61, 2.39)	B.3.5.3
Cost per thrombocytopenia hospitalisation day	£303.52	Normal (£244.03, £363.01)	B.3.5.3
Number of hospitalisation days required to treat pulmonary embolism	1.00	Normal (0.80, 1.20)	B.3.5.3
Cost per pulmonary embolism hospitalisation day	£26.34	Normal (£21.18, £31.50)	B.3.5.3
Palliative care costs			
Palliative care costs: district nurse	£278.00	Normal (£223.51, £332.49)	B.3.5.2
Palliative care costs: nursing and residential care	£1,000.00	Normal (£804.00, £1196.00)	B.3.5.2
Palliative care costs: hospice care - inpatient	£550.00	Normal (£442.20, £657.80)	B.3.5.2
Palliative care costs: hospice care - final 3 months of life	£4,500.00	Normal (£3618.02, £5381.98)	B.3.5.2
Palliative care costs: Marie Curie nursing service	£550.00	Normal (£442.20, £657.80)	B.3.5.2

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Utilities			
Utility: progression free on crizotinib	0.81	Beta (0.79, 0.82)	B.3.4.5
Utility: progression free on pem+cis/carb	0.72	Beta (0.70, 0.74)	B.3.4.5
Utility: progressed on docetaxel	0.66	Beta (0.58, 0.74)	B.3.4.5
2nd line utility: progression free on crizotinib	0.81	Beta (0.79, 0.82)	B.3.4.5
2nd line utility: progression free on docetaxel	0.66	Beta (0.58, 0.74)	B.3.4.5
2nd line utility: progressive disease: 3rd line treatment with BSC	0.47	Beta (0.38, 0.56)	B.3.4.5
Subsequent therapy			
Proportion of patients receiving Pemetrexed (following crizotinib)	0.29	Beta (0.22, 0.35)	B.3.5.4
Proportion of patients receiving Crizotinib (following crizotinib)	0.00	Beta (0.00, 0.00)	B.3.5.4
Proportion of patients receiving Ceritinib (following crizotinib)	0.16	Beta (0.11, 0.22)	B.3.5.4
Proportion of patients receiving Cisplatin (following crizotinib)	0.17	Beta (0.12, 0.23)	B.3.5.4
Proportion of patients receiving Carboplatin (following crizotinib)	0.13	Beta (0.08, 0.18)	B.3.5.4
Proportion of patients receiving Alectinib (following crizotinib)	0.07	Beta (0.04, 0.11)	B.3.5.4
Proportion of patients receiving Docetaxel (following crizotinib)	0.09	Beta (0.05, 0.13)	B.3.5.4
Proportion of patients receiving Gemcitabine (following crizotinib)	0.08	Beta (0.04, 0.12)	B.3.5.4
Proportion of patients receiving Paclitaxel (following crizotinib)	0.02	Beta (0.01, 0.05)	B.3.5.4
Proportion of patients receiving Vinorelbine (following crizotinib)	0.04	Beta (0.01, 0.07)	B.3.5.4
Proportion of patients receiving Pemetrexed (following pemetrexed)	0.05	Beta (0.02, 0.09)	B.3.5.4
Proportion of patients receiving Crizotinib (following pemetrexed)	0.00	Beta (0.00, 0.00)	B.3.5.4
Proportion of patients receiving Ceritinib (following pemetrexed)	0.13	Beta (0.08, 0.18)	B.3.5.4
Proportion of patients receiving Cisplatin (following pemetrexed)	0.00	Beta (0.00, 0.00)	B.3.5.4
Proportion of patients receiving Carboplatin (following pemetrexed)	0.04	Beta (0.02, 0.08)	B.3.5.4
Proportion of patients receiving Alectinib (following pemetrexed)	0.07	Beta (0.03, 0.11)	B.3.5.4

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Proportion of patients receiving Docetaxel (following pemetrexed)	0.08	Beta (0.04, 0.12)	B.3.5.4
Proportion of patients receiving Gemcitabine (following pemetrexed)	0.02	Beta (0.01, 0.05)	B.3.5.4
Proportion of patients receiving Paclitaxel (following pemetrexed)	0.02	Beta (0.00, 0.04)	B.3.5.4
Proportion of patients receiving Vinorelbine (following pemetrexed)	0.00	Beta (0.00, 0.00)	B.3.5.4
Drug cost: Ceritinib 150 tab pack (150mg)	£4,923.45	None	B.3.5.4
Drug cost: Alectinib 224 cap pack (150mg)	£5,032.00	None	B.3.5.4
Drug cost: Gemcitabine 200mg power for solution for infusion vials	£2.76	Normal (£2.72, £2.80)	B.3.5.4
Drug cost: Gemcitabine 1g power for solution for infusion vials	£7.96	Normal (£7.79, £8.13)	B.3.5.4
Drug cost: Gemcitabine 2g power for solution for infusion vials	£20.57	Normal (£19.93, £21.21)	B.3.5.4
Drug cost: Paclitaxel 30mg/5ml	£3.70	Normal (£2.96, £4.44)	B.3.5.4
Drug cost: Paclitaxel 100mg/16.7ml	£9.84	Normal (£9.74, £9.94)	B.3.5.4
Drug cost: Paclitaxel 150mg/25ml	£12.55	Normal (£12.40, £12.70)	B.3.5.4
Drug cost: Paclitaxel 300mg/50ml	£34.33	Normal (£33.74, £34.92)	B.3.5.4
Drug cost: Vinorelbine 10mg/1ml (10 pack)	£43.47	Normal (£40.51, £46.43)	B.3.5.4
Drug cost: Vinorelbine 50mg/5ml (10 pack)	£178.96	Normal (£164.20, £193.72)	B.3.5.4
Survival and progression - 1st line (PROFILE 1001 analysis)			

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Crizotinib vs. Pemetrexed+cis/carb for PFS (HR)	0.45	Log normal (0.35, 0.60)	B.3.3.4
Crizotinib vs. Pemetrexed+cis/carb for OS (HR) - Adjusted: Wilcoxon (new data cut)	[redacted]	[redacted]	B.3.3.4
Survival and progression - 2nd line (PROFILE 1001 analysis)			
Crizotinib vs. docetaxel for PFS (HR) - chemotherapy	0.49	Log normal (0.37, 0.64)	B.3.3.4
Crizotinib vs. docetaxel for OS (HR) - Adjusted (chemotherapy): RPSFTM - Log-rank	0.38	Log normal (0.04, 0.99)	B.3.3.4
Curve fit parameters (OS) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter OS: Rate	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (PFS) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter PFS: Rate	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (TTF) – Exponential (PROFILE 1001 analysis)			
Curve fit parameter TTF: Rate	[redacted]	Multinormal distribution	B.3.3.4
Survival and progression - 2nd line (ALK+ accepted HR; base case)			
Crizotinib vs. docetaxel for OS (HR) - TA422 ALK+ crizotinib	0.49	Log normal (0.37, 0.64)	**Error! Reference source not found.**
Curve fit parameters (OS) - Exponential - Crizotinib 1L ALK+ curve – Adjusted: Wilcoxon (updated PROFILE 1014 data cut) (base case)			
Curve fit parameter OS: Rate - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	B.3.3.4

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter OS: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (OS) - Exponential - Pemetrexed 1L ALK+ curve – Adjusted: Wilcoxon (updated PROFILE 1014 data cut) (base case)			
Curve fit parameter OS: Rate - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Ecog=2) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter OS: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (PFS) – Log-normal - Crizotinib 1L ALK+ curve (base case)			

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter PFS: Mean log- criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: SD log - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (PFS) - Gamma - Pem 1L ALK+ curve (base case)			
Curve fit parameter PFS: Mu - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: Sigma - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: Q - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	B.3.3.4

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter PFS: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Ecog=2) -pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (TTD) - Exponential - Criz 1L ALK+ curve (base case)			
Curve fit parameter TTD: Rate - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Race=Non asian) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Age>=65) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Sex=Male) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Smoke=Smoker or Ex-Smoker) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Ecog=2) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Brain metastases) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Non-adenocarcinoma) - criz	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (TTD) - Gompertz - Pem 1L ALK+ curve (base case)			

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter TTD: Shape -pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: Rate - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Race=Non asian) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Age>=65) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Sex=Male) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Smoke=Smoker or Ex-Smoker) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Ecog=2) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Brain metastases) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter TTD: covariate (Non-adenocarcinoma) - pem	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameters (OS) - Exponential - 2L ALK+ curve (base case)			
Curve fit parameter OS: Rate	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (PFS) - Weibull - Crizotinib 2L ALK+ curve (base case)			
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: ln p	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (PFS) - Log-normal - Crizotinib 2L ALK+ curve (base case)			

Variable	Value	Measurement of uncertainty and distribution (CI)	Reference to section in submission
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: sigma	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter (TTD) - Weibull - Crizotinib 2L ALK+ curve (base case)			
Curve fit parameter PFS: Const	[redacted]	Multinormal distribution	B.3.3.4
Curve fit parameter PFS: ln p	[redacted]	Multinormal distribution	B.3.3.4
Covariates for updated OS - Real world adjusted patient characteristics			
Crizotinib: % Non-Asian	0.88	Beta (0.82, 0.93)	
Crizotinib: % >=65	0.29	Beta (0.22, 0.37)	B.3.3.4
Crizotinib: % MALE	0.68	Beta (0.60, 0.75)	B.3.3.4
Crizotinib: % Smoker or Ex-Smoker	0.63	Beta (0.55, 0.71)	B.3.3.4
Crizotinib: % ECOG=2	0.22	Beta (0.15, 0.29)	B.3.3.4
Crizotinib: % with Brain Mets	0.27	Beta (0.20, 0.35)	B.3.3.4
Crizotinib: % Non-ADENOCARCINOMA	0.06	Beta (0.03, 0.11)	B.3.3.4

Abbreviation: 1L, first-line; 2L, subsequent-line; BSA, body surface area; BSC, best supportive care; carb, carboplatin; CI, confidence interval; cis, cisplatin; criz, crizotinib; CT, computed tomography; FISH, fluorescence in situ hybridization; GP, general practitioner; HR, hazard ratio; IHC, immunohistochemistry, LYs, life years; NSCLC, non-small cell lung cancer; OS, overall survival; OWSA, one-way sensitivity analysis; pem + c/c; pemetrexed + cisplatin or carboplatin; PFS, progression free survival; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; RPSFTM, Rank Preserving Structural Failure Time Models; TA, technology appraisal; TTF, time to treatment failure.

Base case results (first-line, base case, without PAS). Appendix O.1.1; Page 194

Table 15: Base case results: crizotinib without PAS versus pemetrexed plus platinum therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Probabilistic results (first-line, base case, without PAS). Appendix O.1.2; Page 196

Table 16: Probabilistic results (base case): crizotinib without PAS versus pemetrexed plus platinum therapy (deterministic ICER [redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus platinum therapy	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]

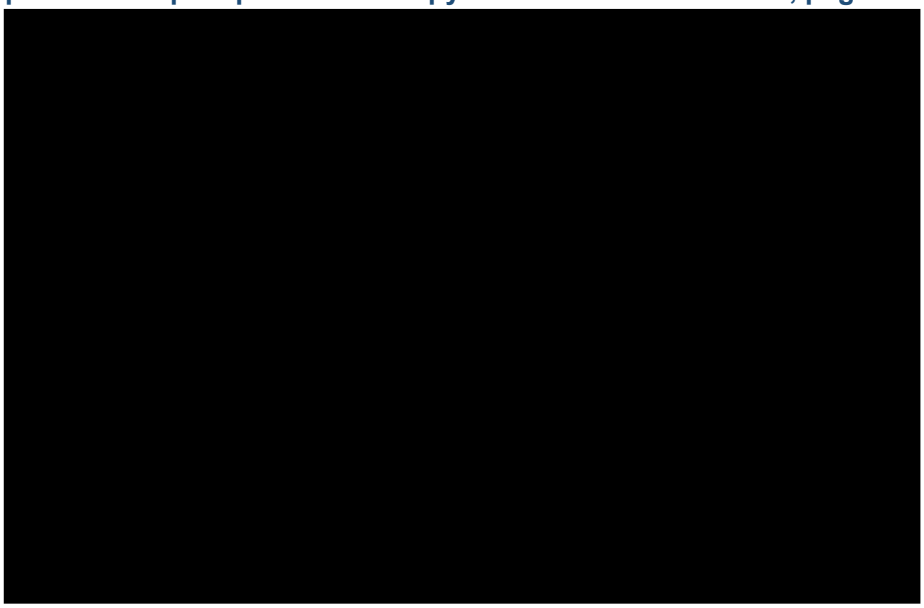
Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life year

Figure 9: Base case: Cost-effectiveness plane: crizotinib versus pemetrexed plus platinum therapy – crizotinib without PAS, page 197

Abbreviation: PSA, probabilistic sensitivity analysis; QALYs: quality-adjusted life year.

Figure 10 shows the CEAC for crizotinib vs. pemetrexed plus platinum therapy on the incremental NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY when crizotinib is without the PAS, for the base case. The CEAC shows crizotinib has a 14% chance of being cost-effective (without its PAS) at a willingness to pay threshold of £50,000.

Figure 10: Base case: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus platinum therapy – crizotinib without PAS, page 197



One-way sensitivity analysis (first-line, base case, without PAS). Appendix O.1.2; Page 203

Figure 11: Base case: Tornado diagram: crizotinib versus pemetrexed plus platinum therapy – crizotinib without PAS (base case ICER [redacted])

Abbreviation: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; TSA, Two-stage adjustment A; TTF, time to treatment failure.

Scenario analysis (first-line, base case, without PAS); Appendix O.1.2; Page 208

Table 17: Results of scenario analysis - crizotinib without PAS

Scenario No.	Scenario setting	ICER: crizotinib versus pemetrexed plus platinum therapy (first-line)	ICER: crizotinib versus docetaxel monotherapy (subsequent-line)
Base case		[redacted]	[redacted]
1	Time horizon equal to 5 years	[redacted]	[redacted]
2	Time horizon equal to 10 years	[redacted]	[redacted]
3	Time horizon equal to 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	Sequential testing for ROS1	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	N/A
7	Crossover adjustment method: Log-rank	[redacted]	N/A
8	Weibull OS models	[redacted]	N/A
9	Gamma OS models	[redacted]	N/A
10	Log normal OS models	[redacted]	N/A
11	Log logistic OS models	[redacted]	N/A
12	Gompertz OS models	[redacted]	N/A
13	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

Abbreviation: ICER, incremental cost-effectiveness ratio; NA., not applicable; PAS, patient access scheme.

Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Crizotinib for treating ROS1-positive non-small cell lung cancer [ID1098]

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

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

2. The relatively recent addition of targeted therapies and immunotherapy, in the treatment of nsclc, has ensured active therapy options for many with nsclc. However, overall outcomes for many of this patient population remains poor. The availability of new targets and therapy choices being of key future 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. Well tolerated
   Oral therapy - therefore, ease of administration.

   Crizotinib has been standard practice in another indication (ALK positive nsclc) for some time. As such, there is considerable experience in the use and side effect profile associated with it. Common adverse effects associated with the use of Crizotinib include diarrhoea, transient visual disorders, asymptomatic bradycardia and fluid retention. Other reported adverse effects include neutropenia, anaemia, leukopenia, decreased appetite, hypophosphataemia, neuropathy, dizziness, cardiac disorders, interstitial lung disease, vomiting, nausea, constipation, dyspepsia, elevated serum transaminases, increased blood alkaline phosphatase levels, rash, renal cysts, oedema and fatigue. In the anecdotal patient experience available to us, it appears to be generally well tolerated – in particular, when compared with current standard cytotoxic therapy for nsclc

2. Very targeted population.

   ROS1 rearrangements are thought to occur in approximately 1% of patients with nsclc.
   Crizotinib is the first targeted treatment option specifically for patients with previously untreated ROS1 positive nsclc. Diagnostic testing ensures segmentation of therapy.

3. Outcome of treatment

   We do not have any additional data, beyond that publically available. We note, however, the results of the mullticentre single-arm Phase 1 study of 53 patients, with ROS1 positive nsclc. This showed an objective response rate (partial or complete responses) of around 70% (37 out of 53 patients), by independent radiological review.

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 many remains poor.

ROS1 rearrangements are found in a very small, segmented number of lung cancer patients. Crizotinib offers the first targeted therapy option for this patient group.

[redacted] **RCLCF.**

July 2017.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	BTOG-NCRI-RCP-ACP

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	British Thoracic Oncology Group, National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, and Royal College of Radiologists.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To improve survival, to improve progression-free survival, to shrink tumours and improve quality of life

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A response rate 10% above that observed for chemotherapy (around 30% for first line and 10% for second line) ie 40% would be clinically significant, or an equivalent response rate but with marked reduction in toxicities. A progression-free survival beyond that seen for chemotherapy (around 5 months for the first line and 3 months for second line).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the outcomes described in #7 with the current standard of care for ROS1+ patients, chemotherapy, are entirely unsatisfactory.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	At presentation of metastatic disease, patients are not routinely ROS1 tested in the UK. Regardless of ROS1 status, the NHS does not fund and ROS1-directed therapies. Therefore these patients are routinely treated with first line chemotherapy contingent on tolerability. This will usually be 4 cycles of cisplatin-pemetrexed followed by maintenance pemetrexed chemotherapy (as per TA402). On progression patients are usually treated with combination docetaxel-nintedanib (TA347) or if unsuitable best supportive care. Patients are not usually treated in first or second lines with pembrolizumab (TA428).

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no UK overarching stage 4 NSCLC systemic therapy management guidelines, and so patients are treated according to European Society of Medical Oncology (ESMO) clinical practice guidelines for advanced NSCLC and American Society of Clinical Oncology (ASCO) guidelines on systemic therapy for stage 4 NSCLC. A recommendation on ROS1 was not included in the most recent update to the ESMO guidelines as crizotinib was not yet licensed for this indication. The ASCO guildeins recommend crizotinib for ROS1+ NSCLC.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The treatment pathway is well defined and little opinion differences between clinicians; all recommend crizotinib for ROS1 positive patients on the basis of data underpinning the EMA license.
• What impact would the technology have on the current pathway of care?	The technology (crizotinib) will require ROS1 testing to be implemented, which is feasible within the NHS and already occurs in some centres.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, crizotinib will be used in its licensed indication

• How does healthcare resource use differ between the technology and current care?	Currently ROS1 patients would receive intravenous chemotherapy with marked toxicities and risk of death from febrile neutropenia as primary GCSF prophylaxis is not NICE approved (CG151). Chemotherapy involves 3-weekly visits to chemotherapy suites for intravenous infusions. By contrast, crizotinib is a simple table taken at home. Once established without toxicities, patients are usually seen 2-3 monthly in the outpatient clinic for evaluation.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, as per all anti-cancer systemic therapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Take account of costs of ROS1 testing implementation
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the magnitude of clinical benefit (response rates, rapidity of response, progression-free survival) are a step-change benefit for ROS1 patients. ROS1 patients can usually return back to normal life, unlike those receiving chemotherapy.
• Do you expect the technology to increase	Yes

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment is licensed for ROS1+ and ALK+ patients. The use of crizotinib for ALK+ patients is already approved by NICE (TA 422 & 406).
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The technology will be far, far easier to implement than the standard chemotherapy that they would receive. As crizotinib is oral and so highly effective, the switch between chemotherapy and crizotinib will be a resource reduction in terms of clinician time, pharmacy time, nursing time, day unit time, radiology time.. ROS1 testing will need to be implemented in England to identify these patients but this will not be problematic for hospitals as all hospitals treating advanced NSCLC have established molecular diagnostics pathways established.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment will continue up to and beyond RECIST-defined progression (in patient with ongoing benefit) as per the clinical trials data underpinning the license.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, crizotinib for ROS1 positive patients is an important 'step change' due to its huge improvement in response rates, progression-free survival, overall survival, and quality of life, compared with usual expectations
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, metastatic NSCLC is a rapidly fatal condition. Crizotinib improves outcomes markedly.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The common toxicities of crizotinib are mild and minimal compared to that for chemotherapy. The toxicities rarely require dose modifications and crizotinib is a far more tolerable drug than chemotherapy.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Response rate, progression-free survival, overall survival. Due to the rarity of the condition it has not been possible to perform a randomized trial. Due to the major efficacy of crizotinib and its identification early in its development, it would now no longer be ethical to perform a randomized study without access to crizotinib.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that are clinically meaningful

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA181, TA402, TA190, TA347]?	No
21. How do data on real-world experience compare with the trial data?	A real-world service evaluation on UK patients that have received crizotinib through a variety of sources to date is underway with no data available as yet.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- NSCLC is disease that ineviatable fatal and is in urgent need of new therapies to improve outcome
- ROS1 NSCLc is a rare subset of NSCLC, usually in youger patients with adenocarcinoma
- Patients with ROS1+ NSCLC are currently treated with standard chemotherapy and the usual poor outcomes
- Crizotinib represents a step change therapy for the treatment of this condition
- Crizotinib resulsts in a large response rate, a rapid respone, a long progression-free survival and overal survival with patienits often returning to their pre-morbid status

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Thoracic Society – a multidisciplinary professional society which aims to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The British Thoracic Society supports the proposed appraisal. There is an urgent need more treatment options for patients with lung cancer given the very poor prognosis.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**ROYAL COLLEGE OF PATHOLOGISTS**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? **x** other (please specify): **pathologist who screens for ROS1 abnormalities**
5a. Brief description of the organisation (including who funds it).	**The Royal College of Pathologists represents pathologists in the UK and provides guidance for reporting lung cancer pathological specimens**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To stop progression of lung cancer and prolong life

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Not applicable for a pathologist to answer
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	It is not, as far as I am aware
• Are any clinical guidelines used in the treatment of the	Not within the NHS, although there are many papers describing response to therapy in patient with ROS1 gene abnormalities

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Not that I am aware of. Testing (FISH and IHC screening) is requested on a case basis.
• What impact would the technology have on the current pathway of care?	It would allow a cohort of patients with lung cancer that have this abnormality access to a treatment that would likely prolong life.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be used in a similar way to patients with ALK gene abnormalities.
• How does healthcare resource use differ between the technology and current care?	Not applicable for a pathologist to answer
• In what clinical setting should the technology be	Not applicable for a pathologist to answer

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Cost of screening either by FISH testing or IHC screening then FISH testing
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In patients with a ROS1 gene rearrangement, yes.
• Do you expect the technology to increase length of life more than current care?	In patients with a ROS1 gene rearrangement, yes.
• Do you expect the technology to increase health-related quality of life more than current care?	In patients with a ROS1 gene rearrangement, yes.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with a ROS1 gene rearrangement
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The means to screen and test for ROS1 gene rearrangements would have to be accommodated into tissue pathways for lung cancer specimens, with impact on cost and staffing

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not applicable for a pathologist to answer As above
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not applicable for a pathologist to answer
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Not applicable for a pathologist to answer

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	In patients with a ROS1 gene rearrangement, yes.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not applicable for a pathologist to answer
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Not applicable for a pathologist to answer

• If not, how could the results be extrapolated to the UK setting?	Not applicable for a pathologist to answer
• What, in your view, are the most important outcomes, and were they measured in the trials?	Not applicable for a pathologist to answer
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable for a pathologist to answer
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not applicable for a pathologist to answer
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not applicable for a pathologist to answer

20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA181, TA402, TA190, TA347]?	Not applicable for a pathologist to answer
21. How do data on real-world experience compare with the trial data?	Not applicable for a pathologist to answer
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • In patients with a ROS1 gene rearrangement, the literature reports good response to therapy • ROS1 gene rearrangements are rare and their identification is potentially costly • Identifying ROS1 gene rearrangements can be done through IHC screening followed by FISH confirmation • ROS1 gene rearrangements are reported as more common in younger patients and never smokers with lung cancer

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission for the NICE Technology Appraisal of crizotinib in the treatment of ROS1 non small cell lung cancer (NSCLC)

1. ROS1 positive NSCLC was discovered in 2011 and thus there is only a small amount of information as to its natural history, particularly in the real world setting, and there is a dearth of clinical outcome data for ROS1 patients treated with conventional cytotoxic chemotherapy.
2. ROS1 pos NSCLC is only seen in adenocarcinoma of the lung and never in patients with EGFR, KRAS or ALK mutations. ROS1 NSCLC and ALK pos NSCLC thus have oncogenic drivers that are mutually exclusive.
3. ROS1 NSCLC shares some demographic and clinical characteristics with ALK pos NSCLC: younger age (median 50 years), female sex (65%) and never smokers (68%). Brain metastases are also common in ROS1 NSCLC.
4. ROS1 NSCLC appears on preliminary evidence to be more sensitive to pemetrexed and possibly also to crizotinib than ALK pos NSCLC. Ceritinib is active in ROS1 NSCLC but probably only in crizotinib-naive patients unlike ALK pos patients where ceritinib is active in ALK pos crizotinib failures . Alectinib is active in ALK pos NSCLC but inactive in ROS1 NSCLC.
5. Some references state that ROS1 and ALK pos NSCLC have similar clinico-pathological features but there are important differences: the seemingly greater sensitivity to crizotinib in ROS1 NSCLC, the differing sensitivity to ceritinib and alectinib and of course the entirely different oncogenic drivers.
6. The most practical testing strategy for ROS1 would be screening of all adenocarcinoma patients at diagnosis. A two stage strategy of only testing the EGFR and ALK negative patients is in theory possible but would still require the testing of >85% of adenocarcinomas.
7. The key comparator for 1st line crizotinib is a platinum preparation plus pemetrexed followed by maintenance pemetrexed. Single agent use of cytotoxic chemotherapy in the 1st line setting is rare. The main comparators for crizotinib in the 2nd line setting are docetaxel and the combination of docetaxel and nintedanib, the latter being used less frequently than the former.
8. NHS England notes that there is better evidence for the use of crizotinib beyond 1st line use but recognises the biological plausibility of at least equal benefit when used 1st line, such use coming at the expense of reduced toxicity when compared with standard combination chemotherapy.
9. The single arm Profile 1001 study is small in size and has a median duration of follow-up of 25 months. It is thus relatively immature when only 30% of patients had died at the last data cut off in November 2015. NHS England is disappointed that no further follow up appears to have been done in the past 2 years.
10. The durations of treatment with 1st- and subsequent line crizotinib in ROS1 patients is highly likely to significantly exceed the durations of progression-free survival

observed in Profile 1001 and NHS England thus would wish to know that this treatment period beyond disease progression has been modelled in the economic analysis of crizotinib.

11. NHS England notes that the correct cost for the HRG chemotherapy tariff for crizotinib administration has not been used by the company: a figure of £14-60 has been used whereas the 2017/18 oral chemotherapy tariff is £120 per month.
12. NHS England notes the rather large contribution of the crizotinib post progression survival figures to the overall survival of both 1st and 2nd line crizotinib patients in the economic modelling, these figures significantly exceeding the total overall survival figures for the relevant comparator populations treated with just chemotherapy. NHS England finds these post progression survival figures after discontinuation of crizotinib as being implausible.
13. Crizotinib is clearly active in ROS1 NSCLC but follow up in the single arm Profile 1001 study is relatively immature. Should NICE recommend this indication to the Cancer Drugs Fund then a large dataset could be collected on treatment duration, subsequent therapies and overall survival. Since there has not been any further follow up data since November 2015 used in this submission by the company, NHS England wonders whether there will be any further data collection and analysis from Profile 1001. If not, then any uncertainties that the NICE TA committee has as to mature outcomes of crizotinib in ROS1 NSCLC would have to be resolved by prolonged follow up in the CDF, potentially for up to 5 years. Such data collection and analysis would be of very great benefit to the world literature of ROS1 NSCLC.

[redacted]

[redacted]

December 2017

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Sanjay Popat**
2. Name of organisation	**BTOG-NCRI-RCP-ACP**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**I concur with the statement from BTOG-NCRI-RCP-ACP**
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	**I concur with the statement from BTOG-NCRI-RCP-ACP**
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**I concur with the statement from BTOG-NCRI-RCP-ACP.** **In addition the American Society Of Clinical Oncology published updated guidelines in August 2017 on systemic therapies for advanced NSCLC recommending the use of crizotinib in all lines if patients identified to be ROS1+ and not previously received crizotinib. It also recommended all patients to be ROS1 tested**
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• What impact would the technology have on the current pathway of care?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**I concur with the statement from BTOG-NCRI-RCP-ACP**

• How does healthcare resource use differ between the technology and current care?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**I concur with the statement from BTOG-NCRI-RCP-ACP**
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• Do you expect the technology to increase length of life more than current care?	**I concur with the statement from BTOG-NCRI-RCP-ACP**

• Do you expect the technology to increase health-related quality of life more than current care?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	**I concur with the statement from BTOG-NCRI-RCP-ACP**

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	**I concur with the statement from BTOG-NCRI-RCP-ACP**

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• Does the use of the technology address any particular unmet need of the patient population?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• If not, how could the results be extrapolated to the UK setting?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• What, in your view, are the most important outcomes, and were they measured in the trials?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
20. Are you aware of any relevant evidence that might	**I concur with the statement from BTOG-NCRI-RCP-ACP**

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA181]?	**I concur with the statement from BTOG-NCRI-RCP-ACP**
22. How do data on real-world experience compare with the trial data?	**Our group have completed a retrospective service evaluation evaluating the outcomes of ROS1+ NSCLC. An abstract of this data has been submitted for presentation at the 2018 British Thoracic Oncology Group Annual Meeting and can be provided to the NICE appraisal committee on request.**
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	**I concur with the statement from BTOG-NCRI-RCP-ACP**

23b. Consider whether these issues are different from issues with current care and why.	**I concur with the statement from BTOG-NCRI-RCP-ACP**
Topic-specific questions	
24. Is testing (to determine ROS1 positive status) currently used in clinical practice?	**No ROS1 testing is not currently routinely performed in the majority of UK centres**
25a. In clinical practice, is pemetrexed in combination with platinum used to treat ROS1 positive non-small-cell lung cancer as a first line treatment? 25b. Are there any other first line treatments that are currently used in clinical practice?	**a. Yes, this currently the main treatment for first line patients since ROS1 testing is not routinely performed and crizotinib is not routinely available for this indication** **b. A very small number of advanced NSCLC patients will not be clinically suitable for platinum-pemetrexed chemotherapy and will receive single agent chemotherapy eg vinorelbine**

26a. In clinical practice, is docetaxel monotherapy used to treat ROS1 positive non-small-cell lung cancer after previous chemotherapy? 26b. Are there any other treatments that are currently used in clinical practice after previous chemotherapy?	**a. Patients are not currently routinely tested for ROS1 status. If identified to be so and in the absence of crizotinib being available, patients are usually treated with combination docetaxel-nintedanib (TA347)** **b. A small number of patients will be treated with pembrolizumab (TA428).**
27. Are people with ALK positive non-small-lung cancer clinically similar to ROS1 positive non-small-lung cancer? (You may wish to comment on similarities in treatment received, symptoms, prognosis, quality of life and the appropriateness of generalising clinical	**Yes, patients with ALK+ NSCLC would behave in a similar manner to patients with ROS1+ NSCLC. Both sets of patients tend to present with metastatic disease, are younger than average NSCLC at diagnosis, and are usually never-smokers.** **Both have similar symptoms and distribution of disease at presentation. Both respond very well to crizotinib with rapid durable responses. Quality of life is markedly improved in both ROS1 and ALK+ NSCLC with crizotinib to near baseline/premorbid status. My clinical experience is of ROS1+ patients gaining similar benefit of crizotinib as ALK+ patients and markedly superior to chemotherapy. Given the marked rarity of the ROS1 genotype it would be reasonable to generalize outcomes for the ROS1+ NSCLC group from that of the ALK+ group.**

effectiveness evidence from one population to the other)	

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

- **I concur with the bullet points from BTOG-NCRI-RCP-ACP**
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

ID1098 STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

This report supersedes all previous versions. This report was produced in response to the company's addendum of 23rd November 2017.

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

Completed 19th December 2017

[redacted]

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

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Boland A	Critical appraisal of the clinical and economic evidence
Kotas E	Cross-check of the company submission search strategy
McEntee J	Critical appraisal of the company submission
Green J	Clinical advice and critical appraisal of the clinical evidence

All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

AE	adverse event
ALK	anaplastic lymphoma kinase
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BSA	body surface area
CDF	Cancer Drugs Fund
CI	confidence interval
CRUK	Cancer Research UK
CS	company submission
CSR	clinical study report
DCR	disease control rate
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EGFR	epidermal growth factor receptor
EORTC	European Organisation for the Treatment of Cancer
EORTC QLQ-C30	European Organisation for the Treatment of Cancer quality of life questionnaire C30
EPAR	European Public Assessment Report
EQ-5D-3L	European quality of life-3 dimensions
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FISH	fluorescence in situ hybridisation
H-H	cumulative hazard versus cumulative hazard
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
IHC	immunohistochemistry
ITT	intention-to-treat
IV	intravenous
IVRS	interactive voice recognition system
K-M	Kaplan-Meier
KRAS	Kirsten rat sarcoma virus
LCH	log-cumulative hazard
LCHP	log cumulative hazard plots
LY	life year
LYG	life years gained
MIMS	Monthly Index of Medical Specialities
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PD	progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PH	proportional hazards
PS	performance status
PSA	probabilistic sensitivity analysis

PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality adjusted life year
RCT	randomised controlled trial
RECIST	response evauation criteria in solid tumours
RR	relative risk
RTK	receptor tyrosine kinases
SAP	statistical analysis plan
SmPC	summary of product characteristics
STA	single technology appraisal
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical evidence and economic evidence have been submitted to NICE by Pfizer Limited in support of the use of crizotinib (Xalkori®) for ROS1-positive (ROS1+) advanced non-small cell lung cancer (NSCLC).

Crizotinib is licensed in Europe for the treatment of patients with ROS1+ advanced NSCLC. Crizotinib is also licensed in Europe for the treatment of adults with anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC.

1.2 Critique of the decision problem in the company submission

Population

The population described in the final scope issued by NICE is people with ROS1+ advanced NSCLC. The population discussed in the company submission (CS) is the population recruited to the PROFILE 1001 study, which is identical to the population described in the final scope. However, data from this small, single-arm study are limited (n=53). The company has used data from a population of patients with ALK+ advanced NSCLC as proxy data for a population of patients with ROS1+ advanced NSCLC.

Treatment line is not specified in the final scope issued by NICE or in the European Medicines Agency (EMA) licence. The company expects that crizotinib will be used as a first- and subsequent-line treatment. However, the company anticipates that the number of patients treated at subsequent-line will reduce over time as patients with ROS1+ advanced NSCLC will be identified when they first present with NSCLC symptoms and treated with crizotinib in the first-line.

In the absence of randomised controlled trial (RCT) evidence for the efficacy of crizotinib in patients with ROS1+ advanced NSCLC, the company uses data from RCTs conducted in patients with ALK+ advanced NSCLC as a proxy for the outcomes of patients with ROS1+ advanced NSCLC. The company considers that ROS1+ and ALK+ advanced NSCLC are similar diseases and that patients with ROS1+ and ALK+ advanced NSCLC have similar characteristics. The ERG considers that the company has focussed on the population specified in the decision problem only if the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

Intervention

Crizotinib is licensed in Europe for the treatment of patients with ROS1+ advanced NSCLC. Crizotinib is administered as hard capsules at a dosage of 250 mg twice daily.

Comparators

The final scope issued by NICE sets out different comparators for (i) people with ROS1+ advanced NSCLC who have not had previous treatment and (ii) people with ROS1+ advanced NSCLC who have received previous chemotherapy treatment.

Direct evidence. No direct evidence is available for crizotinib versus any of the comparators specified in the final scope issued by NICE.

Proxy evidence. Proxy evidence is presented in the CS for the comparison of the effectiveness of crizotinib versus pemetrexed+platinum in patients with previously untreated ALK+ advanced NSCLC. Evidence is also presented in the CS for the comparison of the effectiveness of crizotinib versus chemotherapy (pemetrexed or docetaxel monotherapy) in patients with ALK+ advanced NSCLC who have had previous treatment with chemotherapy.

No evidence. No evidence is presented in the CS for the comparisons of crizotinib for untreated disease with: i) a third generation chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) with a platinum drug (carboplatin or cisplatin), with (for people with non-squamous NSCLC only) or without pemetrexed; ii) single agent chemotherapy with a third generation drug for people who cannot tolerate platinum-based therapy; iii) pemetrexed+platinum (for people with adenocarcinoma or large cell only) with pemetrexed maintenance treatment.

No evidence is presented in the CS for the comparisons of crizotinib after previous chemotherapy with: i) docetaxel+nintedanib; ii) best supportive care (BSC). Treatment with docetaxel+nintedanib in the subsequent care setting is the NHS standard of care for patients with tumours of adenocarcinoma histology.

Outcomes

For the patient population specified in the final scope issued by NICE, i.e., patients with ROS1+ advanced NSCLC, data for progression-free survival (PFS), objective response rate (ORR), overall survival (OS) and adverse events (AEs) are derived from the PROFILE 1001 study. However, median OS has not been reached and the company does not intend to carry out further updates of OS until [redacted] Health-related quality of life (HRQoL) data were not collected.

Comparative clinical effectiveness analyses presented in the CS are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for data from ROS1+ advanced NSCLC patients. Outcome data for patients with untreated ALK+ advanced NSCLC are available from the PROFILE 1014 trial. Data are presented in the CS for the outcomes of PFS, objective response rate (ORR), AEs and HRQoL. Outcome data for patients with previously treated ALK+ advanced NSCLC are available from the PROFILE 1007 trial. Data are presented in the CS for the outcomes of PFS, ORR, AEs and HRQoL. Data for OS are available from both the PROFILE 1014 and PROFILE 1007 trials; however, high levels of crossover occurred in both trials. This means that the true OS associated with crizotinib in patients with untreated ALK+ advanced NSCLC and patients with previously treated ALK+ advanced NSCLC is unknown.

Other considerations

In the summary of product characteristics for crizotinib, it is stipulated that treatment should only be initiated after the patient's ROS1 status has been positively confirmed by a clinical laboratory test using a validated test method. There is currently no routinely funded testing of patients for ROS1 in the NHS. The company points out that if the sequential testing strategy, rather than upfront testing, for the identification of ROS1+ advanced NSCLC is adopted in the NHS, there is the potential for a delay in the diagnosis and treatment of patients.

The existing Patient Access Scheme agreement in place for crizotinib for the treatment of patients with ALK+ advanced NSCLC will be extended to include the ROS1+ patient population.

The company has put forward a case for crizotinib to be considered against the NICE End of Life criteria.

1.3 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company presents evidence for the clinical effectiveness of crizotinib from the PROFILE 1001 study. The PROFILE 1001 study was a single-arm study in which patients with ROS1+ advanced NSCLC were treated with 250 mg of crizotinib twice daily until disease progression. Of the 53 recruited patients, 7 patients had untreated disease and 46 patients had received at least one prior chemotherapy. Most of the 53 patients achieved either a partial or complete response with crizotinib (69.8%), and median PFS was 19.3 months (95% confidence interval [CI]: 14.8 to not reported [NR]). OS data were immature, with only 30% of patients having died at the latest data cut-off date. The most frequently occurring AEs of any grade were vision disorders; these were Grade 1 or Grade 2. The Grade 3 AEs reported included hypophosphataemia and neutropenia. No Grade 4 AEs were recorded. No HRQoL data were collected during the PROFILE 1001 study.

Proxy evidence

The company presents data from the PROFILE 1014 trial in which patients with previously untreated ALK+ advanced NSCLC were randomised to receive treatment with crizotinib 250 mg twice daily (n=172) or pemetrexed+platinum chemotherapy (n=171). Most of the patients treated with crizotinib achieved a partial or complete response (74%) compared with 45% of patients treated with pemetrexed+platinum. Median PFS for patients treated with crizotinib was 10.9 months compared with 7 months for patients treated with pemetrexed+platinum (hazard ratio [HR]=0.45, 95% CI: 0.35 to 0.60; p<0.001). Median OS was not reached for patients treated with crizotinib and was 47.5 months for patients treated with pemetrexed+platinum. Patient crossover from pemetrexed+platinum to crizotinib was 84.2%.

The company presents data from the PROFILE 1007 trial in which patients with previously treated ALK+ advanced NSCLC were randomised to receive treatment with 250 mg of crizotinib twice daily (n=173) or intravenous chemotherapy that was either pemetrexed or docetaxel monotherapy (n=174). Most of the patients treated with crizotinib achieved a partial or complete response (65.3%) compared with 19.5% of patients treated with chemotherapy. Median PFS for patients treated with crizotinib was 7.7 months compared with 3 months for patients treated with chemotherapy (HR=0.49, 95% CI: 0.37 to 0.64; p<0.0001). Median OS was similar in both arms; 21.7 months for patients treated with crizotinib and 21.9 months for patients treated with chemotherapy. Patient crossover from chemotherapy to crizotinib was 88.5%.

The HRQoL results (EQ-5D) appeared to show a benefit of treatment with crizotinib compared with chemotherapy. The type of and incidence of AEs from a pooled analysis of data from the PROFILE 1014 and 1007 trials and two single-arm studies were consistent with the AEs experienced by patients in the PROFILE 1001 study.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers that the company has addressed the decision problem only if the outcome data from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

The ERG is satisfied with the company's search strategy and stated inclusion and exclusion criteria. The ERG is confident that searching was carried out to an acceptable standard and is not aware of any additional studies that should have been included in the company's systematic review.

Direct evidence

The ERG considers that the PROFILE 1001 study is generally of good quality with independent assessment of radiological outcomes, and that the patients recruited to the study are representative of patients who are likely to be treated in the NHS. However, the PROFILE 1001 study is small and only 7 of the 53 patients had untreated disease. Of the patients with previously treated disease, only 37% had received the NHS standard of care in the first-line setting, i.e., pemetrexed+platinum chemotherapy. The OS data from the study are immature and no HRQoL data were collected.

Proxy evidence

The ERG considers the PROFILE 1014 trial to be a good quality trial. Clinical advice to the ERG is that patients recruited to the trial are generally representative of patients with ALK+ advanced NSCLC who are treated in clinical practice in the NHS. However, the ERG notes that in the company's economic model, adjustments were made to the PROFILE 1014 trial population based on the characteristics of patients included in a retrospective cohort study conducted in the US and Canada. A previous appraisal committee considered the adjustments to be conservative.

The ERG considers the PROFILE 1007 trial to be of good quality and that patients recruited to the trial are generally representative of patients with ALK+ advanced NSCLC who are treated in clinical practice in the UK.

The ERG considers that the proportional hazards (PH) assumption was not valid for PFS for either the PROFILE 1014 or PROFILE 1007 trials, and that hazard ratios (HRs) for PFS data from both trials should be interpreted with caution.

The ERG notes that there was a substantial amount of patient crossover from the chemotherapy arm to the crizotinib arm and vice versa in both the PROFILE 1014 and PROFILE 1007 trials. The company presents Rank Preserving Structural Failure Time Model (RPSFTM)-adjusted OS HRs to account for patient crossover in the PROFILE 1014 and PROFILE 1007 trials. The ERG considers that the RPSFTM-adjusted HRs for OS are unlikely to be valid and should be interpreted with caution.

When comparing the ORR results of the PROFILE 1001 study, the PROFILE 1014 trial and the PROFILE 1007 trial, the ERG considers that the ORR results are similar at 69.8%, 74.4% and 65.3% respectively. The results from both the PROFILE 1014 and PROFILE 1007 trials demonstrated a statistically significantly greater ORR for crizotinib patients than for chemotherapy patients.

In comparing the PFS results of the PROFILE 1001 study, the PROFILE 1014 trial and the PROFILE 1007 trial, the ERG considers that median PFS is not similar at 19.3 months (95% CI: 14.8 to not reported), 10.9 months (95% CI: 8.3 to 13.9), 7.7 months (95% CI: 6.0 to 8.8) respectively. The differences in PFS cause the ERG to question whether the ROS1+ and ALK+ advanced NSCLC patient populations are truly similar.

The ERG notes that there are no mature OS data available for patients with ROS1+ advanced NSCLC. The ERG also notes that the OS data from patients with ALK+ advanced NSCLC presented in the CS from the PROFILE 1014 are immature. Overall survival data from the PROFILE 1014 and 1007 trials are both confounded by patient crossover. This means that there are no conclusive OS data from either the population specified in the decision problem (i.e. people with ROS1+ advanced NSCLC) or from the ALK+ advanced NSCLC population used in the CS to mitigate the uncertainty around the limited data available for the population specified in NICE's decision problem.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo cost effectiveness model structure in Microsoft Excel. The same model structure is used for the analysis of first- and subsequent-line treatment with crizotinib, but consider different comparator, cost, efficacy and benefit inputs applied to each population. The model comprises three progressively worse health states: progression-free disease, progressed disease and death. The company uses a 30-day cycle length and has

implemented a half-cycle correction. The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS) and the model time horizon is 20 years. The company states that both costs and benefits are discounted at a rate of 3.5% per annum.

The population reflected in the model is adults with ROS1+ advanced NSCLC. This is split into two populations to encompass first- and subsequent-line treatment with crizotinib. The comparator in the first-line setting is pemetrexed+platinum. The comparator in the subsequent-line setting is docetaxel. Due to the limited availability of time-to-event data for patients with ROS1+ advanced NSCLC, the company has used data from the ALK+ advanced NSCLC population as a proxy for data from ROS1+ patients in the base case analysis.

For the first-line population, extrapolations of PFS and time to treatment discontinuation (TTD) data for patients with ALK+ advanced NSCLC were taken from TA406 (based on the results of the PROFILE 1014 trial). The company has updated its modelling of OS since TA406 and has provided a new analysis based on an updated data cut (9 March 2017) from the PROFILE 1014 trial. Estimates of OS in the first-line model have been adjusted for crossover using the RPSFT method. The company has adjusted the baseline characteristics for all estimates of OS, PFS and TTD from the PROFILE 1014 trial to match the characteristics of patients who participated in a 'real-world' trial based in the UK.

For the subsequent-line population, extrapolations of OS, PFS and TTD data for patients with ALK+ advanced NSCLC were taken from TA422 (based on the results of the PROFILE 1007 trial). OS for treatment with crizotinib in the subsequent-line setting was estimated by applying the PFS HR from the PROFILE 1007 trial to the RPSFTM-adjusted estimates of OS for treatment with docetaxel from the same trial. Survival estimates have not been adjusted for patient baseline characteristics in the subsequent-line model.

The company has provided a scenario analysis using clinical effectiveness data for treatment with crizotinib in patients with ROS1+ advanced NSCLC from the PROFILE 1001 study. Estimates of clinical effectiveness for comparator treatments in the first- and subsequent-line settings have been calculated using HRs from the PROFILE 1014 and PROFILE 1007 trials respectively.

EQ-5D data collected in the PROFILE 1014 and PROFILE 1007 trials were used to estimate PFS utility values in the first- and subsequent-line models for both the base case analysis and the PROFILE 1001 scenario analyses. The utility value for patients treated with a second-line treatment in the first-line model was assumed to be the same as the PFS utility for docetaxel

in the subsequent-line model. A published utility value was used for patients in the first-line model who had completed post-progression treatment and moved onto BSC. The same BSC utility value was used for patients who had progressed after treatment in the subsequent-line model.

The company derived resource use and unit costs from a number of sources, including data from: PROFILE 1007 and PROFILE 1014 trials, national databases, previous technology appraisals of crizotinib in first- and subsequent-line ALK+ advanced NSCLC and clinical advice. The company used the PAS price for crizotinib in all of the cost effectiveness analyses presented in the CS.

In the first-line base case analysis, treatment with crizotinib generates incremental life years gained (LYG) (+2.39 years) and more benefits (+1.28 quality adjusted life years [QALYs]) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case incremental cost-effectiveness ratio (ICER) for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line base case analysis, treatment with crizotinib generates incremental LYG (+1.36 years) and more benefits (+0.93 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

In the first-line PROFILE 1001 scenario analysis, treatment with crizotinib generates incremental LYG (+3.60 years) and more benefits (+1.95 QALYs) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case ICER for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line PROFILE 1001 scenario analysis, treatment with crizotinib generates incremental LYG (+3.43 years) and more benefits (+1.95 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

1.6 Summary of the ERG's critique of submitted cost effectiveness evidence

The company's models are generally well-structured. However, as both the first- and subsequent-line models are contained in the same Excel file, the document is somewhat unwieldy.

Fundamental issues with the economic analysis

The ERG's principal concern is that it has been unable to check and verify many of the inputs into the economic models submitted by the company. The ERG has been unable to verify whether the models appropriately address the decision problem set by NICE for two key reasons:

1. The CS relies heavily on the assumptions and modelling approaches used in three previous STAs (TA406, TA422 and TA296). The company has not provided sufficient justification in the CS for the application of these assumptions and approaches in the current appraisal, beyond the fact that they were previously accepted.

2. Even if the ERG was able to verify the assumptions made by the company, lack of model functionality would impede the ERG's ability to investigate the effects of specific key assumptions in the model.

The company base case analysis is founded on the assumption that the outcomes of treatment with crizotinib in an ALK+ advanced NSCLC population are an appropriate proxy for the outcomes of treatment with crizotinib in a ROS1+ advanced NSCLC population. First- and subsequent-line treatments with crizotinib in an ALK+ advanced NSCLC population have been previously appraised by NICE (TA406, TA422 and TA296); therefore, much of the data and modelling included in the company base case analysis has been discussed in previous STAs. The ERG has prioritised the critique of newly available data in this appraisal (updated OS from the PROFILE 1014 trial and data from the PROFILE 1001 study). However, this does not imply that the ERG is satisfied that inputs and approaches not covered in this critique are appropriate and correctly implemented in the model.

Modelling issues

The company's first-line base case model yields a substantial post-progression survival (PPS) benefit for treatment with crizotinib versus pemetrexed+platinum, which means that the extra survival gained beyond progression constitutes 74% of total OS gain for treatment with crizotinib. This suggests that the treatment effect is better after progression than before progression and, therefore, that the OS treatment effect is better than the PFS treatment effect. The ERG acknowledges that there may be some PPS benefit attributable to treatment with crizotinib, especially since many patients are treated beyond progression. However, the ERG considers it questionable to model an OS treatment effect that is substantially better than the PFS treatment effect without robust evidence to support that assumption. The company's subsequent-line base case model also includes a post-progression treatment effect that is greater than the PFS treatment effect, although the proportion of OS gain accrued post-progression is smaller in the subsequent-line model than in the company's first-line model. The ERG has explored alternative methods of modelling OS treatment effect in the first- and subsequent-line settings to investigate the impact on the ICERs per QALY gained of reducing PPS gain.

The company's PROFILE 1001 scenario analysis is based on data from a small, immature, single-arm trial. Any modelling of this data will likely be subject to substantial uncertainty and the ERG notes that this is acknowledged by the company. However, the company has interpreted the results of its PROFILE 1001 analysis as evidence of reduced uncertainty in the modelling of treatment with crizotinib in a ROS1+ advanced NSCLC population, since the ICERs resulting from its PROFILE 1001 scenario analysis are less than £50,000 per QALY gained. The ERG has explored alternative ways of modelling the time-to-event data from the PROFILE 1001 study to investigate the impact on the ICER per QALY gained of other plausible extrapolation methods and assumptions about treatment effect.

Progression-free utility values used in the company's first-line model are based on EQ-5D response data collected in the PROFILE 1014 trial. This dataset includes only six cycles of responses from patients receiving pemetrexed+platinum versus 50 cycles of responses from patients receiving treatment with crizotinib. The ERG is concerned that the PFS utility value used by the company for patients treated with pemetrexed+platinum in the first-line model may not be representative of the whole time that these patients spend in the progression-free state, as it is based on EQ-5D responses collected only whilst patients are on treatment. The ERG also notes a difference in baseline PFS utility values across the two arms in the PROFILE 1007 trial which has not been adjusted for in the subsequent-line model. The ERG has

explored scenarios using different PFS utility values in the first- and subsequent-line models to investigate the impact of uncertainty around HRQoL.

The ERG has also noted minor issues with the cost of treating AEs and the cost of testing for ROS1 mutations.

1.7 Summary of company's case for End of Life criteria being met

The company has put forward the case that crizotinib meets NICE's End of Life criteria. The company reports that there are limited data for OS for patients with ROS1+ advanced NSCLC and that data from patients with ALK+ advanced NSCLC have been used as supportive evidence.

Life expectancy

For patients treated with chemotherapy, the company states that estimates of median OS in patients with ALK+ advanced NSCLC range between 6 months and 22 months and that median OS in the PROFILE 1007 trial was 21.9 months.

Extension to life of at least 3 months

The company states that PFS for patients with ROS1+ advanced NSCLC in the PROFILE 1001 study was 19.3 months. The company considers 19.3 months to be the minimum value for OS in this patient population and observes that the Appraisal Committee for TA422 accepted, that in the case of targeted therapies, PFS could be considered a conservative indicator of OS. The company also states that in TA422 and in TA406, the Appraisal Committee accepted that patients treated with crizotinib would gain an extension to life of more than 3 months compared with standard of care.

The company's economic models predict an extension to life for patients with ROS1+ advanced NSCLC of 2.39 years compared to pemetrexed+platinum therapy and 1.36 years compared to docetaxel therapy.

1.8 ERG commentary on End of Life criteria

The ERG considers that the evidence for life expectancy and extension to life in patients with ROS1+ advanced NSCLC is uncertain, particularly given the lack of a comparator in the PROFILE 1001 study. The ERG notes the following points from previous appraisals of crizotinib for patients with ALK+ advanced NSCLC:

- The Appraisal Committee in TA406 considered that life expectancy in the ALK+ advanced NSCLC population in the first-line setting was likely to be less than 24 months and that the short life expectancy criterion was met. This consideration was

made taking into account the company's revised model that used an earlier data cut from the PROFILE 1014 trial than is used in this appraisal. This consideration was made based on estimates of OS with adjusted baseline characteristics.

- The Appraisal Committee in TA422 noted that there was some uncertainty around life expectancy in the ALK+ advanced NSCLC population in the subsequent-line setting, but considered that, on balance, it was likely to be less than 24 months and that the short life expectancy criterion was met.
- The Appraisal Committee in TA422 and TA406 considered that treatment with crizotinib in the first-line and subsequent-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population. The Appraisal Committee concluded that the extension to life criterion was met.
- The ERG notes that the NHS standard of care for treatment of patients with advanced NSCLC of adenocarcinoma histology has recently changed and is now docetaxel+nintedanib (which has not been included as a comparator in this appraisal).

1.9 ERG commentary on the robustness of evidence submitted by the company

The appraisal of crizotinib for ROS1+ advanced NSCLC includes two company models that cannot be fully quality assured for the reasons outlined in the previous section. This also means that the ERG cannot be confident that the results of any additional exploratory analyses are reliable. As a result, the critique and information provided in this ERG report is limited and the ERG is unable to provide ERG preferred base case ICERs per QALY gained.

1.9.1 Strengths

Clinical effectiveness evidence

- The PROFILE 1001 study was of good quality with independent assessment of radiological results
- In the absence of any comparative evidence from a RCT in the ROS1+ population, the company made use of the data available from the PROFILE 1014 and PROFILE 1007 trials

Cost effectiveness evidence

- The economic model was well constructed
- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses

1.9.2 Weaknesses and areas of uncertainty

Clinical effectiveness evidence

- Clinical advice to the company is that ROS1+ and ALK+ advanced NSCLC are similar diseases and that patients in these populations have similar characteristics. However, the ERG is uncertain if there is sufficient evidence available to allow the outcomes of patients with ALK+ advanced NSCLC to represent the outcomes of patients with ROS1+ advanced NSCLC
- There is no RCT evidence available to support the use of crizotinib for treating ROS1+ advanced NSCLC for any line of treatment
- The clinical evidence supporting treatment with crizotinib in the ROS1+ advanced NSCLC population is derived from a small, single-arm study (PROFILE 1001)
- The OS data from the PROFILE 1001 study were immature (30% of events had occurred at the time of the 2014 data analysis)
- The company was unable to compare crizotinib in patients with ROS1+ advanced NSCLC with any of the comparators listed in the final scope issued by NICE due to a lack of relevant clinical effectiveness evidence
- In the absence of RCT evidence in a population of patients with ROS1+ advanced NSCLC, the company has used data from RCTs that recruited patients with ALK+ advanced NSCLC (PROFILE 1014 and 1007)
- The company was unable to compare crizotinib versus docetaxel+nintedanib in the subsequent-line setting due to lack of published data

- The OS data from the PROFILE 1014 trial are immature and are confounded by crossover; data from the PROFILE 1007 trial are confounded by crossover
- The proportional hazard assumption is not valid for PFS for PROFILE 1014 and 1007 trials
- There are no reliable OS data available for patients treated with ROS1+ advanced NSCLC or patients with ALK+ advanced NSCLC
- There are concerns about the generalisability of the adjusted results of the PROFILE 1014 trial. Clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS

Cost effectiveness evidence

- The evidence underpinning the base case first- and subsequent-line models is from a proxy population (ALK+ advanced NSCLC) rather than the population of interest (ROS1+ advanced NSCLC). The impact of this assumption on cost effectiveness estimates is unknown, since the evidence for the ROS1+ advanced NSCLC population is severely limited
- The evidence used to estimate time-to-event data for treatment with docetaxel in the subsequent-line setting is based on the pooled results of treatment with pemetrexed and docetaxel. The impact of this assumption on cost effectiveness estimates is unknown, although the assumption is expected to be conservative
- The OS evidence for the proxy ALK+ advanced NSCLC population is compromised in both first- and subsequent-line models, which leads to substantial uncertainty in the modelling of OS in the base case analyses
- Estimates of PPS gain in the first- and subsequent-line base cases are substantially greater than estimates of PFS gain. This means that OS treatment effect is modelled to be greater than the PFS treatment effect, which the ERG does not consider to be supported by the evidence available
- Estimates of OS, PFS and TTD in the PROFILE 1001 scenario analysis are based on parametric models with low levels of face validity and clinical plausibility
- Utility values for treatment with pemetrexed+platinum in the progression-free state in the first-line setting are based on only six cycles of EQ-5D data, which may bias the mean result
- There are differences in the baseline EQ-5D data collected during the PROFILE 1007 trial across the two trial arms. These data have not been adjusted for and may bias the mean utility values used for PFS in the subsequent-line model
- Testing for ROS1 rearrangements in the subsequent-line setting is assumed to be carried out upfront. The ERG considers that it is more plausible to assume that patients treated in the subsequent-line would already have been tested for ALK and/or other mutations, so the cost of testing these patients need not be taken into account. The ERG also notes that there may be a discount available for upfront testing that has not been taken into account by the company
- The cost of treating pulmonary embolism may have been underestimated which affects the cost of treating AEs

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

Given the fundamental uncertainties in this appraisal, the ERG is not able to provide preferred base case ICERs per QALY gained. It has instead provided a number of individual revisions and scenario combinations that explore the sensitivity of the ICERs generated by the company models to alternative methods of estimating OS and utility values for PFS.

The ERG has amended estimates of OS in the first-line base case model to investigate the effects of two ERG assumptions: that the OS HR is equal to the PFS HR from the PROFILE 1014 trial; and that PPS is the same for treatment with crizotinib and treatment with pemetrexed+platinum. The ERG has investigated similar scenarios in the subsequent-line model: that the OS HR is equal to the PFS HR from the PROFILE 1007 trial (and is applied to estimates of crizotinib OS that are unadjusted for crossover instead of to RPSFTM-adjusted estimates of docetaxel OS); and that PPS is the same for treatment with crizotinib and treatment with docetaxel.

The ERG has investigated the impact of assuming that the different OS treatment effects explored in the base case models are also applicable in the PROFILE 1001 scenario, whilst using the company's own modelling of OS for treatment with crizotinib. The ERG has also remodelled the OS, PFS and TTD data from the PROFILE 1001 study as an alternative to the company's modelling of time-to-event data from that trial.

The ERG has explored the impact of using different PFS utility values in the first-line model to evaluate the possible effect of bias in the reporting of EQ-5D from the PROFILE 1014 trial. The ERG has investigated three scenarios for the first-line PFS utility values: both treatments have a PFS utility equal to treatment with crizotinib in the base case (0.81); both treatments have a PFS utility equal to treatment with pemetrexed+platinum in the base case (0.72); and treatment with pemetrexed+platinum has a PFS utility of 0.75 (versus 0.72 in the base case).

Finally, the ERG has investigated the effect of combining the time-to-event scenarios with the PFS utility scenarios in the appropriate treatment lines.

1.10.1 Cost effectiveness conclusions

The resulting ICERs per QALY gained in the first-line base case when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted]. The resulting ICERs per QALY gained in the subsequent-line base case when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted].

The resulting ICERs per QALY gained in the first-line PROFILE 1001 scenario when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted]. The resulting ICERs per QALY gained in the subsequent-line PROFILE 1001 scenario when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted].

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Sections B.1.3 and B.1.3.1 of the company submission (CS) include an overview of non-small cell lung cancer (NSCLC) and a description of ROS1+ advanced NSCLC. Key points from these sections of the CS are included as bulleted items in Box 1 and Box 2. The Evidence Review Group (ERG) considers that these points are largely accurate, but that they lack detail on the burden of ROS1+ advanced NSCLC experienced by patients, carers and society.

Box 1 Company overview of NSCLC

- Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases.[1] According to the National Lung Cancer Audit Report (2016),[2] 38,232 cases of lung cancer were reported in England and Wales in 2015.
- Lung cancer is often diagnosed at an advanced stage due to the low index of suspicion surrounding the symptoms or the presence of symptoms only at an advanced stage of the disease.[3] In England, 75.3% of lung cancer cases are diagnosed at an advanced stage of disease (21.4% and 53.9% for stages III and IV, respectively).[4] Due to late diagnosis, the prognosis for patients diagnosed with lung cancer is often poor.[5]
- Lung cancer can be categorised into two major types: small-cell lung cancer and non-small cell lung cancer (NSCLC).[2] NSCLC accounts for the majority (88% in England and Wales)[2] of lung cancer cases and can be sub-typed further into three histological types: adenocarcinoma (63.5% of NSCLC), large-cell undifferentiated carcinoma (4.2% of NSCLC) and squamous cell carcinoma (32.4% of NSCLC).[6] Both adenocarcinoma and large-cell undifferentiated carcinoma are classified as non-squamous histological sub-types of NSCLC.
- There are different molecular subtypes of lung cancer and there is a shift towards practising precision medicine with the availability of targeted therapies which can treat specific molecular subtypes of cancer. Targeted therapies are now the standard of care for patients with epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC. ROS1+ advanced NSCLC is considered to represent another group of patients who would benefit from a targeted treatment option.

EGFR=epidermal growth factor receptor
Source: CS, pp19 and 20

Box 2 Company description of ROS1+ advanced NSCLC

- ROS1+ advanced NSCLC is estimated to occur in 1.1–1.8% of NSCLC patients and to be found almost exclusively in non-squamous tumours.[7-9] This incidence is considerably lower than tumours harbouring ALK, EGFR or Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations, which account for between 3.4%, 15.3% and 32.6% of NSCLC, respectively.[6] This suggests that ROS1+ advanced NSCLC is rare in England and Wales. ROS1-translocations are usually mutually exclusive to other oncogenic drivers.[7,10]
- ROS1 was ….. identified as a key oncogenic driver in a number of other cancers, including NSCLC in 2007.[11] In lung cancer, there is no single most common fusion partner with ROS1, with several being described.[12] Different fusion partners are not thought to impact on the efficacy of crizotinib, as the ROS1 tyrosine kinase protein (and binding site for crizotinib) is consistent.[13] Inhibition of ROS1 is associated with anti-tumour activity in preclinical models, as demonstrated in both in vitro phenotypic assays and in vivo transgenic mouse and xenograft models. As in ALK, crizotinib, via inhibition of ROS1, has demonstrated dose-dependent inhibition of cell proliferation and induced apoptosis in cell-based assays, as well as dose-dependent tumour regression in in vivo xenograft models.[14,15]

- The clinical and pathologic features of ROS1+ tumours have been characterised, with ROS1-positivity showing associations with non-smoker status and a younger age of diagnosis.[14] In addition, ROS1-translocations are almost exclusively detected in non-squamous tumour types, and predominantly in adenocarcinoma tumour types.[14] NSCLC associated with an underlying ROS1 gene-rearrangement is, however, fundamentally different from unselected NSCLC and unselected adenocarcinoma, as disease progression in ROS1+ NSCLC patients is dependent on the activated ROS1 receptor tyrosine kinase (RTK).[11,16] Similarly, the clinical benefit of specific targeted therapies, such as crizotinib, is dependent on the role of the activated ROS1 RTK in driving cancer progression.[11,16]

EGFR=epidermal growth factor receptor; RTK=receptor tyrosine kinase
Source: CS, p20

In Section B.1.3.1 of the CS (CS, p20), the company compares ROS1+ and anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC (Box 3).

Box 3 Company comparison of ROS1+ and ALK+ NSCLC

- The ROS1 oncogene encodes an orphan RTK related to ALK.[17] In both ROS1+ and ALK+ NSCLC the genetic translocation events lead to gene fusions that result in deregulated expression of the respective kinase domain, ALK or ROS1, with constitutive activation of the kinase activity.[11,16,18,19] This oncogene activation event means that ROS1+ and ALK+ NSCLC are fundamentally different from unselected NSCLC and unselected adenocarcinoma, as disease progression is dependent on these activated RTKs.[11,16]

- The kinase domains of ALK and ROS1 share 77% amino acid identity within the adenosine triphosphate-binding sites, and crizotinib binds with high affinity to both ALK and ROS1, as expected based on their homology.[20] This was recognised by the EMA as supporting the biology of ALK and ROS1 fusions in NSCLC as being analogous.[14]

- As with ALK+ NSCLC patients, patients with ROS1+ NSCLC patients are usually non-smokers or light smokers, predominantly have histologic features of adenocarcinoma and are young.[7,21] A small proportion of patients in both the ROS1+ and ALK+ NSCLC populations have demonstrated sensitivity to pemetrexed-based chemotherapy, providing further evidence to support the similarities between these two populations.[18] These similarities were supported and validated by leading UK clinical experts.[22]

EMA=European Medicines Agency; RTK=receptor tyrosine kinase
Source: CS, p20

The ERG agrees with the company that ROS1+ and ALK+ advanced NSCLC are different diseases from undifferentiated NSCLC. The ERG accepts the company's view (supported by 12 UK clinicians who attended the company's advisory board meeting[22]) and the opinion of the European Medicines Agency[14] (EMA), that biological and clinical similarities exist between ROS1+ and ALK+ advanced NSCLC and that there are similarities between patients with ROS1+ and ALK+ advanced NSCLC. However, the ERG notes that the incidence of ROS1+ advanced NSCLC is low (between 1% and 2% of NSCLC tumours)[7] and that, throughout the CS, the company refers to ROS1+ advanced NSCLC as an 'ultra-orphan disease' (e.g. CS, pp20-21, p54, p81, p85). Clinical advice to the ERG is that the small numbers of patients with ROS1+ advanced NSCLC thus far identified does not allow robust comparisons to be made between the outcomes from patients with ROS1+ and ALK+ advanced NSCLC who are treated with crizotinib.

The company puts forward the case that clinical evidence data derived from randomised controlled trials (RCTs) of patients with ALK+ advanced NSCLC are an appropriate proxy for clinical data from patients with ROS1+ advanced NSCLC (Box 4).

Box 4 Company rationale for the relevance of data from trials of patients with ALK+ advanced NSCLC

- Given the similarities between ROS1+ and ALK+ advanced NSCLC patients, data from randomised controlled trials of crizotinib in ALK+ advanced NSCLC patients are deemed relevant to the clinical efficacy and safety of crizotinib in ROS1+ patients. The PROFILE 1007[23-28] trial provided evidence for the approval of crizotinib for previously treated ALK+ advanced NSCLC by the EMA and NICE,[29,30] and the PROFILE 1014[31-34] trial provided data on the activity of crizotinib in the approval of crizotinib for first-line ALK+ advanced NSCLC.[35,36] As such, the data from the PROFILE 1007[23-28] and 1014[31-34] trials in ALK+ advanced NSCLC has been deemed suitable by clinical experts[22] as an appropriate proxy for ROS1 and will be used where data for crizotinib versus a comparator in ROS1+ advanced NSCLC are limited..

EMA=European Medicines Agency
Source: CS, p20

Throughout the CS, the company states that the generalisability of data from ALK+ advanced NSCLC patients to ROS1+ advanced NSCLC patients was strongly supported by the 12 leading UK experts who attended the company's advisory board meeting.[22] The company also states that the EMA considered the clinical evidence from trials in the ALK+ advanced NSCLC population when granting the marketing authorisation[14] for the use of crizotinib in patients with ROS1+ advanced NSCLC. The ERG notes that the opinion given in the clinical expert statement[37] submitted to NICE on behalf of The British Thoracic Oncology Group, The National Cancer Research Institute, The Royal College of Physicians and The Association of Cancer Physicians, is that patients with ROS1+ and ALK+ advanced NSCLC are clinically similar, and that it is reasonable to generalise outcomes from the ALK+ population to the ROS1+ population.

Clinical advice to the ERG is that it is uncertain if the currently documented similarities between ROS1+ and ALK+ advanced NSCLC will be supported as more patients with ROS1+ advanced NSCLC are identified. The ERG questions whether the evidence thus far available allows the outcomes from patients with ALK+ advanced NSCLC to be robustly generalised to patients with ROS1+ advanced NSCLC.

The ERG notes that the data presented in the CS in support of the clinical effectiveness of crizotinib in patients with ROS1+ advanced NSCLC are derived from a single-arm study, known as the PROFILE 1001[13,38-42] study. The study recruited 53 patients with ROS1+ advanced NSCLC, 7 of the patients had untreated disease and 46 patients had received 1 (or more) prior treatments. The results of the PROFILE 1001 study were the basis for the EMA European marketing authorisation[14] and for the Food and Drug Administration (FDA) approval

in the US of the use of crizotinib in the treatment of ROS1+ advanced NSCLC. The ERG notes that the EMA[14] has acknowledged that ROS1+ is a rare form of NSCLC and, that therefore, the current evidence base for ROS1+ NSCLC is immature. In particular, the EMA highlighted in the European Public Assessment Report[14] (EPAR) that the prognosis for patients with ROS1+ NSCLC is unknown as the evidence available is limited to the results of a small number of retrospective studies, with some that have contradictory results. The EMA concluded that '…benefit of a therapy selectively addressing patients with ROS1+ NSCLC is at present not fully evaluable' EPAR, p42).[14]

It is highlighted in the CS (CS, p26, p29, p31, p54) that data are unlikely to ever be available from an RCT of crizotinib conducted in patients with ROS1+ advanced NSCLC. Clinical advice to the company (CS, p26, p29, p31, p54) is that given the small number of patients with ROS1+ advanced NSCLC and the clinical efficacy of crizotinib as demonstrated in the PROFILE 1001 study, clinical equipoise would not be feasible and, therefore, it would be unethical to conduct an RCT in this patient population.

The company's case for the clinical and cost effectiveness of the use of crizotinib in the treatment of patients with ROS1+ advanced NSCLC rests on the assumption that RCT data derived from patients with ALK+ advanced NSCLC can be used as proxy data for the ROS1+ advanced NSCLC patient population.

2.2 Critique of company's overview of current service provision

An overview of current service provision is presented in Section B.1.3.2 of the CS. The company expects that crizotinib will be used in place of non-targeted chemotherapy treatments in the untreated and subsequent treatment settings.

The company presents a treatment algorithm outlining the existing treatment pathway for patients with advanced NSCLC (Figure 1). The company has referred to relevant published NICE guidance in footnotes in the CS. The company correctly points out (CS, p23) that, at present, there are no recommended treatments for patients with ROS1+ advanced NSCLC and, that testing for ROS1 is not carried out routinely in the NHS. However, the company anticipates (CS, p23) that, with the advent of routine testing for ROS1 NSCLC, crizotinib will be mostly used to treat previously untreated patients.

The ERG considers that the algorithm presented by the company largely reflects current clinical practice and would capture the treatment pathway if crizotinib were recommended by NICE for use in patients with ROS+ advanced NSCLC in the NHS. The ERG notes that in the

first-line setting, NICE also recommends single agent third-generation chemotherapy for patients who cannot tolerate platinum-based chemotherapy (not shown in algorithm).[43]

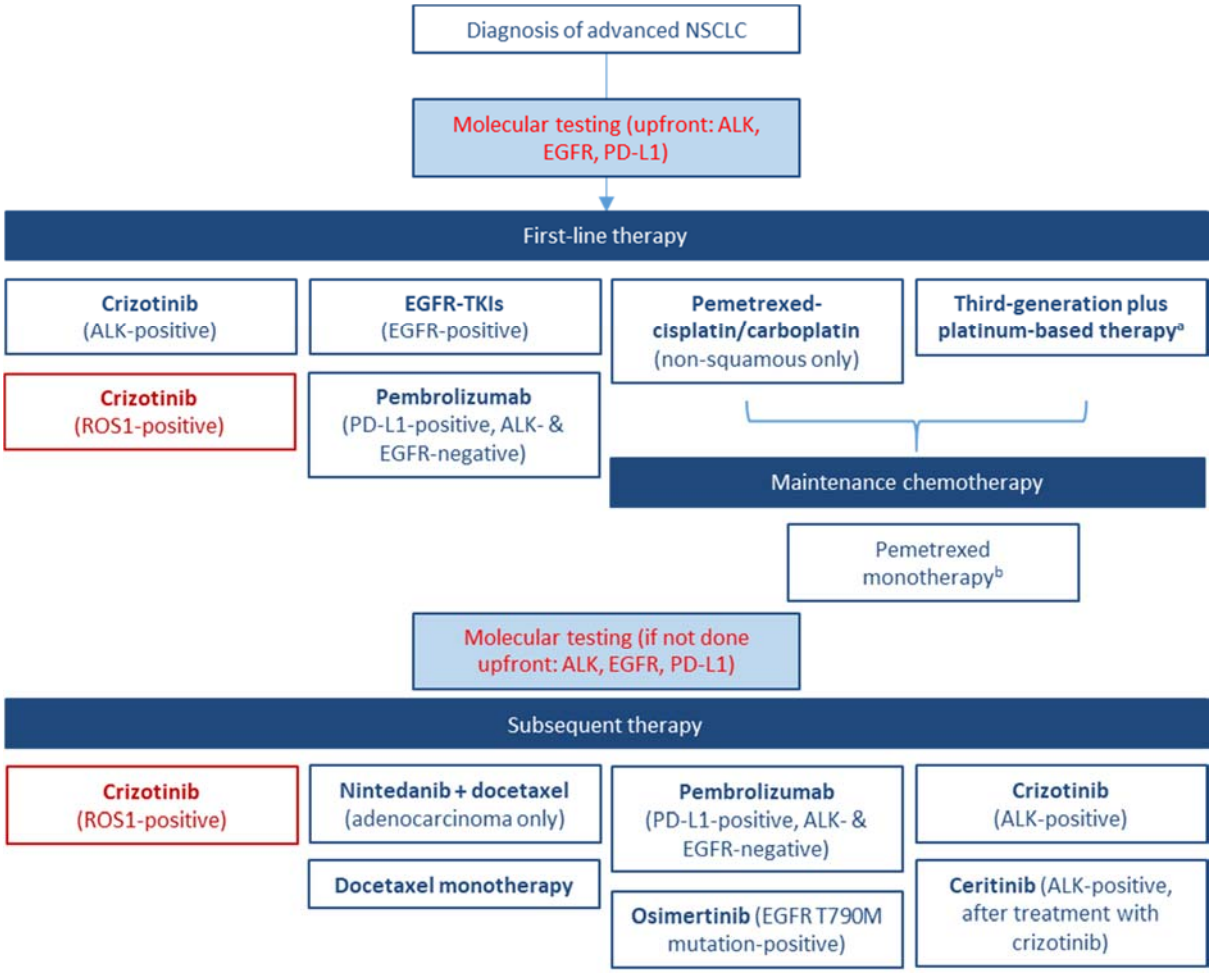

Figure 1 NHS treatment algorithm presented by the company

Source: CS, Figure 2

2.3 Summary of relevant clinical guidance and guidelines

In the footnotes of the treatment algorithm presented in the CS, the company has included references to relevant published guidance and treatment guidelines for NSCLC, however, no further details are provided. A summary of the available NICE guidelines[43] and published guidance[15,30,44-55] for the treatment of NSCLC is presented in Table 1.

The ERG notes that crizotinib is currently recommended by NICE for use in patients with untreated ALK+ advanced NSCLC (TA406)[36] and for patients with previously treated ALK+ advanced NSCLC (TA422).[30]

Table 1 ERG summary of published NICE guidelines and guidance

NICE guideline or guidance	Summary of NICE recommendations
Guideline	
Lung cancer: diagnosis and management CG121[43] (2011)	• For patients with tumours of negative or unknown EGFR status and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) chemotherapy should be offered; where the chemotherapy should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) • Patients who are unable to tolerate combination therapy may be offered single-agent chemotherapy with a third-generation drug
First-line treatment	
TA181[45] (2009)	• **Pemetrexed in combination with cisplatin**: if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma
TA192[47] (2010)	• **Gefinitib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA258[48] (2012)	• **Erlotinib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA310[49] (2014)	• **Afatinib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA406[15] (2016)	• **Crizotinib**: patients whose tumours test positive for ALK mutation

TA447[55] (2017)	• **Pembrolizumab** is recommended for use within the Cancer Drugs Fund as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults, only if:
	  • their tumours express PD-L1 with at least a 50% tumour proportion score and have no EGFR- or ALK+ mutations
	  • pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
	  • the conditions in the managed access agreement for pembrolizumab are followed

Maintenance treatment	
TA190[46] (2010)	• **Pemetrexed**: patients with other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel
TA402[53] (2016)	• **Pemetrexed**: patients with non-squamous disease whose disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and who have an ECOG PS 0 or 1 at the start of maintenance treatment
Second-line treatment	

TA374[44] (2015)	• **Erlotinib** is an option for patients who have:
	  • had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive
	  • progressed after non-targeted chemotherapy and who have tumours of unknown EGFR-TK mutation status, but only if the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA; the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive; and there is an observed response within the first 2 cycles of treatment

TA395[51] (2016)	• **Ceritinib**: adults with advanced ALK+ disease who have previously received crizotinib
TA347[50] (2015)	• **Nintedanib+docetaxel**: for patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy,
TA416[52] (2016)	• **Osimertinib**: patients with EGFR T790M mutation-positive disease whose disease has progressed after first-line treatment with an EGFR-TK inhibitor (only available via the CDF)
TA422[30] (2016)	• **Crizotinib:** previously treated adults with ALK+ NSCLC (after a rapid re-review by the CDF)
TA428[54] (2017)	• **Pembrolizumab:** patients with PD-L1 positive NSCLC in adults who have had at least one prior chemotherapy (and EGFR/ALK targeted treatment, if relevant) if treatment is stopped at 2 years of uninterrupted treatment and no documented disease progression

CDF=Cancer Drugs Fund; DNA=Deoxyribonucleic acid; ECOG=Eastern Co-operative Oncology Group; EGFR=epidermal growth factor receptor; EGFR TK=epidermal growth factor receptor tyrokinase; PD-L1=programmed death ligand 1; WHO=World Health Organisation

2.4 Testing for ROS1 status in the NHS

In the summary of product characteristics (SmPC)[56] for crizotinib, it is stipulated that treatment should only be initiated after the patient's ROS1 status is positively confirmed by a clinical laboratory test using a validated test method. The company discusses the issues relevant to testing for ROS1 NSCLC within the NHS (CS, p25).

The company states that testing for ROS1 status is not generally available in the NHS and is not part of routine clinical practice. The ERG understands that the main methods of testing for ROS1 status are immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) testing. Clinical advice to the company (CS, p25) is that IHC testing followed by a confirmatory FISH test is considered optimal; however, next generation sequencing (NGS) may be routinely available within the NHS in the future.

The company reports that strategies for testing for ROS1 positivity in NHS patients are in development in some NHS laboratories. The company describes two possible testing strategies, the first is to test for ROS1 positivity in patients with non-squamous NSCLC at the same time that tests for epidermal growth factor receptor (EGFR) and ALK positivity are conducted. The second strategy is to test for ROS1 positivity only after tumours are confirmed to be negative for EGFR and ALK NSCLC. The company states that a working group of pathologists, sponsored by Pfizer Ltd, recommended that testing for ROS1 positivity is carried out at the same time as other molecular tests and that this approach is also included in published expert recommendations.[57] The company points out (CS, p27) that if the sequential testing strategy (as discussed in Section 2.3.1 of this ERG report) for the identification of ROS1+ advanced NSCLC is adopted in the NHS, there is the potential for a delay in the diagnosis and treatment of patients.

2.5 Innovation

The company puts forward the case that crizotinib is an innovative treatment (CS, p78). The company states that:

- Crizotinib is the only available targeted treatment for ROS1+ advanced NSCLC that is licensed in Europe and the UK
- The FDA granted crizotinib "Breakthrough Therapy designation" and "Priority Review"[58]
- The EMA granted a marketing authorisation for crizotinib based on the results of a single-arm study[14]

- Crizotinib is an oral treatment and is therefore more convenient and less onerous compared with intravenously administered treatment options

- Treatment with crizotinib is associated with considerable treatment benefits for patients with ROS1+ advanced NSCLC compared with treatment with chemotherapy.

The ERG agrees that crizotinib is the only targeted treatment for ROS1+ advanced NSCLC that is licensed in Europe and the UK and, that compared with treatment with chemotherapy, oral treatment is more convenient and less onerous.

2.6 Number of patients eligible for treatment with crizotinib

The company estimates that 289 patients will be diagnosed with ROS1+ advanced NSCLC annually in England and Wales. The company's estimate, presented in the 'Budget Impact' section of Document A of the CS, is based on an incidence rate of 1.7% in patients with non-squamous disease.

The ERG's own estimate of the number of patients who are likely to be diagnosed with ROS1+ NSCLC in England and Wales and who may be eligible for treatment with crizotinib is presented in Table 2. The ERG estimate of 274 is consistent with the company's estimate of 289 patients. The ERG is uncertain how many of the patients currently being treated in the NHS are likely to be identified as having ROS1+ advanced NSCLC.

Table 2 ERG estimation of number of patients eligible for treatment with crizotinib in England and Wales annually

Parameter	Data source	Percentage	Number of patients
Percentage of cases of lung cancer in 2015	National Lung Cancer Audit Report[2]		38,232
Percentage of patients with non-squamous NSCLC	Clinical Lung Cancer Genomics Project[6]	67.7%	25,883
Percentage of patients diagnosed with advanced lung cancer (England) in 2014	National Lung Cancer Audit Report[2] Stage IIIb and Stage IV	59%	15,271
Percentage of patients with ROS1+ advanced NSCLC	Scheffler[9]	1.8%	274

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

A summary of the decision problem outlined in the final scope issued by NICE[59] and that addressed in the CS is presented in Table 3. Each parameter in Table 3 is discussed in more detail in the text following the table.

Table 3 Comparison between NICE scope and company decision problem

Final scope issued by NICE **Parameter and specification**	**Decision problem addressed in the company submission**
Population: People with ROS1+ advanced NSCLC	People with ROS1+ advanced NSCLC. However, with the exception of the 53 patients with ROS1+ advanced NSCLC, all of the data discussed in the CS are derived from patients with ALK+ advanced NSCLC.
Intervention: Crizotinib	Crizotinib
Comparators <u>Untreated disease</u> • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) with a platinum drug (carboplatin or cisplatin) - With (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) - With (following cisplatin containing regimens only) or without pemetrexed maintenance treatment • Single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based therapy <u>After previous chemotherapy treatments</u> • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care	Pemetrexed+platinum (data are derived from patients with ALK+ advanced NSCLC) Docetaxel monotherapy (data are derived from patients with ALK+ advanced NSCLC who received either pemetrexed or docetaxel monotherapy)
Outcomes • OS • PFS • RR • AEs • HRQoL	PFS, RR and AEs presented for the population and intervention in the final scope issued by NICE Comparative clinical effectiveness analyses presented are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for ROS1+ advanced NSCLC patients
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any PAS for the intervention or comparator technologies will be taken into account The use of crizotinib is conditional on ROS1+ status. The economic modelling should include the costs associated with diagnostic testing for ROS1 status in people with advanced non-small cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals	Economic analysis based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for data from ROS1+ advanced NSCLC patients Data from PROFILE 1001 study evaluating the use of crizotinib in ROS1+ advanced NSCLC patients used in a scenario analysis An agreed PAS is in place for crizotinib for the treatment of patients with ALK+ advanced NSCLC. The PAS will be extended to the ROS1+ advanced NSCLC indication if the treatment is recommended for this group of patients The company did not provide a sensitivity analysis without the cost of the diagnostic test
Subgroups to be considered: None specified	None identified
Special considerations: None specified	None identified

AE=adverse event; HRQoL=health-related quality of life; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; RR=response rate

3.1 Clinical effectiveness evidence presented in the company submission

The only clinical effectiveness data available for the ROS1+ advanced NSCLC population are from the PROFILE 1001, single-arm study. The study recruited 53 patients, 7 patients with untreated disease and 46 patients who had received one or more prior chemotherapies. The overall survival (OS) data from the PROFILE 1001 study are, at present, immature (median OS is not reached). This means that there are no median OS data for patients with ROS1+ advanced NSCLC who have been treated with crizotinib.

The ERG notes that the EMA's marketing authorisation for crizotinib for the treatment of ROS1+ advanced NSCLC is based on the outcomes of the 53 patients recruited to the PROFILE 1001 study. The ERG also notes from the EPAR[14] for crizotinib that the EMA considered the data for the efficacy of crizotinib for patients treated at first-line (n=7) were 'limited'. However, the EMA noted that the results of the PROFILE 1001 study of crizotinib in patients with untreated ALK+ advanced NSCLC were supported by the subsequent PROFILE 1014[31-34] trial (crizotinib versus pemetrexed+platinum in patients with untreated ALK+ advanced NSCLC). The EMA concluded that similarities between ROS1+ and ALK+ advanced NSCLC are sufficient to assume that crizotinib would also be clinically effective in the first-line treatment of ROS1+ advanced NSCLC.[14]

There is no direct clinical evidence comparing crizotinib for the treatment of patients with ROS1+ advanced NSCLC in any setting with any of the comparators listed in the final scope issued by NICE. To compare crizotinib with pemetrexed+platinum in an untreated patient population and docetaxel in a previously treated population, the company has provided evidence from a patient population not specified in the final scope issued by NICE, i.e. patients with ALK+ advanced NSCLC. The company's economic base case incorporates the outcomes of patients with ALK+ advanced NSCLC in the PROFILE 1014 and PROFILE 1007 RCTs.

The PROFILE 1014 trial was designed to compare the clinical effectiveness of crizotinib with pemetrexed+platinum in patients with previously untreated ALK+ advanced NSCLC. The PROFILE 1007 trial was designed to compare the clinical effectiveness of crizotinib with chemotherapy (pemetrexed or docetaxel) in patients with previously treated ALK+ advanced NSCLC.

Clinical advice to the ERG is that it is too early to be certain if the data from trials in patients with ALK+ advanced NSCLC can be used as proxy data for patients with ROS1+ advanced NSCLC (see Section 2.1 of this ERG Report).

The ERG considers that the company has met the criteria stipulated in the decision problem in the final scope issued by NICE, **only** if it is accepted that the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

3.2 Population

The population described in the final scope issued by NICE is people with ROS1+ advanced NSCLC. The population discussed in the CS is the population recruited to the PROFILE 1001 study, which is identical to the population described in the final scope issued by NICE. However, the ERG notes that the direct evidence presented in the CS for the use of crizotinib in patients with ROS1+ advanced NSCLC is from a small, single-arm study (PROFILE 1001).

Most of the evidence presented in the CS is proxy evidence derived from two RCTs conducted in patients with ALK+ advanced NSCLC. The ERG considers that the company has met the population parameter specified in the decision problem only if the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

Treatment line is not specified either in the final scope issued by NICE or in the EMA licence. The company expects that crizotinib will be used as a first- and subsequent-line treatment. However, the company anticipates that the number of patients treated at subsequent-line will reduce over time as more patients with advanced ROS1+ advanced NSCLC are identified at initial diagnosis and treated with crizotinib in the first-line (CS, p25).

The trial centres in the PROFILE 1001 study were based in the USA, Australia and South Korea. None of the trial centres were based in the UK. Clinical advice to the ERG is that patients recruited to the PROFILE 1001 study are broadly comparable to patients with ROS1+ advanced NSCLC who are likely to be treated in the NHS, with the proviso that the patients recruited to the trial are younger and fitter and have fewer co-morbidities than NHS patients. Clinical advice to the ERG is that, as crizotinib is a targeted treatment in a mutation-driven subtype cancer, patients in the NHS are likely to achieve similar response rates and disease control regardless of these differences.

The company considers that data derived from the PROFILE 1014 and PROFILE 1007 trials in patients with ALK+ advanced NSCLC provide appropriate proxy data for patients with ROS1+ advanced NSCLC. The ERG notes that, compared with patients in the PROFILE 1014 and PROFILE 1007 trials, patients recruited to the PROFILE 1001 study were older, heavier

and were more likely to have never smoked. In addition, patients in the PROFILE 1001 study were fitter than patients in the PROFILE 1014 trial.

The company's rationale for and the ERG's comments on this assumption are discussed in Section 2.1 of this ERG Report. In summary, the ERG is uncertain whether there is enough evidence at present for conclusions to be drawn regarding similarities between these conditions and to allow robust comparisons to be made between the clinical efficacy of crizotinib for treating patients with ROS1+ and ALK+ advanced NSCLC.

3.3 Intervention

The intervention identified in the final scope issued by NICE is crizotinib. Crizotinib is a small molecule inhibitor of receptor tyrosine kinase (RTK) and is selectively active against RTKs associated with ROS1, ALK, hepatocyte growth factor receptor (HGFR) and Recepteur d'Origine Nantais (RON). Crizotinib is licensed in Europe for i) the treatment of ROS1+ advanced NSCLC[14] and ii) the treatment of ALK+ advanced NSCLC.[29,35]

Crizotinib is available as a hard capsule (200 mg or 250 mg). The daily dose is 500 mg (250 mg twice daily).

3.4 Comparators

The comparators in the final scope issued by NICE vary by line of treatment, i.e. untreated or previously treated disease. In the absence of RCT evidence from patients with ROS1+ advanced NSCLC, the company has used clinical evidence from two RCTs conducted in patients with ALK+ advanced NSCLC.

Data available to the company for the clinical efficacy of crizotinib in patients with ALK+ advanced NSCLC were limited to two RCTs i.e., the PROFILE 1014 trial and the PROFILE 1007 trial. The company has presented the results from the PROFILE 1014 and PROFILE 1007 trials in narrative form.

3.4.1 Comparators addressed in the company submission

Untreated disease (PROFILE 1014)

Pemetrexed+platinum. The company has provided clinical effectiveness evidence for the comparison of crizotinib with pemetrexed+platinum. Clinical advice to the company (CS, p25) is that, in the UK, patients with ROS1+ advanced NSCLC who are fit enough to be treated with chemotherapy would be treated with pemetrexed+platinum. The ERG agrees with the company that pemetrexed+platinum is recommended by NICE in TA181[45] for treating patients with non-squamous NSCLC. The ERG notes that current knowledge of ROS1+ NSCLC

suggests that most ROS1+ tumours are of adenocarcinoma (and therefore of non-squamous) histology.

The company has presented evidence from the PROFILE 1014 trial in which patients with ALK+ advanced NSCLC who had not received previous systemic treatment were randomised to receive either crizotinib or pemetrexed+platinum chemotherapy.

After previous chemotherapy (PROFILE 1007)

Docetaxel. The company has provided clinical effectiveness evidence for the comparison of crizotinib with docetaxel. The evidence for the effectiveness of docetaxel is derived from the PROFILE 1007 trial in which patients with advanced ALK+ NSCLC who had received up to three lines of previous systemic treatment were randomised to receive either crizotinib or either pemetrexed or docetaxel monotherapy. The ERG notes that in the UK, NICE recommends[50] docetaxel+nintedanib as a treatment for patients with tumours of adenocarcinoma histology that have progressed after first-line chemotherapy. Clinical advice to the ERG is that docetaxel monotherapy is also used to treat patients who are not fit enough for treatment with docetaxel+nintedanib. The ERG notes that pemetrexed monotherapy is not listed as a comparator in the final scope issued by NICE and it is not used in UK clinical practice to treat patients with previously treated NSCLC.

3.4.2 Comparators not addressed in the company submission

The company discusses (CS, p25 to p27) issues relevant to the comparators not addressed in the CS (Table 4 and Table 5).

Table 4 Comparators not addressed in the company submission (untreated disease)

Comparator	Company rationale for exclusion	ERG comment
Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) +platinum with or without pemetrexed maintenance treatment Single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based chemotherapy	• Following consultation with UK clinical experts, it was noted that first-line docetaxel, paclitaxel or vinorelbine are rarely used in patients with non-squamous disease in the first-line setting. These are instead comparators more commonly used to treat patients with squamous disease. It is also understood that gemcitabine is not commonly used in patients with non-squamous disease, however may be an alternative therapy offered to a small number of patients with non-squamous disease who are not able to tolerate pemetrexed-platinum doublet therapy This approach was also used for the NICE appraisal of crizotinib for untreated ALK+ NSCLC (TA406[15]) • As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC, efficacy data for first-line docetaxel, gemcitabine, paclitaxel or vinorelbine in unselected NSCLC is not deemed applicable in the ROS1+ advanced NSCLC population. Therefore, there are no data to form a reliable comparison to first-line docetaxel, gemcitabine, paclitaxel or vinorelbine, and as such it has not been addressed in the decision problem	The ERG agrees that in clinical practice in the UK, patients with tumours of non-squamous histology are unlikely to be treated with platinum based chemotherapy treatment plus docetaxel, gemcitabine, paclitaxel or vinorelbine The ERG notes that in TA406, the company submission discussed patients with tumours of adenocarcinoma histology as most ALK+ NSCLC tumours are of adenocarcinoma histology (approximately 98%) The ERG agrees that ROS1+ NSCLC is different to unselected NSCLC and that there is no clinical effectiveness evidence for the use of third-generation chemotherapies specific to patients with ROS1+ advanced NSCLC
Pemetrexed maintenance treatment (for patients with non-squamous NSCLC)	• Clinical experts have suggested that approximately 15% of patients with advanced NSCLC would be eligible for pemetrexed maintenance after platinum doublet first-line chemotherapy, based on fitness. Given the small proportion of patients who receive maintenance therapy, this was not considered as a comparator in this submission • The exclusion of this comparator is in line with the final NICE scope for crizotinib for untreated ALK+ NSCLC • Furthermore, there is insufficient evidence on the efficacy of pemetrexed maintenance in patients with ROS1+ NSCLC, and the data available from the ALK+ NSCLC population is from a mixed chemotherapy comparator (pemetrexed plus platinum followed by pemetrexed maintenance/ASCEND-4)	The ERG agrees that approximately 15% of patients with advanced NSCLC are likely to receive pemetrexed maintenance after platinum doublet first-line chemotherapy The ERG notes that pemetrexed maintenance therapy was not a listed comparator in the final scope issued by NICE for TA406 The ERG notes that the ASCEND-4 RCT compares the clinical efficacy of ceritinib versus pemetrexed+platinum in patients with advanced ALK+ NSCLC. In the ASCEND-4 trial, 127 of 175 patients treated with pemetrexed+platinum continued treatment with pemetrexed maintenance therapy. Subgroup data from the ASCEND-4 trial are not available

Table 5 Comparators not addressed in the company submission (previously treated disease)

Comparator	Company rationale for exclusion	ERG comment
Docetaxel with (for adenocarcinoma histology) nintedanib	• Data for nintedanib with docetaxel were only available from the broader unselected NSCLC population, with subgroup analysis for patients with adenocarcinoma, and not from the ROS1+ NSCLC population. As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC or unselected adenocarcinoma,[11,16] the efficacy data from the unselected NSCLC population (including unselected adenocarcinoma) is not deemed applicable to the ROS1+ NSCLC population • No data in the proxy ALK+ NSCLC population exists for nintedanib with docetaxel	The ERG agrees that ROS1+ NSCLC is different to unselected NSCLC and unselected adenocarcinoma and that there are no data relevant to patients with ROS1+ advanced NSCLC and that there are also no data relevant to patients with ALK+ advanced NSCLC However, the ERG considers that docetaxel+nintedanib is standard of care for patients with tumours of adenocarcinoma histology and has more favourable outcomes than docetaxel monotherapy
BSC	• Data for BSC as a subsequent-line option in patients who have received upfront chemotherapy are only available in the unselected NSCLC population and not from the ROS1+ advanced NSCLC population. As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC, efficacy data for BSC in unselected NSCLC is not deemed applicable in the ROS1+ NSCLC population. Therefore, there are no data to form a reliable comparison to BSC, and as such it has not been addressed in this decision problem. This aligns with comments from the ERG where the mixed treatment comparison to BSC was criticised for lacking robustness due to key differences between the selected and unselected patient populations. (TA296[60] and TA422[30]) • Furthermore, patients with ROS1+ NSCLC are typically young and otherwise fit enough for chemotherapy, and as such BSC is likely to be used in a smaller proportion of patients with ROS1+ NSCLC compared to patients with unselected NSCLC	The ERG agrees that there are no data available to compare crizotinib with BSC, in either patients with ROS1+ NSCLC or ALK+ NSCLC The ERG notes that the mixed treatment comparison presented in the TA296 and TA422 was not considered by the AC to be robust as it included patients with unselected NSCLC The ERG agrees that patients with ROS1+ NSCLC are likely to be fit for further treatment

3.5 Outcomes

Outcome data for patients with ROS1+ advanced NSCLC are available from the PROFILE 1001 study. Data are presented in the CS for the outcomes of progression-free survival (PFS) and adverse effects of treatment (AEs). Several measures of response rate (RR) are also presented, including objective response rate (ORR), disease control rate (DCR), duration of response (DR) and time to tumour response (TTR). Immature data (30% at the time of the 2014 analysis) for OS are presented in the CS; however, median OS was not reached and the company does not intend to carry out further updates of OS until [redacted]. No health-related quality of life (HRQoL) data were collected during the PROFILE 1001 study.

Outcome data for patients with untreated ALK+ advanced NSCLC are available from the PROFILE 1014 trial. Data are presented in the CS for the outcomes of PFS, ORR, AEs and HRQoL. Data for OS are also presented (44.3% mature) however, median OS was not

reached and data are confounded by crossover. This means that the true OS associated with crizotinib in patients with untreated ALK+ advanced NSCLC is unknown.

Outcome data for patients with previously treated ALK+ advanced NSCLC are available from the PROFILE 1007 trial. Data are presented in the CS for the outcomes of PFS, ORR, AEs and HRQoL. Data for OS are also presented (69.8% mature); however, the ERG notes that high levels of crossover were allowed in the trial. This means that the true OS associated with crizotinib in patients with previously treated ALK+ advanced NSCLC is unknown.

Limitations of the overall survival data presented by the company

The ERG notes that there are no mature OS data available for patients with ROS1+ advanced NSCLC. The ERG also notes that the OS data from patients with ALK+ advanced NSCLC presented in the CS, i.e. the PROFILE 1014 and PROFILE 1007 trials, are immature and problematic. This means that there are no useful OS data for either the population specified in the decision problem (i.e. people with ROS1+ advanced NSCLC) or for the ALK+ advanced NSCLC population used in the CS to mitigate the uncertainty around the limited data available for the population specified in NICE's decision problem.

3.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 20-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS and Personal Social Services perspective. The evidence for the company's base case is derived from two RCTs that were conducted in patients with ALK+ advanced NSCLC, the PROFILE 1014 and 1007 trials. The company has used data from the PROFILE 1001 study of patients with ROS1+ advanced NSCLC in a scenario analysis. The company considers that the use of the data from the PROFILE 1014 and PROFILE 1007 trials reduces the uncertainty associated with the small dataset available from the PROFILE 1001 study of patients with ROS1+ advanced NSCLC.

3.7 Equality considerations

In the SmPC for crizotinib, it is stipulated that treatment should only be initiated after the patient's ROS1 status is positively confirmed by a clinical laboratory test using a validated test method. The ERG notes that there is currently no routinely funded testing for ROS1 in the NHS. The company points out (CS, p27) that, if the sequential testing strategy (as discussed in Section 2.3.1 of this ERG report) for the identification of ROS1+ advanced NSCLC is adopted in the NHS, there is the potential for a delay in the diagnosis and treatment of patients.

The existing PAS agreement in place for crizotinib for the treatment of ALK+ advanced NSCLC[15,30] will be extended to include the ROS1+ advanced NSCLC patient population if crizotinib is recommended by NICE for this group of patients.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The CS adequately describes the search strategies used to identify relevant studies relating to the use of crizotinib for the treatment of patients with ROS1+ advanced NSCLC. The company conducted a systematic search for clinical effectiveness evidence and separate systematic searches were conducted for the retrieval of cost effectiveness studies, HRQoL studies and cost and healthcare resource identification studies.

The ERG notes that the company has used the results from trials of patients with ALK+ advanced NSCLC who were treated with crizotinib as proxy data for patients with ROS1+ advanced NSCLC. The company has not reported if systematic searches were conducted to identify relevant studies relating to the use of crizotinib for the treatment of patients with ALK+ advanced NSCLC.

Searches for evidence indexed in electronic databases

Full details of the search terms used to locate clinical evidence are reported in the CS (Section B.2 and Appendix D). The company states that they searched the following databases: MEDLINE, MEDLINE in Process, EMBASE (all via OvidSP) and The Cochrane Library (limited to the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Database Abstracts of Reviews of Effects). Searches were run from database inception to 16 March 2017 and animal studies were removed. The company searches did not include drug-related search terms (i.e. crizotinib, Xalkori); however, the searches did include relevant and comprehensive disease terms, which means that despite the searches being broad, it is unlikely any relevant papers would have been missed by the omission of the drug-related terms. No clinical trial registries were searched, possibly resulting in relevant trials being missed.

Overall, the ERG considers that the strategies used to search the electronic databases are appropriate and are adequately described in the CS. The ERG has run its own searches and is confident that no relevant publications have been missed.

Searches for evidence presented at conferences

In addition to searches of bibliographic databases, the company also conducted hand searches of six conference sites on 1 June 2017: American Society of Clinical Oncology (ASCO), European Lung Cancer Conference (ELCC), European Society for Medical Oncology (ESMO), International Society for Pharmacoeconomics and Outcomes Research (ISPOR),

International Association for the Study of Lung Cancer and the Italian Association of Medical Oncology's National Congress of Medical Oncology. The keywords for these searches are included in the CS and are relevant. The company states that the searches of conference proceedings were limited to those published between 2015 and 2017. The company assumed that older, pre-2015 conference abstracts would be published as full-text articles in peer reviewed journals. The ERG considers that the hand searches for evidence presented at conferences are appropriate and adequately described in the CS.

The data sources searched and the time spans for the searches are provided in Table 6. A summary of, and ERG comments on, the review methods used by the company are presented in Table 7.

Table 6 Data sources for the clinical systematic review

Search strategy component	**Source**	**Search date range**	
		Start	**End**
Electronic database searches	EMBASE	From inception	March 2017
	MEDLINE		
	MEDLINE In-Process		
	Cochrane Central Library of Controlled Trials (CENTRAL)		
Congress proceedings	American Society of Clinical Oncology (ASCO) European Lung Cancer Conference (ELCC) European Society for Medical Oncology (ESMO) International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International Association for the Study of Lung Cancer Italian Association of Medical Oncology's National Congress of Medical Oncology	2015	2017
Clinical trial registries	ClinicalTrials.gov	Not searched	
	WHO's meta-registry 'International Clinical Trials Registry Platform Search Portal' (ICTRP)		
	EU Clinical Trial Registry		

EU=European Union; WHO=World Health Organisation
Source: CS, Appendix D

Table 7 Summary of, and ERG comment on, the systematic review methods used by the company

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	512 non-duplicate titles	• The search was carried out in March 2017 meaning that there is a risk that some relevant studies may not have been included in the search results • Clinical trial registries were not searched. However, details of ongoing trials were presented • Reference lists of identified studies were searched for other relevant studies
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on the criteria presented in Table 4 of Appendix D of the CS (p14), i.e. Patients: ROS1+ advanced or metastatic NSCLC Intervention: crizotinib, docetaxel (with or without nintedanib), nivolumab, pembrolizumab or pemetrexed Comparator: any or no comparator Study type: RCT, interventional clinical trial or observational study	14 unique studies from 28 publications	• Use of two independent assessors improves the quality of the review
Additional eligibility criteria		
Search limits		The searches were restricted to studies published in English language. Relevant non-English language studies were not included
Quality assessment		
The company assessed the risk of bias of the non-randomised studies using the Downs and Black checklist.[61] The risk of bias of the RCTs presented by the company to provide comparative data for the clinical effectiveness of crizotinib was assessed using the criteria specified by the Centre for Reviews and Dissemination at the University of York.[62] The results of the company's assessment of risk of bias are presented in Tables 11, 12 and 13 of Appendix D of the CS		

Source: CS, Appendix D

4.1.2 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of crizotinib for the treatment of ROS1+ advanced NSCLC from one single-arm study, PROFILE 1001. The company identified 13 other non-randomised studies that included patients with ROS1+advanced NSCLC (CS, p31). The company has provided details of the 13 studies in Table 7 of the CS. The company has provided full study information in the appendices to the CS.

Nine of the identified studies included crizotinib as the intervention. Four were prospective, single-arm, phase II studies: AcSé,[63] EUCROSS,[64] METROS[65] and OX-ONC.[66] The EUCROSS[64] and METROS[65] studies were conducted in European centres and the OX-ONC[66]

study was conducted in centres in East Asia. The ERG notes that only the EUCROSS[64] and OX-ONC[66] studies are complete.

The company has presented data from the EUCROSS[64] study (n=34) in support of the results from the PROFILE 1001 study. The company states (CS, p31) that the EUCROSS[64] study was conducted in European patients and the results are therefore applicable to patients treated in the NHS. The company states (CS, p31) that data from the EUCROSS[64] study are not included in the submitted economic model as Kaplan-Meier (K-M) curves for PFS and OS were not available at the time the submission was prepared; however, the company provided the K-M curves via the clarification process.

The company does not consider that the results of the OX-ONC[66] study are generalisable to a UK population (CS, Table 7) and has not included the results in the clinical- or cost-effectiveness section of the CS. The ERG notes that a substantial number of patients (n=127) were recruited to the OX-ONC[66] study; however, all patients in the OX-ONC[66] study were of East Asian origin and their results may be not be applicable to a UK patient population.

The company reports that the EUROS,[10] Bennati,[67] Lu[68] and Zhang[69] studies were small, retrospective studies of patients treated with crizotinib for ROS1+ advanced NSCLC and that the studies reported by Chen,[70] Drilon,[71] Liang[72] and Song[73] were small, retrospective studies of patients with ROS1+ advanced NSCLC who were treated with pemetrexed-based chemotherapy. The company has not included the results of the retrospective studies in the clinical or cost effectiveness section of the CS. The ERG agrees that this is appropriate. The study by Oz[74] was a subgroup analysis of results from five patients located in Turkey who were recruited to the PROFILE 1001 expansion study.

In the absence of any evidence for the efficacy of crizotinib in the treatment of ROS1+ advanced NSCLC with other comparators listed in the final scope issued by NICE, the company presents the data from two RCTs conducted in patients with ALK+ advanced NSCLC i.e., the PROFILE 1014 and the PROFILE 1007 trials. The PROFILE 1001 study and the PROFILE 1014 and 1007 trials are described narratively in the CS.

4.2 ERG critique of clinical effectiveness evidence

4.2.1 Identified studies and trials

Pivotal study

The PROFILE 1001 study is a single-arm, phase I study, which provides evidence to support the use of crizotinib to treat ROS1+ advanced NSCLC.

Supportive trials

The company states (CS, p26) that, given the efficacy of crizotinib in patients with ROS1+ advanced NSCLC, as demonstrated by the results of the PROFILE 1001 study, clinical experts to the company consider that it would be unethical to conduct comparative trials due to the lack of clinical equipoise. Clinical equipoise exists when there is no good basis for a choice between two or more treatment options.[75] Consequently, no comparative trials have been conducted to investigate the effectiveness of crizotinib in the ROS1+ advanced NSCLC population. The company presents data from the PROFILE 1014 and PROFILE 1007 trials, which investigated the efficacy of crizotinib in comparison to chemotherapy in patients with ALK+ advanced NSCLC, to support the claim that crizotinib is a clinically effective treatment for patients with ROS1+ advanced NSCLC. The company's rationale for this approach is discussed in Section 2.1 of this ERG report.

Other non-randomised studies identified in the company's systematic review

The company identified 13 non-randomised studies in their systematic review. The company considers that the studies provide limited clinical data describing crizotinib and/or chemotherapy for the treatment of ROS1+ advanced NSCLC. Since these studies are not used to provide estimates of clinical or cost effectiveness, the ERG does not provide a full description and critique of these studies in the subsequent sections. However, the ERG has summarised the key findings from these studies and discussed whether data from these studies support the use of crizotinib to treat ROS1+ advanced NSCLC in Section 4.6 of this report.

4.2.2 Key characteristics of the included study and trials

Key characteristics of the pivotal PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials are provided in Table 8.

Table 8 Key characteristics of the included study and trials

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Location	International: 8 locations across USA, Australia and South Korea	International: 251 locations across USA, Canada, Mexico, Australia, Asia, Europe (9 UK sites), South America and South Africa	International sites in North America, Australia, Brazil, China, Japan, Korea, Taiwan, Hong Kong and Europe (9 UK sites)
Study design	Multicentre, open-label, single-arm, phase I study. Initial dose-escalation phase followed by an expansion phase in ROS1+ advanced NSCLC patients (n=53)	Multicentre, open-label, phase III randomised controlled trial (n=343) Patients in the chemotherapy group who had PD defined using RECIST v1.1, as verified by IRR, could cross over to crizotinib treatment if the safety criteria were met	Multicentre, double-blind, phase III randomised, controlled clinical trial (n=347) Patients in the chemotherapy group who had PD defined using RECIST could cross over to crizotinib treatment as part of a separate study
Population	Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic ROS1+ NSCLC (Three patients were included in the trial who were ALK- and retrospectively determined to be ROS1+)	Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic non-squamous NSCLC that was positive for an ALK rearrangement, who had not received previous treatment for advanced disease	Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic NSCLC that was positive for an ALK rearrangement, who had progressive disease only after one prior (platinum-based) chemotherapy regimen
Intervention and comparator	Intervention: crizotinib 250 mg twice daily Patients with RECIST-defined PD or clinical deterioration could continue on crizotinib treatment at the investigator's discretion and with the approval from the Sponsor Comparator: N/A	Intervention: crizotinib 250 mg twice daily Patients could continue crizotinib treatment beyond RECIST-defined PD, at the discretion of the investigator if the patient was perceived to be experiencing clinical benefit Comparator: pemetrexed, 500 mg/m^2 BSA, plus platinum-based therapy; iv administered every 3 weeks for a maximum of 6 cycles Platinum-based therapy consisted of either cisplatin, 75 mg/m^2 BSA, or carboplatin, target AUC of 5–6 mg/mL/min	Intervention: crizotinib 250 mg twice daily Comparator: docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2 BSA Patients could continue treatment as assigned beyond the time of RECIST-defined progression, as assessed by the IRR, at the discretion of the investigator if the patient was perceived to be experiencing clinical benefit
Reported outcomes specified in the scope	Primary outcome: ORR Secondary outcomes: OS, PFS, TTF, safety	Primary outcome: PFS Secondary outcomes: ORR, OS, safety, EQ-5D	Primary outcome: PFS Secondary outcomes: ORR, OS, safety, EQ-5D

ALK=anaplastic lymphoma kinase; AUC=area under the concentration-time curve; BSA=body surface area; EQ-5D=EurQoL-5 Dimensions; IRR=independent radiology review; iv=intravenous; N/A=not applicable; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumours; BSA=body surface area; TTF=time to treatment failure
Source: adapted from CS, Table 6 and Table 10, PROFILE 1014 CSR and PROFILE 1007 CSR

Further details of the methodology of the PROFILE 1001 study (including ROS1 testing methodology and treatment schedule) are provided in Table 8 of the CS. A comparative summary of the methodologies used in the PROFILE 1001 study and in the PROFILE 1014 and PROFILE 1007 trials (including eligibility criteria and concomitant medications) is provided in Table 10 of the CS.

The ERG is of the opinion that the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials were generally well designed and well conducted. The patient population recruited to the PROFILE 1001 study matches the patient population specified in the final scope issued by NICE. Clinical advice to the ERG is that the eligibility criteria used in the PROFILE 1001 study are appropriate. The main limitations of the PROFILE 1001 study are the small sample size (n=53) and the fact that there was no comparator arm to provide direct evidence of the effectiveness of crizotinib in comparison to a relevant comparator in the patient population of interest.

Both the PROFILE 1014 and PROFILE 1007 trials permitted patients to switch from the chemotherapy arm to the crizotinib arm on disease progression (and vice versa). Valid OS estimates for the efficacy of crizotinib versus chemotherapy are difficult to obtain due to high levels of patient crossover. Patient crossover in the PROFILE 1014 and PROFILE 1007 trials is discussed further in Section 4.3.2 of this ERG report.

4.2.3 Characteristics of patients in the included study and trials

The baseline characteristics of patients in the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials are provided in Table 9.

Table 9 Patient characteristics of the included study and trials

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
Age (years): median, (min, max)		55 (25–81)	52.0 (22–76)	54 (19–78)	51 (22–81)	49 (24–85)
Category (years) – no. (%)	<65	38 (71.7)	[redacted]	[redacted]	146 (84.4)	151 (86.8)
	≥65	15 (28.3)	[redacted]	[redacted]	27 (15.6)	23 (13.2)
Sex – no. (%)	Male	23 (43.4)	68 (39.5)	63 (36.8)	75 (43.4)	78 (44.8)
	Female	30 (56.6)	104 (60.5)	108 (63.2)	98 (56.6)	96 (55.2)
Race – no. (%)	White	30 (56.6)	91 (52.9)	85 (49.7)	90 (52.0)	91 (52.3)
	Black	2 (3.8)	[redacted]	[redacted]	2 (1.2)	3 (1.7)
	Asian	21 (39.6)	77 (44.8)	80 (46.8)	79 (45.7)	78 (44.8)
	Other	NR	4 (2.3)	2 (1.2)	2 (1.2)	2 (1.2)
Weight (kg)	Mean (SD)	71.9 (16.0)	[redacted]	[redacted]	65.3 (17.3)	[redacted]
	Median (range)	70.0 (48.0-106.3)	[redacted]	62.5 (35.8–151.6)[a]	62.0 (35.2-160.0)	[redacted]
ECOG performance status	0	23 (43.4)	[redacted]	[redacted]	72 (41.6)	65 (37.4)
	1	29 (54.7)	[redacted]	[redacted]	84 (48.6)	95 (54.6)
	2	1 (1.9)	9 (5.2)	[redacted]	16 (9.2)	14 (8.0)
Smoking status – no. (%)	Never smoker	40 (75.5)	106 (61.6)	112 (65.5)	108 (62.4)	111 (63.8%)
	Ex-smoker	13 (24.5)	56 (32.6)	54 (31.6)	59 (34.1)	54 (31.0%)
	Current smoker	NR	10 (5.8)	5 (2.9)	5 (2.9)	9 (5.2%)
Histological classification – no. (%)	Adenocarcinoma	51 (96.2)	158 (91.9)	159 (93.0)	163 (94.2)	160 (92.0%)
	Non-adenocarcinoma	2 (3.8)	14 (8.1)	12 (7.0)	9 (5.2)	14 (8.0)

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
Prior radiation therapies – no. (%)	No	34 (64.2)	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	19 (35.8)	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior systemic therapy regimens:	0	7 (13.2)	172 (100)	171 (100)	[redacted]	[redacted]
	1	20 (37.7)	0	0	[redacted]	[redacted]
	2	13 (24.5)	0	0	[redacted]	[redacted]
	3	3 (5.7)	0	0	[redacted]	[redacted]
	>3	10 (18.9)	0	0	[redacted]	0
	Not reported	0	0	0	[redacted]	0
Extent of disease[c]- no. (%)	Locally advanced	NR	4 (2.3)	3 (2)	7 (4.0)	8 (4.6%)
	Metastatic	NR	168 (97.7)	168 (98.2)	165 (95.4)	166 (95.4%)
Prior surgeries – no. (%)		53 (100)	NR	NR	NR	NR
Brain metastases present – no. (%)		NR	45 (26.2)	47 (27.5)	60 (35)	
Time since first diagnosis median		1.16 years (0.0 to 11.2)	1.2 months (0–114.0)	1.2 months (0–93.6)	[redacted]	[redacted]

[a] One person's weight incorrectly reported as 151.6kg instead of 151.6 pounds
[b] Two patients in the crizotinib group did not report their prior radiation therapy status
[c] Data missing for 4 patients in the crizotinib arm in the PROFILE 1007 trial
ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group; ITT=intention to treat; NR=not reported; SD=standard deviation
Source: CS, Table 11

The ERG did not note any important differences in baseline characteristics between the treatment arms of the PROFILE 1014 and PROFILE 1007 trials.

The company presents results from the PROFILE 1014 and PROFILE 1007 trials (two ALK+ advanced NSCLC trials) as estimates of the effectiveness of treatment with crizotinib for ROS1+ advanced NSCLC patients in first-line and subsequent-line settings. The following two assumptions must hold for the company's approach to be valid:

1) ROS1+ advanced NSCLC and ALK+ advanced NSCLC patient populations must be comparable in terms of baseline characteristics

2) Patients recruited to the ALK+ advanced NSCLC trials must be representative of the ALK+ advanced NSCLC patient population (and consequently the ROS1+ advanced NSCLC patient population, if assumption 1 holds) that would be seen in NHS clinical practice.

For assumption 1, clinical advice to the ERG is that ROS1+ advanced NSCLC and ALK+ advanced NSCLC patient populations are comparable in terms of baseline characteristics.

For assumption 2, as noted in TA406, when the patient population in the PROFILE 1014 trial is compared with a 'real-life' cohort of ALK+ advanced NSCLC patients from the US and Canada,[76] the results suggest that the PROFILE 1014 trial patients are younger, have better performance status and are less likely to be smokers than the real-life patients. Furthermore, patients from a small UK retrospective cohort of ALK+ advanced NSCLC patients (details of which were provided by the company in their clarification response during TA406) were also older than the PROFILE 1014 population. In light of this information, the company performed adjustments to the PFS and OS data from the PROFILE 1014 trial that were used in the submitted economic model by incorporating the baseline characteristics from the 'real-life' cohort described by Davis et al.[76] These adjustments are discussed further in Section 5.4.5 of this ERG report. However, clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS.

The estimates presented in the clinical effectiveness section of the CS (and in this ERG report) have not been adjusted to account for any differences between the patient characteristics of the PROFILE 1014 trial population and the cohort study described by Davis.[76] Clinical advice to the ERG is that patients recruited to the PROFILE 1014 trial are generally representative of patients treated in the NHS and the ERG questions the adjustments made in the company's

economic model. The ERG notes that the Appraisal Committee for TA406 considered that the adjustments were 'conservative'.

In TA296, no adjustments were performed on the PFS and OS data from the PROFILE 1007 trial as the ERG considered the patient population to be reflective of the patients with ALK+ advanced NSCLC in who would be treated in the NHS.

Prior therapy in the PROFILE 1001 study and the PROFILE 1007 trial

Most patients in the PROFILE 1001 study (n=46, 86.8%) and all patients in the PROFILE 1007 trial had received prior therapy for advanced disease. Clinical advice to the ERG is that all patients are offered pemetrexed as a first-line therapy in current NHS clinical practice. It is therefore informative to consider how many of the patients who received prior therapy in the PROFILE 1001 study and in the PROFILE 1007 trial received pemetrexed+platinum as a first-line treatment.

For the 46 pre-treated patients in the PROFILE 1001 study, only 17 (37.0%) received pemetrexed as a first-line treatment (company response to the ERG clarification letter, Table 2). In the PROFILE 1007 trial, [redacted] patients had received prior pemetrexed chemotherapy. Consequently, 63% of patients in the PROFILE 1001 study, and [redacted] of patients in the PROFILE 1007 trial, received first-line treatments that did not include pemetrexed+platinum and would not be commonly administered in NHS clinical practice.

4.2.4 Statistical approach adopted for the analysis of the included study and trials

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the trial protocols,[24,32,38] the trial statistical analysis plans (TSAPs),[23,31,39] the clinical study reports (CSRs),[26,33,41] and the CS. There is also a supplemental TSAP[40] for the PROFILE 1001 study that outlines the statistical analyses for the ROS1+ advanced NSCLC patient group and a preliminary CSR[25] for the PROFILE 1007 trial that includes the final results for several efficacy endpoints and patient-reported outcomes (PROs). The final CSR for the PROFILE 1007 trial presents the final analysis for OS, an update of the Visual Symptom Assessment Questionnaire-ALK (VSAQ-ALK) and an update of safety.

Analysis populations

The analysis populations used for the analyses in each of the included study and trials are provided in Table 47 (Appendix 10.1) of this ERG report. The ERG is satisfied that the analysis

populations were pre-specified in the TSAPs and that results for each outcome for the relevant populations were provided in the CSRs.

Efficacy outcomes

The definitions, assessment measures and statistical analysis methodology used for the primary outcomes of each of the included studies and trials are provided in Table 48 (Appendix 10.2) of this ERG report.

The ERG is satisfied that the definitions, assessment measures and statistical analysis methodology used for the primary outcomes of the included studies were pre-defined in the TSAPs.

OS and PFS were secondary efficacy outcomes of the PROFILE 1001 study. The definitions of OS, PFS, and other secondary efficacy outcomes are provided in Table 9 of the CS. Time-to-event data (OS, PFS, duration of response [DR], and time to progression [TTP] were analysed using the K-M method with 2-sided 95% confidence intervals (CIs) using the Brookmeyer-Crowley method.

OS and ORR were secondary outcomes of both the PROFILE 1014 and PROFILE 1007 trials. The definitions and methods of analysis for each of these outcomes were pre-specified in the TSAPs for each of the trials (PROFILE 1014: TSAP, pp13-14, pp23-25; PROFILE 1007: TSAP, p12, pp20-23). The ERG is satisfied that the results of all pre-planned efficacy analyses were reported in the CSRs.

The ERG notes that the Cox proportional hazards (PH) method was used to estimate the PFS and OS hazard ratios (HRs) for both the PROFILE 1014 and PROFILE 1007 trials. The validity of this method relies on the event hazards associated with the intervention and comparator data being proportional over time within each trial. The ERG assessed the validity of the PH assumption for all analyses provided in the CS that included a HR result (see Appendix 10.3 for methods and results). The ERG concluded that there is insufficient evidence to reject the PH assumption for the unadjusted OS and RPSFTM-adjusted (log-rank and Wilcoxon tests) OS data from the PROFILE 1014 trial, and for the unadjusted OS data from the PROFILE 1007 trial. The ERG did not assess PH for crossover-adjusted OS from the PROFILE 1007 trial, since the company used the PFS HR reported in the PROFILE 1007 trial to represent a crossover-adjusted OS HR (see Section 4.3.2 for further details of this approach). The ERG concluded that the PH assumption was not valid for PFS for either of the PROFILE 1014 or PROFILE 1007 trials. Consequently, the ERG considers that the reported HRs for PFS data from both the PROFILE 1014 and PROFILE 1007 trials should be interpreted with caution.

ERG critique of statistical approach

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used to analyse data from the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials is provided in Table 49 (Appendix 10.4) of this ERG report.

Having carried out these checks, the ERG is satisfied with the pre-planned statistical approach employed by the company, with the exception that the Cox PH method was not suitable for the analyses of PFS data for either the PROFILE 1014 trial or for the PROFILE 1007 trial.

4.2.5 Risk of bias assessment of the included study and trials

The company assessed the quality of the PROFILE 1001 study using the Downs and Black checklist;[61] this is a risk of bias tool that can be used to assess non-randomised studies. The company's quality assessment is presented alongside the ERG's comments in Table 10. The company carried out quality assessments for the PROFILE 1014 and PROFILE 1007 trials using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[77] The company's risk of bias assessments for the PROFILE 1014 and PROFILE 1007 trials, and ERG comments, are presented in Table 11.

Overall, the ERG agrees with the company's assessment that the PROFILE 1001 study is a good quality study, and notes that, although the study was open-label, an analysis of ORR by independent radiology review (IRR) enables the robustness of the primary analysis to be verified, since assessments made by IRR would not be subject to detection bias. The ERG notes however, that the PROFILE 1001 study is a small, single-arm, phase I study.

The PROFILE 1014 and PROFILE 1007 trials also used open-label study designs. Assessments for the primary outcome and response-based secondary outcomes were made by IRR in both trials, so analyses of these endpoints would not be subject to detection bias. The results for subjective outcomes may be subject to bias since patients and care providers were not blinded. Furthermore, the TA406 ERG raised the issue that, as a result of the open-label nature of the trial, patients in the chemotherapy arm may have initiated second-line therapy (including switching to crizotinib) earlier in the PROFILE 1014 trial than they might have been able to do in NHS clinical practice. The ERG agrees with the TA406 ERG's assessment and considers that this may be an issue that also affects the interpretation of data from the PROFILE 1007 trial.

The ERG agrees with the company's assessment that both the PROFILE 1014 and the PROFILE 1007 RCTs are of good quality, although the ERG notes that a substantial amount

of HRQoL data (~84%) was missing for patients in the crizotinib arm of the PROFILE 1014 trial. This issue is discussed further in Section 5.6.3 of this ERG report.

Table 10 Quality assessment results for the PROFILE 1001 study

Company's QA of the PROFILE 1001 study		**ERG comment**
Reporting		
1. Is the hypothesis/aim/objective of the study clearly described?	Y	Agree
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Y	Agree
3. Are the characteristics of the patients included in the study clearly described?	Y	Agree
4. Are the interventions of interest clearly described?	Y	Agree
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A	Agree
6. Are the main findings of the study clearly described (This question does not cover statistical tests which are considered below)?	Y	Agree
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Agree
8. Have all important adverse events that may be a consequence of the intervention been reported?	Y	Agree
9. Have the characteristics of patients lost to follow-up been described?	N	Agree - 1 patient was lost to follow-up so not concerning
10. Have actual probability values been reported (eg. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N	Agree
External validity		
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	No	Unable to determine
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes	Unable to determine
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	No	Disagree
Internal validity - bias		
14. Was an attempt made to blind study subjects to the intervention they have received?	No	Agree
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	No (although IRR was conducted)	Agree
16. If any of the results of the study were based on "data dredging", was this made clear?	Yes	Unable to determine
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	N/A	Agree
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Agree

19. Was compliance with the intervention/s reliable?	Unable to determine	Agree
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Agree
Internal validity – confounding (selection bias)		
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	Agree
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A	Agree
23. Were study subjects randomised to intervention groups?	No	Agree
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No, study not randomised	Agree
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unable to determine if an investigation of known confounders was performed but not reported	N/A (single-arm trial)
26. Were losses of patients to follow-up taken into account?	Yes	Agree
Power		
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	Agree

IRR=independent radiology review; N/A=not applicable; QA=quality assessment
Source: CS Appendix D, Table 11; ERG comment

Table 11 Quality assessment results for the PROFILE 1014 and PROFILE 1007 trials

	PROFILE 1014		PROFILE 1007	
	Company's QA	**ERG comments**	**Company's QA**	**ERG comments**
Was randomisation carried out appropriately?	Yes	Agree	Yes	Agree
Was the concealment of treatment allocation adequate?	Unclear	Disagree - participants were randomised via IVRS/website and therefore allocation was concealed	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, for care providers and participants Yes, for outcome assessors	Agree – the ERG notes that the open-label nature of the trials provides an opportunity for subjective results to be biased	Blinding of patients and care providers was not feasible, as each treatment arm utilised different methods of drug administration Outcome assessors for the IRR were blind to treatment allocation	Agree – the ERG notes that the open-label nature of the trials provides an opportunity for subjective results to be biased
Were there any unexpected imbalances in drop‑outs between groups?	No	Agree for efficacy outcomes PROs and HRQoL information were missing for the crizotinib arm (~84%)	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree	Yes - some outcomes are not yet available from PROFILE 1007 trial	Agree – although this is not a concerning issue if results for these outcomes are published in due course. The ERG is not aware of any updated data
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree	Yes	Agree

HRQoL=health-related quality of life; IRR=independent radiological review; ITT=intention-to-treat; IVRS=interactive voice response system; PRO=patient-reported outcomes; QA-=quality assessment
Source: CS Appendix D, Table 12 and Table 13; ERG comment

4.3 Results of the included studies and trials

4.3.1 Results of the PROFILE 1001 study

The data cut-off date for the primary analysis of the PROFILE 1001 study was 30th November 2014; the median duration of follow-up for OS at this time was 25.4 months. The data cut-off date for the ALK-negative (ALK-) patients who were retrospectively defined to be ROS1+ (n=3) was 24th June 2014. A summary of efficacy results for the PROFILE 1001 study is provided in Table 12.

Table 12 Summary of efficacy results from the PROFILE 1001 study

Outcome		PROFILE 1001 (N=53)
ORR based on investigator assessment	ORR (%) (95% CI)	37 (69.8) [55.7 to 81.7]
	Complete response (%)	5 (9.4)
	Partial response (%)	32 (60.4)
	SD (≥6 weeks) (%)	11 (20.8)
	PD (%)	3 (5.7)
	Early death (%)	1 (1.9)
	Indeterminate (%)	1 (1.9)
ORR based on IRR (n=50)	ORR (%) (95% CI)	33 (66.0) [51.2 to 78.8]
	Complete response (%)	1 (2.0)
	Partial response (%)	32 (64.0)
	SD (≥6 weeks) (%)	12 (24.0)
	PD (%)	4 (8.0)
	Early death (%)	1 (2.0)
	Indeterminate (%)	0 (0.0)
DCR	DCR at Week 8 (%) (95% CI)	46 (86.8) [74.7 to 94.5]
	DCR at Week 16 (%) (95% CI)	42 (79.2) [65.9 to 89.2]
DR (n=37[a])	Median months (range)	NR (15.2 to NR)
TTR (n=37[a])	Median weeks (range)	7.9 (4.3 to 32.0)
PFS	Patients with event (%)	26 (49.1)
	Median months (95% CI)	19.3 (14.8 to NR)
TTP	Patients with event (%)	23 (43.4)
	Median months (95% CI)	19.8 (15.2 to NR)
TTF	Median months (95% CI)	23.2 (15.0 to NR)
OS	Median months	NR
	HR (95% CI, p-value)	N/A
	Probability of survival at 6 months (95% CI)	90.6% (78.8 to 96.0)
	Probability of survival at 12 months (95% CI)	79.0% (65.3 to 87.8)
	Median duration of follow up months (95% CI)	25.4 (22.5 to 28.5)

[a] objective responders only

CI=confidence interval; DCR=disease control rate; DR=duration of response; IRR=independent radiology review; HR=hazard ratio; N/A=not available; NR=not reported; ORR=objective response rate; OS=overall survival; PD=progressed disease; PFS=progression-free survival; SD=stable disease; TTF=time to treatment failure; TTP=time to tumour progression; TTR=time to tumour response

Source: CS, Table 14

For ORR based on investigator assessment, the majority of patients achieved either a partial or complete response with crizotinib. Of the seven treatment-naïve patients, six achieved an objective response (85.7%, 95% CI: 42.1 to 99.6) compared to 31 out of 46 (67.4%, 95% CI: 52.0 to 80.5) patients who had received one or more prior therapies in the advanced setting. The company provides a plot showing individual patient responses to crizotinib in terms of percentage decrease or increase in tumour size from baseline in Figure 3 of the CS.

The ORR based on investigator assessment and the ORR based on IRR were similar, with a total event agreement rate between the derived-tumour assessment and IRR of 82.0%.

Median PFS was 19.3 months (95% CI: 14.8 to not reported [NR]), with 27 censored patients (50.9%), and 21 patients (39.6%) still on follow-up for disease progression on the data cut-off date. The company provides a K-M plot of PFS in Figure 5 of the CS. On the data cut-off date, three (42.9%) of the seven previously untreated patients had experienced an event (n=2 with objective progression, n=1 death without objective progression). Amongst previously treated patients (n=46), 23 patients (50.0%) had experienced an event by the data cut-off date (n=21 with objective progression, n=2 death without objective progression).

Median OS was not reached by the time of data cut-off, at which time 16 deaths had been recorded and 37 patients were censored. The company provides a K-M plot of OS in Figure 7 of the CS.

Inclusion of ROS1 negative patients in the PROFILE 1001 study

All patients underwent local diagnostic testing for ROS1 rearrangements; 51 of the 53 patients were diagnosed as having ROS1+ advanced NSCLC by FISH, while the remaining two patients were diagnosed as ROS1+ by reverse transcriptase polymerase chain reaction (RT-PCR). Available tissues samples (n=37 from 36 patients) were retrospectively tested for ALK rearrangement. Two patients were subsequently shown to be ROS1 negative by NGS (one of whom was also ALK+). Data from these two patients were kept in the analysis, as the trial protocol specified patients' gene translocations to be classified according to local testing (initial testing). The company discusses the impact of the inclusion of data from these two patients, concluding that the inclusion of data from these two patients was a conservative approach, since the outcomes for these patients were worse than or comparable to the outcomes reported for the whole trial population in terms of ORR, PFS and OS. [redacted]. The PFS durations of these patients were [redacted] (ALK-) and [redacted] (ALK+), respectively. The OS was [redacted] for the ROS1 negative, ALK- patient, whilst the OS was censored at [redacted] for the ROS1 negative, ALK+ patient. The ERG agrees with the company's

assessment that the inclusion of patients with ROS1 negative advanced NSCLC in the analyses was a conservative approach, and would not have biased the outcomes in favour of crizotinib.

Data immaturity

At the time of the PFS analysis, OS data from the PROFILE 1001 study were immature with only 30% of patients having died at the latest data cut-off date. The company states in their response to the ERG's clarification that the next data-cut for the PROFILE 1001 study is planned for [redacted]. No explanation as to why there is a 10-year gap in the timing of OS analyses was provided; the ERG notes that reliable estimates of OS from the PROFILE 1001 study will not be available until this time.

4.3.2 Results from the PROFILE 1014 and PROFILE 1007 trials

A summary of the key efficacy results from the PROFILE 1014 and PROFILE 1007 trials is provided in Table 13.

Table 13 Summary of the key efficacy results from the PROFILE 1014 and PROFILE 1007 trials

Outcome	PROFILE 1014 (N=343)	PROFILE 1007 (N=347)
Median PFS		
Crizotinib, months (95% CI)	10.9 (8.3 to 13.9)	7.7 (6.0 to 8.8)
Chemotherapy, months (95% CI)	7.0 (6.8 to 8.2)	3.0 (2.6 to 4.3)
HR, (95% CI; p-value)	0.45 (0.35 to 0.60; p<0.001)[a]	0.487 (0.371 to 0.638; p<0.0001)
Patients who crossed-over		
Crizotinib	33/172 (19.2%)	65/173 (37.6%)
Chemotherapy	[redacted]	151/174 (86.8%)
ORR[b]		
Crizotinib, no. of patients (%) [95% CI][c]	128 (74.4) [67.2 to 80.8]	112 (65.3) [57.7 to 72.4]
Chemotherapy, no. of patients (%) [95% CI][c]	77 (45) [37 to 53]	34 (19.5) [13.9 to 26.2]
Median OS		
Crizotinib, months (95% CI)	[redacted]	21.7 (18.9 to 30.5)
Chemotherapy, months (95% CI)	[redacted]	21.9 (16.8 to 26.0)
Unadjusted HR, (95% CI, p-value)	[redacted]	0.854 (0.66 to 1.10; p=0.11)
Crossover adjusted HR, (95% CI, p-value)	[redacted]	0.49 (0.37 to 0.64)

[a]For between-group comparisons (crizotinib vs chemotherapy), 2-sided log-rank test stratified according to baseline stratification factors were used; stratified Cox regression models were applied to estimate HRs
[b]Tumour response was assessed using RECIST v1.1 for the PROFILE 1014 and PROFILE 1007 trials and were confirmed by IRR
[c]P<0.001 for between-group comparison
CI=confidence interval; HR=hazard ratio; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria on Solid Tumours
Source: CS, Table 15

The ORRs for patients in the crizotinib arms of the PROFILE 1014 and PROFILE 1007 trials were comparable with the observed ORR for patients in the PROFILE 1001 study. Both the PROFILE 1014 and PROFILE 1007 trials demonstrated a statistically significantly greater ORR for crizotinib patients than for chemotherapy patients.

Median PFS data for crizotinib were not similar between the PROFILE 1001 study (19.3 months, 95% CI: 14.8 to NR) and the PROFILE 1014 and PROFILE 1007 trials (10.9 months, 95% CI: 8.3 to 13.9, and 7.7 months, 95% CI: 6.0 to 8.8, respectively). The ERG notes that the CIs for the estimates of median PFS do not overlap, so median PFS is statistically significantly longer for crizotinib patients with ROS1+ advanced NSCLC in the PROFILE 1001 study than for crizotinib patients with ALK+ advanced NSCLC in the PROFILE 1014 and PROFILE 1007 trials. The differences in median PFS between the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials causes the ERG to question whether the ALK+ and ROS1+ advanced NSCLC patient populations are truly similar, as discussed in Section 2.1 of this ERG report. In both the PROFILE 1014 and PROFILE 1007 trials, PFS was statistically significantly longer for crizotinib patients in comparison to chemotherapy patients.

Since median OS was not reached at the time of data cut-off in the PROFILE 1001 study, it is not possible to compare the OS results between the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials. Results for OS (unadjusted for patient crossover) from the PROFILE 1014 and PROFILE 1007 trials suggest that there are no statistically significant differences between crizotinib and chemotherapy in each of these trials. However, crossover-adjusted HR results from the PROFILE 1014 and PROFILE 1007 trials suggest that crizotinib statistically significantly improves OS in comparison to chemotherapy in ALK+ advanced NSCLC patients. A critique of how the company generated these crossover-adjusted HRs is provided in the subsequent sections of this ERG report.

Patient crossover in the PROFILE 1014 trial

The number of patients crossing over from the chemotherapy arm to the crizotinib arm and vice versa in the PROFILE 1014 trial is provided in Table 13.

At the time of the first data cut for OS analysis (30 November 2013), the rank preserving structural failure time model (RPSFTM), the iterative parameter estimation (IPE) and the two-stage method were applied to adjust for treatment switching from the chemotherapy arm to the crizotinib arm (but not to adjust for treatment switching from the crizotinib arm to the chemotherapy arm). The RPSFTM and the IPE methods are randomisation-based methods for estimating survival times that would have been observed in the absence of crossover. The two methods are similar; however, the IPE method requires the additional assumption that

survival times follow a parametric distribution. The company states that given the similarity between the methods and the almost identical results at the time of first OS analysis, the IPE model was not implemented at the time of the final analysis.

Furthermore, the company states that results of the two-stage method performed at the time of the first OS analysis were comparable to the results of the RPSFTM and IPE methods. However, the company explains that, for the two-stage method to provide a valid estimate of crossover-adjusted OS, it must be assumed that the post-progression survival (PPS) of non-crossover patients is representative of the PPS that crossover patients would have experienced had they not crossed over. At the time of the final OS analysis, a very small number of chemotherapy patients had disease progression who did not crossover to the crizotinib arm. The company explains that the uncertainty associated with treatment effect estimates derived using this methodology may be high and that the two-stage method was considered inappropriate for the final data cut of the PROFILE 1014 trial due to the high level of patient crossover.

Therefore, at the time of the final OS analysis, only the RPSFTM method was performed. Data used in the final OS analysis were adjusted for crossover from the chemotherapy arm to the crizotinib arm, and vice versa. The ERG assumes that, at the time of the final analysis, the company adjusted for crossover in both directions because in TA406, the company was criticised for only adjusting for crossover from the chemotherapy arm to the crizotinib arm.[36] Adjusted survival times were estimated using two variations of the RPSFTM method; log-rank and Wilcoxon (see Table 13 for results). The ERG is satisfied with the company's rationale for not implementing both the IPE and two-stage method at the time of the final OS analysis.

However, the ERG is also unsure whether the RPSFTM method is appropriate for adjusting for crossover, since the RPSFTM, and indeed the IPE, assumes a "common treatment effect", i.e., that the treatment effect received by patients who switch must be the same as the treatment effect received by patients initially randomised to the experimental group. The ERG notes that it is unclear whether this assumption would hold since patients randomised to pemetrexed+platinum who switch to crizotinib may, at that time, have more advanced disease than patients who were originally randomised to crizotinib; the patients randomised to pemetrexed+platinum, therefore may not have the same capacity to benefit from crizotinib treatment following disease progression as patients randomised to crizotinib. The ERG recognises that it is not possible to test the "common treatment effect" assumption, and that, in practice, this assumption is highly unlikely to ever be exactly true.

The ERG considers that the RPSFTM-adjusted HR for OS is unlikely to be valid, since the HR for RPSFTM-adjusted OS suggests an even greater benefit with crizotinib treatment than the PFS HR, suggesting that patients experience more benefit from treatment with crizotinib post-progression, than pre-progression.

In summary, the ERG considers that there is no method of adjusting for treatment switching that the ERG can confidently conclude would generate unbiased OS risk estimates for crizotinib versus chemotherapy for patients in the PROFILE 1014 trial. The ERG considers that the crossover-adjusted OS results presented for the PROFILE 1014 trial in Table 13 should be interpreted with caution.

Patient crossover in the PROFILE 1007 trial

The number of patients crossing over from the chemotherapy arm to the crizotinib arm and vice versa in the PROFILE 1007 trial is provided in Table 13.

For the PROFILE 1007 trial, the company estimates the crossover-adjusted OS HR to be 0.49 (95% CI: 0.37 to 0.64), without any explanation of how this crossover-adjusted HR was calculated. In TA422, the company submitted OS evidence using the RPSFTM crossover adjustment method to adjust survival times for patients in the chemotherapy arm. In TA422, the company also assessed the feasibility of the inverse probability of treatment and censoring weighted (IPTCW) method and the inverse probability of censoring weights (IPCW) methods. The company observed that the number of patients in the chemotherapy group who did not switch was too low for these methods to generate valid estimates of survival, since these methods use patients from the control group that never switched to create a counterfactual control group.

In TA422, the company presented three sets of crossover-adjusted OS results using the RPSFTM method with three different tests of equality, the log-rank, Wilcoxon and Cox model-based Wald tests. The TA422 ERG was concerned that the company did not report the CI of the estimated acceleration factor and also, that the company did not provide sufficient information regarding the estimation procedure of the RPSFTM method. The TA422 ERG concluded that the estimates of the treatment effect of crizotinib obtained by implementing the RPSFTM method should be considered highly uncertain.

In the absence of any exploration by the company of alternative methods to generate crossover-adjusted estimates of OS, the TA422 ERG considered two alternative ways of estimating the OS HR for use in cost effectiveness scenario analyses. The first approach was to use the same HR for OS as was reported in the original trial publication for PFS (HR=0.49,

95% CI: 0.37 to 0.64), and the second was to use the same HR for OS as per the crossover-adjusted OS HR reported for crizotinib versus pemetrexed+platinum patients in the PROFILE 1014 trial (at the time of the first OS analysis: HR=0.60, 95% CI: 0.27 to 1.42), estimated using the RPSFTM method with the Wilcoxon test. The TA422 Appraisal Committee preferred the TA422 ERG's first scenario (with an OS HR of 0.49) because it used data from the PROFILE 1007 trial and the HR for PFS was not confounded by crossover. The ERG assumes that it is for this reason that the company chose to present the PFS HR as a proxy for the true OS HR for the PROFILE 1007 trial in the current appraisal.

The rationale for adopting the TA422 ERG's first scenario (equal PFS and OS HRs) was that generally (although not universally) HRs for OS are normally not greater than HRs for PFS. Furthermore, the TA422 ERG referred to an analysis by the FDA[78] which explored trial-level and patient-level associations between PFS and OS in 14 advanced NSCLC trials (including crizotinib). A relationship between PFS and OS was not established at the trial-level, with the authors indicating that this was possibly because of crossover and longer survival after progression in the targeted therapy and first-line trials. However, in the patient-level responder analyses of the 14 trials, 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). The ERG agrees with the TA422 ERG that it is preferable to use the PFS HR as a proxy for the OS HR, instead of using the RPSFTM-adjusted OS HR, since the RPSFTM-adjusted HR demonstrates a greater treatment benefit with crizotinib than the PFS HR, suggesting that patients experience more benefit from treatment with crizotinib post-progression, than pre-progression. However, the ERG also notes that the true OS HR could be less than the PFS HR, and so the quoted HR for "crossover-adjusted" OS should be interpreted with caution.

At a late stage in the STA process, the company provided a crossover-adjusted OS HR for the PROFILE 1007 trial (HR=0.38; 95% CI 0.28 to 0.52), but without any detail of how this HR was calculated. The ERG notes that the HR does not match the RPSFTM-adjusted OS HR presented by the company in TA422, and so the ERG cannot comment on the validity of this HR. The ERG recommends that this estimate is interpreted with caution.

Proportional hazards

As previously discussed in Section 4.2.4 of this ERG report, the ERG concluded that the PH assumption was not valid for PFS data from the PROFILE 1014 or PROFILE 1007 trials. Consequently, the ERG considers that the reported HRs for PFS data from both the PROFILE 1014 and PROFILE 1007 trials and the reported "crossover-adjusted" OS HR for the PROFILE 1007 trial (which is actually the PFS HR from the same trial) should be interpreted with caution.

Inclusion of pemetrexed patients in the PROFILE 1007 trial comparator arm

The results presented in the CS from the PROFILE 1007 trial incorporate data from all patients in the chemotherapy arm, regardless of whether they received docetaxel (the company's comparator of interest for the second-line and later-line patient population) or pemetrexed. In the company's response to the ERG clarification letter, the company provided key results for the PROFILE 1007 trial stratified by type of chemotherapy administered in the comparator treatment arm, as provided in Table 14 of this ERG report.

The ORR of patients treated with docetaxel was lower ([redacted]) than the ORR of patients treated with pemetrexed ([redacted]), suggesting that patients treated with pemetrexed responded better than patients treated with docetaxel. Patients treated with docetaxel also had a numerically shorter PFS than patients treated with pemetrexed. The company states that, since patients in the PROFILE 1007 trial performed better with pemetrexed than docetaxel, the use of results from the pooled chemotherapy arm is a conservative approach, as it overestimates the treatment effect of docetaxel on OS. The ERG agrees with the company that it is highly likely that the inclusion of pemetrexed patients in the comparator arm would be a conservative approach when estimating the effectiveness of crizotinib in comparison to chemotherapy. However, the ERG also notes that docetaxel is not the standard NHS treatment option in this setting, most patients are treated with docetaxel+nintedanib which is more effective than docetaxel monotherapy.

Table 14 Key clinical efficacy results from the PROFILE 1007 trial stratified by type of chemotherapy received in the comparator treatment arm

Outcome	Crizotinib (N=172)	Pemetrexed (N=99)	Docetaxel (N=72)
Tumour response, ORR			
No. of patients (%) [95% CI]	[redacted]	[redacted]	[redacted]
RR, crizotinib vs comparator (95% CI; p-value)		[redacted]	[redacted]
PFS			
PFS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR, crizotinib vs comparator (95% CI; p-value)		0.59 (0.43–0.80; p<0.001)[34]	0.30 (0.21 to 0.43; p<0.001)[34]
OS			
OS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR (not adjusted for crossover), crizotinib vs comparator (95% CI; p-value)		0.901 (0.667 to 1.216; p=0.25)	0.791 (0.563 to 1.111; p=0.09)

CI=confidence interval; HR=hazard ratio; NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RR=relative risk; vs=versus
Source: Company response to ERG clarification letter, Table 3

4.4 Health-related quality of life

The company states (CS, p65) that HRQoL data were not collected during the PROFILE 1001 study. This means that there are no direct HRQoL data for patients with ROS1+ advanced NSCLC.

The company has summarised the HRQoL data collected during the PROFILE 1014 and 1007 trials using the EuroQol-Five Dimensions (EQ-5D-3L[79]) questionnaire. (Table 15). EQ-5D data are used in the company's economic models for first-line and subsequent-line therapy with crizotinib. The ERG considers that patients in the crizotinib arm of the PROFILE 1014 and 1007 trials experienced a greater HRQoL benefit compared with patients treated with chemotherapy. However, the magnitude of the benefit is unknown, as the ERG has some concerns with HRQoL from both trials.

Table 15 Company summary of EQ-5D results for PROFILE 1014 and PROFILE 1007

PROFILE 1014	PROFILE 1007
Completion rates of all questions of the EQ-5D questionnaire from evaluable patients in PROFILE 1014 ranged from [redacted] for crizotinib (over the first 30 of a total of 50 cycles) and [redacted] for chemotherapy (over the maximum six cycles). All but eight patients in the crizotinib group ([redacted]) and seven patients in the chemotherapy group ([redacted]) from the intention-to-treat (ITT) population completed all questions of the EQ-5D questionnaire at baseline	Completion rates of all questions of the EQ-5D questionnaire ranged [redacted]
Whereas no statistically significant changes from baseline where observed in the chemotherapy group over six cycles, patients in the crizotinib group showed a significant improvement from baseline ([redacted]) in EQ-5D VAS general health status scores in cycles 3 to 16 and 18 to 21 In a mixed-model analysis, crizotinib was associated with a statistically significant greater improvement in EQ-5D VAS scores compared to chemotherapy ([redacted])	[redacted] Throughout the study, absolute EQ-5D index scores were [redacted] The difference between groups became [redacted] only found to be statistically significant for Cycles 6 and 7
In a mixed-model analysis the overall EQ-5D index score (utility) was found to be statistically significantly higher in the crizotinib group compared to chemotherapy ([redacted]); improvements from baseline in EQ-5D index scores were also statistically significantly greater in the crizotinib group relative to chemotherapy ([redacted]	Absolute EQ-5D index scores and the change from baseline in EQ-5D index scores for crizotinib compared to docetaxel are presented in Table 17. [redacted]
Statistically significant improvements from baseline ([redacted]) in EQ-5D index scores were observed in some cycles in the crizotinib group (Cycles 2 to 20, 22, 24, 25, 29 and 30), but were not observed in any cycles in the chemotherapy group (Cycles 1 to 6)	

EQ-5D= EuroQol-Five Dimensions; ITT=intention to treat; VAS=visual analogue scale
Source: CS, pp55-57

The company reports (CS, p65) that HRQoL data were collected during the PROFILE 1014 and 1007 trials using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC-QLQ-C30[80]) questionnaire and the EORTC QLQ-Lung Cancer LC13[81] module. The company has not reported the results from the EORTC questionnaires in the CS, but signposts the reader instead to the CS for TA406 and TA442.

The ERG notes that the company also collected data during the PROFILE 1014 and 1007 trials using the Visual Symptom Assessment Questionnaire (VSAQ-ALK) questionnaire. The questionnaire was designed to provide information about visual problems experienced by patients in the trials. The results of the questionnaire are not reported in the CS, but are reported in the CSRs for the trials.

The company claims (CS, p77) that the improvements in HRQoL seen in patients with ALK+ advanced NSCLC in untreated and previously treated settings are likely to be experienced by patients with ROS1+ advanced NSCLC. Clinical advice to the ERG is that HRQoL outcomes

of patients with ALK+ advanced NSCLC from the PROFILE 1014 and 1007 trials would be similar for patients with ROS1+ advanced NSCLC.

4.5 Adverse events

The company presents details of the AEs experienced by the 53 patients with ROS1+ advanced NSCLC who were recruited to the PROFILE 1001 study (CS, Section B.2.10). The ERG notes that the data from the PROFILE 1001 study are the only AE data available for patients with ROS1+ advanced NSCLC.

In support of the AE data from the PROFILE 1001 study, the company also presents details of the AEs experienced by patients with ALK+ advanced NSCLC who were treated with crizotinib in the PROFILE 1014 and 1007 trials and from patients in two single-arm studies i.e., PROFILE 1005[82] and PROFILE 1001[83] (ALK cohort).

PROFILE 1001 study

The company states (CS, p71) that the median treatment duration of crizotinib was 23.2 months (95% CI: 15.0 to NR) and, at data cut-off, 47.2% of patients remained on treatment. Treatment-emergent AEs reported during the PROFILE 1001 study are listed in Table 16. The company considers that crizotinib was well-tolerated due to the low numbers of patients who discontinued treatment due to AEs. The ERG notes that 98.1% patients experienced an AE considered to be treatment-related and 30.2% of patients experienced a Grade 3 or Grade 4 AE considered to be treatment-related.

Table 16 PROFILE 1001 Treatment-emergent AEs

Adverse event, No. of patients (%)	Crizotinib (N=53)	
	All cause n (%)	Treatment-related n (%)
Number of patients		
With AEs	53 (100)	52 (98.1)
With SAEs	22 (41.5)	2 (3.8)
With Grade 3 or 4 AEs	28 (52.8)	16 (30.2)
With Grade 5 AEs	9 (17.0)	0
With AEs associated with:		
Permanent discontinuation	4 (7.5)	1 (1.9)
Dose reduction	6 (11.3)	6 (11.3)
Temporary discontinuation	24 (45.3)	13 (24.5)

AE=adverse events; SAE=serious adverse event.
Source: CS, Table 18

The most frequently reported AEs (≥10%) in the PROFILE 1001 study are listed in Table 17. The most commonly occurring AE was vision disorder, experienced by almost 90% of patients.

The company reports (CS, p71) that treatment discontinuations and dose reductions were not associated with vision disorders. Other frequently reported AEs were nausea, oedema, vomiting, diarrhoea and constipation. The company reports (CS, p71) that most AEs were managed by either dose interruptions of dose reductions. One patient with nausea discontinued treatment.

Table 17 PROFILE 1001 Most frequently (≥10%) reported AEs

Adverse event	Crizotinib (N=53)	
	All cause n (%)	Treatment-related n (%)
Vision disorder	46 (86.8)	45 (84.9)
Nausea	31 (58.5)	26 (49.1)
Oedema	29 (54.7)	24 (45.3)
Vomiting	27 (50.9)	20 (37.7)
Diarrhoea	24 (45.3)	22 (41.5)
Constipation	23 (43.4)	18 (34.0)
Dizziness	21 (39.6)	10 (18.9)
Upper respiratory infection	21 (39.6)	0
Elevated aminotransferases	19 (35.8)	16 (30.2)
Fatigue	17 (32.1)	10 (18.9)
Neuropathy	16 (30.2)	5 (9.4)
Dyspnoea	15 (28.3)	1 (1.9)
Rash	14 (26.4)	7 (13.2)
Bradycardia	14 (26.4)	11 (20.8)
Decreased appetite	13 (24.5)	6 (11.3)
Headache	13 (24.5)	0
Abdominal pain	12 (22.6)	3 (5.7)
Dysgeusia	12 (22.6)	10 (18.9)
Cough[c]	11 (20.8)	0
Pyrexia	10 (18.9)	0
Disease progression	9 (17.0)	0
Hypophosphataemia	9 (17.0)	8 (15.1)
Neutropenia	9 (17.0)	7 (13.2)
Arthralgia	8 (15.1)	0
Pneumonia	8 (15.1)	0
Back pain	7 (13.2)	0
Pulmonary embolism	7 (13.2)	0
Pain in extremity	7 (13.2)	0
Pruritus	7 (13.2)	3 (5.7)
Blood creatinine increased	6 (11.3)	2 (3.8)
Chest pain	6 (11.3)	0
Dyspepsia	6 (11.3)	5 (9.4)
Fall	6 (11.3)	0
Stomatitis	6 (11.3)	1 (1.9)
Wheezing	6 (11.3)	0

Source: CS, Table 19

Grade 3 and 4 AEs (≥2%) from the PROFILE 1001 study are listed in Table 18. The company reports that, except for pulmonary embolism, all AEs were considered to be Grade 3.

Table 18 PROFILE 1001 Grade 3 and Grade 4 AEs (≥2%)

Adverse event	Crizotinib (N=53)	
	All cause n (%)	Treatment-related n (%)
Hypophosphatemia	8 (15.1)	7 (13.2)
Neutropenia	5 (9.4)	5 (9.4)
Headache	4 (7.5)	0
Dyspnoea	3 (5.7)	0
Syncope	3 (5.7)	0
Vomiting	3 (5.7)	1 (1.9)
Electrocardiogram QT prolonged	2 (3.8)	1 (1.9)
Elevated transaminases	2 (3.8)	2 (3.8)
Pneumonia	2 (3.8)	0
Pulmonary embolism	6 (11.3)	0

Source: CS, Table 19

The company states (CS, p74) that 16 patients in the PROFILE 1001 study died due to progressive disease, 9 deaths occurred within 28 days of the last treatment and 7 deaths occurred more than 28 days since their last treatment. One patient died from unknown causes 8 months after their last treatment.

Supporting evidence from trials and studies in patients with ALK+ advanced NSCLC

The company reports the results of a pooled analysis of AE data from four sources of clinical evidence, the PROFILE 1014 and 1007 trials and the PROFILE 1005[82] and 1001[83] (ALK+ cohort) studies. The company states that the results of the pooled analysis are described in the EPAR[84,85] for crizotinib.

The company compares the baseline characteristics of the 53 patients with ROS1+ advanced NSCLC from the PROFILE 1001 study with the characteristics of the 1669 patients with ALK+ advanced NSCLC who are included in the pooled safety analysis (CS, Table 23). The company states that the two patient populations have similar baseline characteristics; however, the ERG notes from Table 23 of the CS that the 53 patients with ROS1+advanced NSCLC are slightly younger than the 1669 patients with ALK+ advanced NSCLC and that the smoking status of the patients with ALK+ advanced NSCLC is not available for comparison.

The company compares the AEs (any grade and Grades 3 or 4) experienced by the 53 patients with ROS1+ advanced NSCLC from the PROFILE 1001 study with the AEs (any grade and Grades 3 or 4) experienced by the 1669 patients with ALK+ advanced NSCLC who are included in the pooled safety analysis (CS, Table 24). The ERG agrees with the company that

the types and frequency of AEs are similar between patients with ROS1+ advanced NSCLC (PROFILE 1001) and patients with ALK+ advanced NSCLC who were treated with crizotinib.

Summary of AE evidence

The most frequently occurring AE of any grade experienced by the 53 patients in the PROFILE 1001 study was 'vision disorder'. The company reports that vision disorders were Grade 1 or Grade 2 and were managed with dose reductions. The company also reports that other common AEs (e.g. nausea, vomiting) were also Grade 1 or Grade 2 events that were managed with dose interruptions or reductions. The most frequently experienced Grade 3 AEs were hypophosphataemia and neutropenia. The only Grade 4 AEs recorded during the PROFILE 1001 study were six cases of pulmonary embolism. These were not considered by the company to be treatment-related. The ERG notes that the AE data from the PROFILE 1001 study are the only AE data that are available for a patient population with ROS1+ advanced NSCLC.

The company states (CS, p77) that the AE profile of crizotinib as recorded in the PROFILE 1001 study is consistent with the AE profile of crizotinib as reported in the pooled analysis of 1669 patients with ALK+ advanced NSCLC. The ERG notes that the EMA[14] (EPAR, p60) considered the safety profile of crizotinib in the 53 patients with ROS1+ advanced NSCLC to be consistent with the known safety profile of crizotinib.

4.6 Results of other studies identified in the clinical systematic review

In this section, the ERG summarises the key findings from two studies identified by the company as being relevant to a ROS1+ UK population and discusses whether data from these studies support the use of crizotinib in ROS1+ patients. The company summarises the results of the other 13 studies identified in the clinical systematic review in Appendix D of the CS (Table 8). None of these studies were used to provide estimates of clinical or cost effectiveness in the CS, as discussed in Section 4.2.1.

The EUCROSS study (n=34) is a phase II single-arm study conducted in a European ROS1+ NSCLC population. The company presents preliminary results from this recently completed study as supportive evidence for the clinical effectiveness of treatment with crizotinib. The ORR from EUCROSS ([redacted]) was very similar to the ORR reported in the PROFILE 1001 study. Median PFS ([redacted] months, 95% CI: [redacted]) and the probability of survival at 12 months ([redacted]) in the EUCROSS study were also comparable to the corresponding results from the PROFILE 1001 study. The probability of survival at 24 months in the EUCROSS study was [redacted]). The company claims that, as results from EUCROSS support the observations from the PROFILE 1001

study, the results from ROS1 patients in the PROFILE 1001 study may be generalisable to the UK population. The ERG agrees that the EUCROSS study results suggest that the PROFILE 1001 study results are generalisable to the UK population. The company states that because of the lack of K-M curves for PFS and OS from the EUCROSS study at the time of the economic analysis, evidence from the EUCROSS study could not be incorporated in the economic analysis.

The company also refers to the recent audit of ROS1 patients from the [redacted], UK, explaining that this audit provides supportive data for the use of crizotinib in ROS1+ advanced NSCLC patients. The preliminary results from the [redacted] audit were presented to the company by the lead investigator [redacted] during an advisory board meeting[22] in July 2017. This audit identified [redacted] patients with ROS1+ NSCLC in the UK, of whom [redacted] received first-line pemetrexed+platinum and [redacted] received first-line and subsequent-line crizotinib. [redacted] The preliminary median PFS was [redacted] months for patients treated by pemetrexed+platinum and maintenance pemetrexed in the first-line setting, and [redacted] months for treatment with crizotinib in the first-line and subsequent-line settings. The median PFS observed for crizotinib-treated patients from the audit is lower than the median PFS for patients receiving crizotinib in the PROFILE 1001 study. The company states that at the advisory board meeting[22] where the audit data were reviewed, the difference in the PFS data between the [redacted] audit and the PFS data from the PROFILE 1001 study was "…felt to be due to the real-world nature of the audit of UK patients". Median OS [redacted] The survival rate at Year 1 is comparable to the 12-month survival rate for patients in the PROFILE 1001 study.

4.7 Critique of the company's approach to obtaining estimates of the clinical effectiveness of crizotinib in the ROS1+ patient population

The company presents evidence for the effectiveness of crizotinib in comparison to chemotherapy from the PROFILE 1014 and PROFILE 1007 trials, which were conducted in the ALK+ advanced NSCLC patient population, as a proxy for evidence for the effectiveness of crizotinib in comparison to chemotherapy in the ROS1+ advanced NSCLC patient population. The company's justification for this approach with regards to the similarity of the two patient populations is discussed in Section 2.1 of this ERG report. In this section, the ERG outlines and critiques the company's statistical rationale for this approach.

The company considered performing unanchored matched adjusted indirect comparisons (MAIC) to compare crizotinib treated ROS1+ patients in the PROFILE 1001 study with the chemotherapy arm of the PROFILE 1014 trial and with the chemotherapy arm of the PROFILE 1007 trial in separate analyses. The company refers to the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 which recommends that an unanchored MAIC should adjust for all effect modifiers and prognostic variables. The company considered it implausible to fit complex models including multiple variables given the small sample size in the PROFILE 1001 study. The ERG agrees with the company's assessment.

The company explains (CS, p68) that "…given the structural similarities between the ALK and ROS1 rearrangements and the comparable patient characteristics between ALK+ and ROS1+ NSCLC patients, it was preferable to use HRs from the PROFILE 1014 and PROFILE 1007 trials rather than attempting to implement complex methods with only limited data". However, the ERG notes that the CIs for the estimates of median PFS do not overlap, so median PFS is statistically significantly longer for ROS1+ NSCLC patients treated with crizotinib in the PROFILE 1001 study than for ALK+ NSCLC patients treated with crizotinib in the PROFILE 1014 and PROFILE 1007 trials. The 95% CI for median PFS for the PROFILE 1001 study takes into consideration the small sample size of the study. The difference between PFS in the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials causes the ERG to question whether the ALK+ and ROS1+ NSCLC patient populations are truly comparable.

In the company's response to the ERG's clarification letter, the company suggests that selection bias in the PROFILE 1001 study could be to blame for the differences in PFS results between the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials. However, the ERG notes that, in the CS, it is stated that "UK clinical experts confirmed that the baseline characteristics in the PROFILE 1001 study are representative of patients encountered in UK clinical practice, and as such selection bias is unlikely to be a concern".

The company also states that real-world evidence from the [redacted] shows PFS outcomes for UK crizotinib-treated ROS1+ NSCLC patients to be in line with the PFS results seen in the ALK+ NSCLC trials. However, if the differences between the [redacted] PFS results and the PROFILE 1001 study PFS results are considered to be due to the "real-world" nature of the data as explained by the company, the ERG is unsure why the company believes that it is appropriate to compare data from the [redacted] with data from the RCTs to demonstrate that PFS results are similar for ROS1+ and ALK+ advanced NSCLC patient populations.

Finally, the company states that, if there were differences in the PFS for ROS1+ and ALK+ NSCLC patients treated with crizotinib, then the results of the PROFILE 1001 study would indicate that the ALK data provide a conservative estimate of the clinical benefits of crizotinib in patients with ROS1+ advanced NSCLC. The ERG agrees that this is the case, but highlights that, since patients are treated until progression, underestimating PFS (and consequently the time on treatment) would have important implications for the cost effectiveness of crizotinib.

4.8 Conclusions of the clinical effectiveness section

The ERG considers that the company has addressed the decision problem **only** if the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

Direct clinical evidence (PROFILE 1001)

The direct clinical effectiveness evidence for crizotinib in the treatment of patients with ROS1+ advanced NSCLC was derived from the PROFILE 1001 study. The ERG highlights the following points:

- The PROFILE 1001 study is a small, single-arm phase I study (n=53). Patients recruited to the study were previously untreated (n=7) or had received one or more previous treatments. Of the previously treated patients, 63% had not received treatment with pemetrexed+platinum at first-line. Pemetrexed+platinum is the standard of care in the UK as a first-line treatment for patients with tumours of adenocarcinoma histology

- ROS1+ NSCLC (PROFILE 1001) and ALK+ NSCLC (PROFILE 1014 and PROFILE 1007) patient populations are broadly comparable in terms of baseline characteristics

- The ERG considers that the PROFILE 1001 study was well designed and conducted and included an independent review of radiological outcomes

- In the PROFILE 1001 study, most of the patients achieved either a partial or complete response with crizotinib (69.8%), and median PFS was 19.3 months (95% CI: 14.8 to not reported [NR]). OS data were immature, with only 30% of patients having died at the latest data cut-off date (2014)

- No HRQoL data were collected during the PROFILE 1001 study

- There are no robust OS data available for patients with ROS1+ advanced NSCLC

Proxy clinical evidence (PROFILE 1014, PROFILE 1007)

The company presents data from the PROFILE 1014 and PROFILE 1007 RCTs, which investigated the efficacy of first-line (PROFILE 1014) and subsequent-line (PROFILE 1007) crizotinib in comparison to chemotherapy in ALK+ advanced NSCLC patients, as supportive evidence for the use of crizotinib in patients with ROS1+ advanced NSCLC. The ERG highlights the following points:

- The ERG considers that the PROFILE 1014 and 1007 trials well generally well designed and conducted
- In the PROFILE 1007 trial, [redacted] of patients were not treated with pemetrexed+platinum in the first-line setting. Pemetrexed+platinum is the standard of care in the UK as a first-line treatment for patients with tumours of adenocarcinoma histology
- None of the patients in the PROFILE 1007 were treated with docetaxel+nintedanib (NHS standard care)
- Patients in the PROFILE 1014 trial were considered by a previous Appraisal Committee not be representative of patients likely to be treated with crizotinib in the NHS. However, clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS
- The ERG concluded that the PH assumption was not valid for PFS in the PROFILE 1014 or PROFILE 1007 trials, and that HRs for PFS data from both trials should be interpreted with caution
- The ORRs for crizotinib patients in the PROFILE 1014 (74.4%) and PROFILE 1007 (65.3%) trials were comparable with the observed ORR for patients in the PROFILE 1001 study. Both the PROFILE 1014 and PROFILE 1007 trials demonstrated a statistically significantly greater ORR for crizotinib patients than for chemotherapy patients
- Median PFS varied across the PROFILE 1001 study (19.3 months, 95% CI: 14.8 to NR), the PROFILE 1014 trial (10.9 months, 95% CI: 8.3 to 13.9) and the PROFILE 1007 trial (7.7 months, 95% CI: 6.0 to 8.8; respectively). The variation in PFS brings into question the comparability of the ALK+ and ROS1+ NSCLC patient populations

- There was a substantial amount of patient crossover from the chemotherapy arm to the crizotinib arm and vice versa in both the PROFILE 1014 and PROFILE 1007 trials

- The company presents RPSFTM-adjusted OS HRs to account for patient crossover in the PROFILE 1014 trial. The ERG considers that the RPSFTM-adjusted HRs for OS are unlikely to be valid and should be interpreted with caution

- For the PROFILE 1007 trial, the company presents the PFS HR as a proxy for the true OS HR, instead of using the RPSFTM-adjusted OS HR. The ERG considers that the PFS HR is likely to be closer to the true OS HR than the RPSFTM-adjusted OS HR. However, the ERG also notes that the true OS HR may still be less than the PFS HR, and the company's HR for "crossover-adjusted" OS should be interpreted with caution

- There are no reliable OS data available from either the PROFILE 1014 or PROFILE 1007 trials to support treatment with crizotinib

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of crizotinib for the treatment of patients with ROS1+ advanced NSCLC. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluations. The company has also provided an electronic version of their economic models, which were developed in Microsoft Excel.

5.2 ERG comment on company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company conducted a systematic review of published cost effectiveness studies relevant to the decision problem on 17 March 2017. The company states that they searched the following databases: MEDLINE, MEDLINE in Process, EMBASE, The Cochrane Library (NHS Economic Evaluation Database [NHS-EED; Issue 2 of 4, April 2015] and Health Technology Assessment Database [Issue 4 of 4, October 2016]) and EconLit. The search strategy included relevant disease terms and a cost effectiveness filter. Details of the search strategies employed by the company are provided in Appendix G of the CS. Electronic database searches were supplemented by additional hand searches of proceedings from the ASCO, ELCC, ESMO, ISPOR and WCLC meetings on 1st June 2017. The company states that the searches of conference proceedings were limited to those published between 2015 and 2017. The company assumed that older, pre-2015 conference abstracts would have since been published as full-text articles in peer reviewed journals. NICE and Scottish Medicines Consortium (SMC) websites were searched on 1st December 2016 for economic evaluations presented in relevant health technology assessment appraisals.

The company conducted additional systematic reviews to identify HRQoL studies and cost and healthcare resource identification studies using the search results from a previous STA submission to NICE (TA406). The searches were updated from 31st July 2015 up to 17th March 2017. The ERG considers the approach to update the previous searches to be appropriate.

5.2.2 Eligibility criteria used in study selection

The eligibility criteria used by the company to facilitate study selection are described in Table 23, Appendix G of the CS. The ERG considers that the eligibility criteria were appropriate to the objective of the company's review of cost effectiveness evidence.

5.2.3 Included and excluded studies

The company did not identify any cost effectiveness studies that were relevant to the ROS1+ advanced NSCLC population.

5.3 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and considers that the databases searched and search terms used appear to be reasonable. The ERG updated the company searches for the period between March 2017 and 9th November 2017 and is satisfied that no relevant economic studies have been missed by the company.

5.4 Summary and critique of company's submitted economic evaluation by the ERG

5.4.1 Model structure

The company developed a de novo cost effectiveness model structure in Microsoft Excel. The same model structure is used for the analysis of first- and subsequent-line treatment with crizotinib, but considering different comparator, cost, efficacy and benefit inputs applied to each population. The model comprises three progressively worse health states: progression-free disease, progressed disease and death (Figure 2). All patients begin in the model in the progression-free state and are at risk of moving to a worse state in each subsequent cycle, where death is an absorbing health state.

The company uses a 30-day cycle length and has implemented a half-cycle correction. This model structure was used in the appraisal of crizotinib for untreated and previously treated patients with ALK+ advanced NSCLC (NICE TA406[36] and TA422[60]).

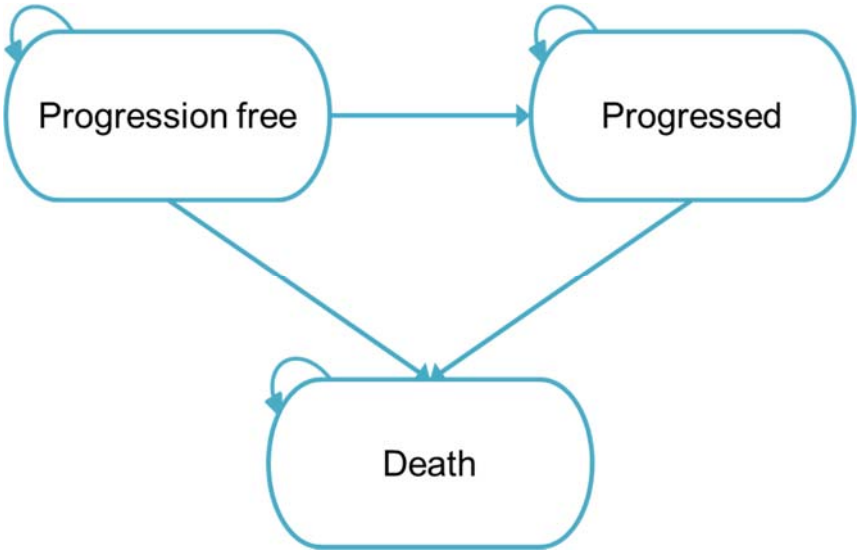

Figure 2 Company model structure

Source: CS, Figure 9

5.4.2 Population

The population reflected in the model is adults with ROS1+ advanced NSCLC. This is split into two populations to encompass first- and subsequent-line treatment with crizotinib. Due to the limited availability of time-to-event data for patients with ROS1+ advanced NSCLC, the company has used data from the ALK+ advanced NSCLC population as a proxy for data fromROS1+ patients in the base case analysis.

5.4.3 Interventions and comparators

Intervention

Crizotinib is supplied as a capsule and is used to treat patients in line with its EMA marketing authorisations (i.e. 250 mg twice daily until disease progression). Treatment beyond progression was allowed in the pivotal studies (PROFILE 1001 study, PROFILE 1014 trial and PROFILE 1007 trial), which is reflected in the company's model.

Comparators (first-line treatment)

Pemetrexed+platinum therapy (cisplatin or carboplatin) is the only comparator included in the cost effectiveness analysis for first-line treatment. The dose of pemetrexed is 500 mg/m², followed by cisplatin (75 mg/m²) or carboplatin (target area under the concentration-time curve of 5-6 mg/mL/min) administered intravenously on the first day of each 21-day cycle.[36] Treatment is administered in the base case model based on the time on treatment curves from TA406.

Comparators (subsequent-line treatment)

Docetaxel monotherapy is the only comparator included in the cost effectiveness analysis for subsequent-line treatment; however, evidence for docetaxel monotherapy used in the subsequent-line model is based on the pooled outcomes of patients treated with either docetaxel monotherapy or pemetrexed+platinum ('pooled chemotherapy') in the PROFILE 1007 trial. The company cites paucity of data in either the ROS1+ or ALK+ advanced NSCLC population for the omission of a comparison with docetaxel+nintedanib or with BSC. Docetaxel is administered intravenously at a dose of 75 mg/m^2 every 21 days. Treatment is administered in the base case model for a maximum of three cycles.

Subsequent treatment (first-line treatment)

Patients who progress after first-line treatment with crizotinib or pemetrexed+platinum therapy (and are no longer receiving treatment with crizotinib or pemetrexed+platinum therapy) are treated with docetaxel or receive BSC.

Subsequent treatment (subsequent-line treatment)

Patients who progress after subsequent-line treatment after receiving treatment with crizotinib or docetaxel receive BSC.

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS) and the model time horizon is 20 years. The company states that both costs and benefits are discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation

The company has used clinical effectiveness data from patients with ALK+ advanced NSCLC as a proxy for data from patients with ROS1+ advanced NSCLC in the base case analysis for both first-line and subsequent-line treatment with crizotinib (the company's rationale for this approach and further details are presented in Sections 2.1, 3.1-3.3 of this ERG report).

For the first-line population, extrapolations of PFS and time to treatment discontinuation (TTD) data for patients with ALK+ advanced NSCLC were taken from TA406 (based on the results of the PROFILE 1014 trial). The company has updated its modelling of OS since TA406 and has provided new results based on an updated data cut (9 March 2017) from the PROFILE 1014 trial.

For the subsequent-line population, extrapolations of OS, PFS and TTD data for patients with ALK+ advanced NSCLC were taken from TA422 (based on the results of the PROFILE 1007 trial).

The company has provided a scenario analysis using clinical effectiveness data for patients with ROS1+ advanced NSCLC from the PROFILE 1001 study.

A summary of all time-to-event modelling is presented in Table 19.

Table 19 Time-to-event modelling in company base case and scenario analysis

		Base case		Scenario	
		First-line (ALK+, PROFILE 1014)	**Subsequent-line (ALK+, PROFILE 1007)**	**First-line (ROS1+, PROFILE 1001)**	**Subsequent-line (ROS1+, PROFILE 1001)**
OS	**Crizotinib**	Exponential (independent) adjusted for: • RPSFTM [Wilcoxon] • patient characteristics	Exponential (PH) adjusted from comparator HR=0.49 (CI=0.37 to 0.64)	Exponential (PH)	Same as first-line
	Comparator	Exponential (independent) adjusted for: • RPSFTM [Wilcoxon] • patient characteristics	Exponential (PH) Adjusted for: • RPSFTM [log rank]	Exponential (PH) adjusted from intervention HR=[redacted]	Exponential (PH) adjusted from intervention HR=[redacted]
PFS	**Crizotinib**	Stratified log-normal adjusted for: • patient characteristics	Weibull	Exponential (PH)	Same as first-line
	Comparator	Stratified generalised gamma adjusted for: • patient characteristics	Log-normal	Exponential (PH) adjusted from intervention HR=[redacted]	Exponential (PH) adjusted from intervention HR=[redacted]
TTD	**Crizotinib**	Stratified exponential (independent) adjusted for: • patient characteristics	Weibull	Exponential	Same as first-line
	Comparator	Stratified gompertz (independent) adjusted for: • patient characteristics	3 cycles only	Stratified gompertz (independent) adjusted for: • patient characteristics	3 cycles only

HR=hazard ratio; PFS=progression-free survival; OS=overall survival; PH=proportional hazard; RPSFTM=rank-preserving structural failure time method; TTD=time to treatment discontinuation
Source: CS, company model

Base case: first-line treatment

Overall survival

Data from the PROFILE 1014 trial (data cut-off: March 09, 2017) were used as the basis for identifying parametric models to represent OS for patients treated with first-line treatments. The RPSFTM (Wilcoxon) method was used in the base case analysis to adjust OS for the effect of patients in the pemetrexed arm who crossed over to treatment with crizotinib on progression (n=144 [84.2%] of patients who had progressed at the time of the final OS analysis).

Parametric curves were fitted separately to the RPSFTM-adjusted for treatment with crizotinib and for treatment with pemetrexed+platinum therapy. The parametric models considered were: exponential, weibull, log-normal, log-logistic, gompertz and generalised gamma. Model fit was assessed using visual inspection, comparison of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), and consideration of the clinical plausibility of long-term extrapolation results. The exponential curve was selected in the base case analysis for the intervention and the comparator treatments. Alternative curve fits are tested in the sensitivity analysis.

As discussed in TA406, the baseline characteristics of patients participating in a 'real-life' cohort study conducted by Davis[76] were considered to be more representative of the characteristics of patients likely to be seen in NHS clinical practice than those of patients in the PROFILE 1014 trial. In TA406, the company adjusted the PFS and OS data from the PROFILE 1014 trial to account for the baseline characteristics of the patients in the Davis[76] study (Table 20). For the current appraisal, the company has adjusted the chosen exponential OS curves to take account of the baseline patient characteristics reported by Davis[76] to provide consistency with the PFS and TTD modelling from TA406.

Table 20 Baseline demographics and patient characteristics for covariate-adjustment

Covariate	Real-world data (Davis[76])	Crizotinib (PROFILE 1014)	Pemetrexed+platinum therapy (PROFILE 1014)	Pooled treatments (PROFILE 1014)
% non-Asian	87.6%	55.2%	53.2%	54.2%
% age ≥ 65	29.2%	13.4%	18.7%	16.0%
% male	67.9%	39.5%	36.8%	38.2%
% smoker or ex-smoker	62.8%	38.4%	34.5%	36.4%
% ECOG PS 0-1	78.1%	94.2%	95.3%	94.7%
% ECOG PS 2	21.9%*	5.8%	4.7%	5.3%
% with brain metastases	NR	26.2%	27.5%	26.8%
% non-adenocarcinoma	NR	6.4%	5.8%	6.1%

ECOG=Eastern Cooperative Oncology Group; NR=not reported; PS=performance status
Source: CS, Table 29

The OS curves used in the company's first-line base case analysis are shown in Figure 3. Mean OS in the company's first-line base case model is 46.4 months for treatment with crizotinib and 17.6 months for treatment with pemetrexed+platinum, which yields an OS gain of 28.7 months.

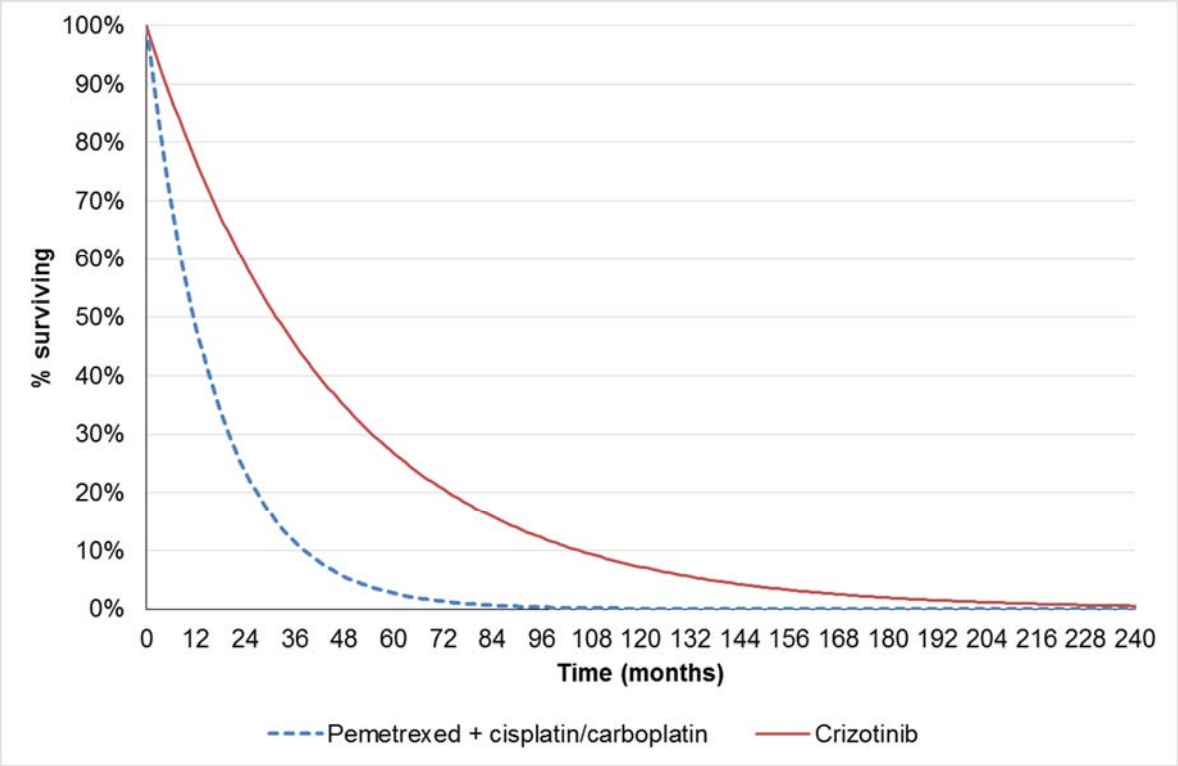

Figure 3 Company model first-line base case OS

Source: company model

Progression-free survival

Data from the PROFILE 1014 trial (data cut-off: 30 November 2013) were used as the basis for identifying parametric models to represent PFS in the first-line setting. Fully stratified log-normal curve is used to estimate PFS for treatment with crizotinib and a fully stratified gamma curve is used to estimate PFS for treatment with pemetrexed+platinum in the first-line setting for this appraisal; the curves have been adjusted according to the baseline characteristics of the patients in the Davis study.[76]

The company states that the PFS curves used in the company model replicate directly those accepted by the Appraisal Committee during TA406. No additional rationale was provided for the choice of PFS curves in the current CS. The ERG notes that it is not clear from the Final Appraisal Determination document for TA406 that the curves used in the company's base case were in fact accepted by the Appraisal Committee, only that the ERG's alternative analyses were not considered to be plausible.

The PFS curves used in the company's first-line base case analysis are shown in Figure 4. Mean PFS in the company's first-line base case model is 16.8 months for treatment with crizotinib and 7.3 months for treatment with pemetrexed+platinum, which yields a PFS gain of 9.5 months.

Figure 4 Company model first-line base case PFS

Source: company model

Time to treatment discontinuation

The company states that the TTD curves used in the company model replicate directly those accepted by the Appraisal Committee during TA406. Data from the PROFILE 1014 trial (data cut-off: November 30, 2013) were used as the basis for identifying parametric models to represent TTD in the first-line setting for treatment with crizotinib and with pemetrexed+platinum therapy in TA406. A fully stratified (independent) exponential curve is used to estimate TTD for treatment with crizotinib and a fully stratified gompertz curve is used to estimate TTD for treatment with pemetrexed+platinum in the first-line setting for this appraisal, which have been adjusted to take account of the baseline characteristics of the patients in the Davis study.[76]

The company has not presented any further information regarding the development of TTD estimates in this CS. The development of the TTD curves is outlined in the Appraisal Committee papers for TA406; however, much of the detail has been redacted and cannot be examined by the ERG.

Mean TTD in the company first-line base case model is 17.7 months for treatment with crizotinib and 3.8 months for treatment with pemetrexed+platinum.

Base case: subsequent-line treatment

Overall survival

The OS curves used in the company model replicate directly those accepted by the Appraisal Committee during TA422 and the company has not given any further information about their development in the current CS.

Data from the PROFILE 1007 trial were used as the basis for identifying a parametric model to represent OS in the subsequent-line setting in TA422. The Appraisal Committee's most plausible ICER per QALY gained for treatment with crizotinib versus docetaxel in TA422 included estimates of OS based on an exponential PH model using a HR of 0.49 (Section 4) and the company has replicated this approach in its subsequent-line model.

The OS curves used in the company's subsequent-line base case analysis are shown in Figure 5. Mean OS in the company subsequent-line base case model is 33.0 months for treatment with crizotinib and 16.7 months for treatment with docetaxel, which yields an OS gain of 16.3 months.

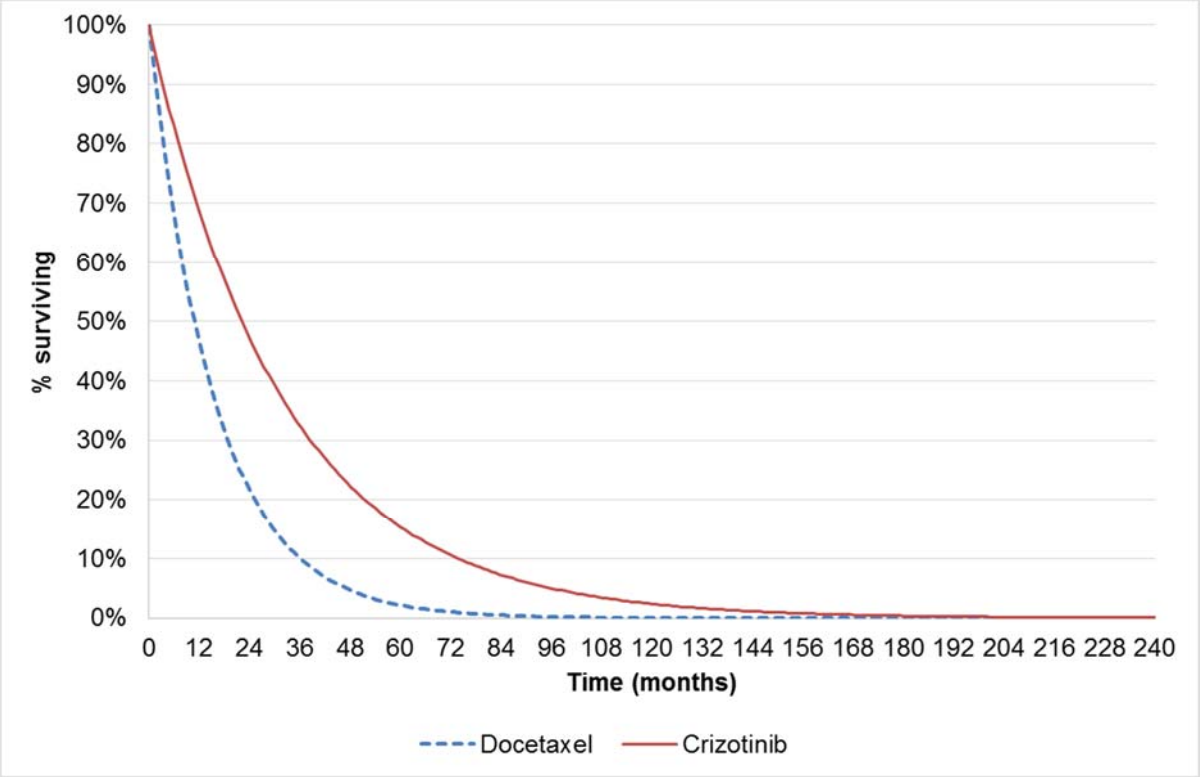

Figure 5 Company model subsequent-line base case OS

Source: company model

Progression-free survival

The company states that the PFS curves used in the company model for subsequent-line treatment replicate directly those accepted by the Appraisal Committee during TA422. Data from the PROFILE 1007 trial were used as the basis for identifying parametric models to represent PFS in TA422. The company used weibull and log-normal curves to model PFS in the subsequent-line setting for crizotinib and docetaxel respectively.

In TA296, the modelling of PFS was not an issue for consideration during the appraisal. TA296 was then superseded by TA422. As the modelling of PFS had not been an issue in TA296, there was no detailed description of the PFS model used in TA422. The company did not provide any further information to explain how the previously used PFS models were developed in the original submission for this appraisal. The company provided justification for the choice of modelling approaches at a late stage in the STA process.

The PFS curves used in the company's subsequent-line base case analysis are shown in Figure 6. Mean PFS in the company's subsequent-line base case model is 10.6 months for treatment with crizotinib and 4.9 months for treatment with docetaxel, which yields a PFS gain of 5.7 months.

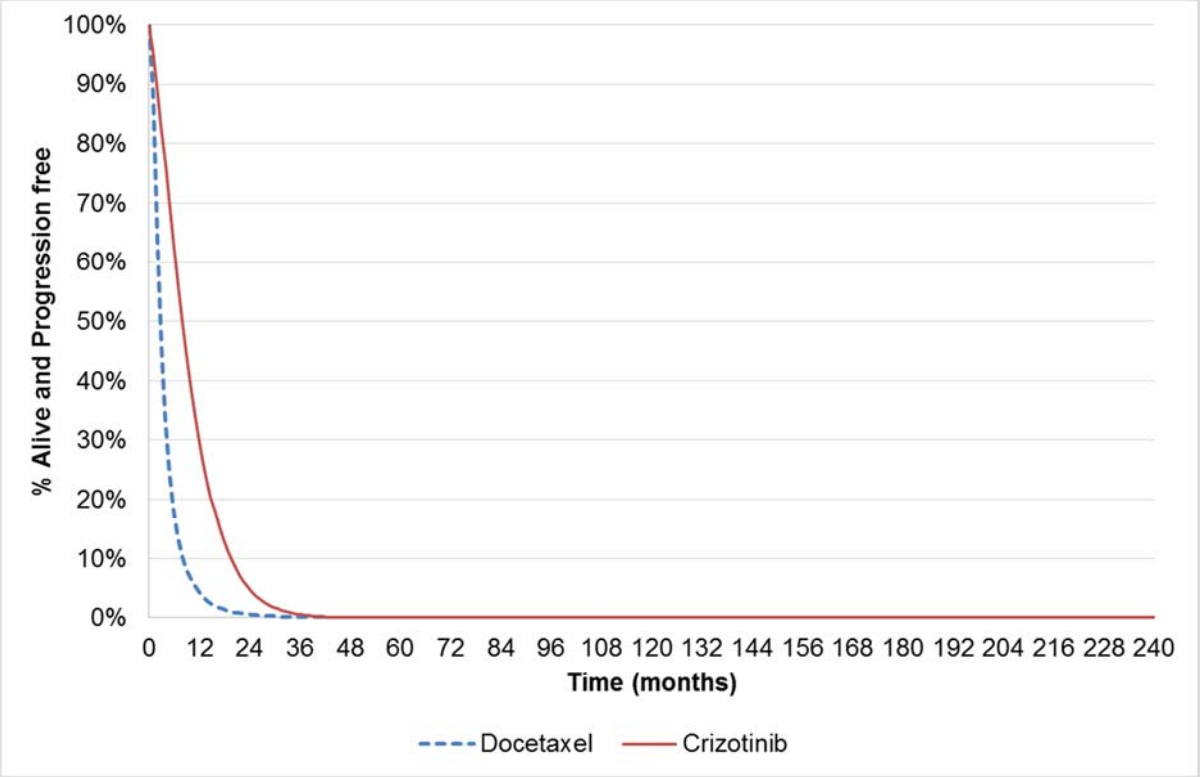

Figure 6 Company model subsequent-line base case PFS

Source: company model

Time to treatment discontinuation

The company states that the TTD curve used in the company's model for subsequent-line treatment with crizotinib replicate directly the model accepted by the Appraisal Committee during TA422. TTD was not modelled for treatment with docetaxel in TA422. Instead, a maximum of three doses was assumed for docetaxel and this is repeated in the current model. Data from the PROFILE 1007 trial were used as the basis for identifying a parametric model to represent TTD in TA422. The company used weibull curves to model TTD in the subsequent-line setting for treatment with crizotinib.

The ERG notes that the TTD curve was also used in TA296 (which was superseded by TA422). The modelling of TTD was an issue for consideration in TA422, as the company had updated the base case analysis from TA296. The Appraisal Committee did not accept the company's updated modelling of TTD and preferred the original base case analysis from TA296. In the current CS, the company did not originally provide any further information to explain how the previously used TTD models were developed. The company provided further information on model development at a late stage in the STA process.

Mean TTD in the company subsequent-line base case model is 15.5 months for treatment with crizotinib and 1.9 months (maximum 3 cycles) for treatment with docetaxel.

Scenario analysis

Time-to-event modelling (crizotinib)

The company used data from the single-arm PROFILE 1001 study to estimate OS, PFS and TTD for treatment with crizotinib in the ROS1+ advanced NSCLC population in a scenario analysis. Given the limited number of patients (n=7) and events (OS, n=2; PFS, n=3; TTD, n=4) for patients treated with crizotinib as a first-line treatment in the PROFILE 1001 study, the company considered it more robust to model all treatment lines together. The company notes that the majority of patients (n=46, 87%) in the PROFILE 1001 study received crizotinib as a subsequent-line treatment and that these patients therefore drive survival estimates for the overall population. The company considers this approach to be conservative, as it states that treatment-naïve patients would be expected to have greater survival estimates than previously treated patients.

The company states that, although the 'all-lines' approach to modelling data from the PROFILE 1001 study is less uncertain than modelling first- and subsequent-line treatments separately, there is still a lot of uncertainty due to the small sample size (n=53) and the immaturity of the data (30% of patients had died by data cut-off).

For each time-to-event outcome, the company fitted standard parametric curves to the K-M data for treatment with crizotinib from the PROFILE 1001 study and assessed the curves using visual inspection, consideration of the AIC and BIC, and the clinical plausibility of the results. The company notes in each case that there was little difference in the AIC and BIC for any of the curves. Exponential curves were chosen for OS, PFS and TTD based on clinical plausibility and marginally better statistical fit. Alternative distributions are considered in a scenario analysis.

The company has used the same 'all-lines' curves to estimate outcomes for first- and subsequent-line treatment with crizotinib. It then applied different HRs to OS, PFS and TTD for treatment with crizotinib to generate estimates of the outcomes for the first- and subsequent-line comparators.

Overall survival (comparators)

The company estimated OS for treatment with pemetrexed+platinum therapy in the first-line setting using the inverse of the crossover-adjusted HR from the updated PROFILE 1014 trial OS analysis (HR=[redacted]_applied to the chosen exponential curve for treatment with crizotinib. The RPSFT (Wilcoxon) method of crossover adjustment was preferred as it produced a conservative HR (Table 21).

Table 21 OS HRs from PROFILE 1014 used in the PROFILE 1001 scenario analysis (first-line setting)

	Crossover method	
	RPSFTM – Wilcoxon	**RPSFTM – log-rank**
HR (95% CI)	[redacted]	[redacted]
Inverse HR applied to the crizotinib OS curve (95% CI)	[redacted]	[redacted]

HR=hazard ratio; RPSFTM=rank preserving structural failure time method
Source: CS, Table 33

The company used the inverse of the crossover-adjusted HR from the pooled chemotherapy arm of the PROFILE 1007 trial (HR=2.61, CI: 1.01 to 23.81) to estimate OS for treatment with docetaxel in the subsequent-line setting. The company explains that the crossover-adjusted HR was not available for the docetaxel subgroup from the PROFILE 1007 trial and states that the HR from the pooled chemotherapy arm is a conservative assumption. The RPSFT (log-rank) method of crossover adjustment was preferred by the company as it was used in TA422 (Table 22).

Table 22 OS HRs from PROFILE 1007 used in the PROFILE 1001 scenario analysis (subsequent-line setting)

	Crossover method	
	RPSFTM – log-rank (base case)	**RPSFTM – Wilcoxon**
HR (95% CI)	0.38 (0.04 to 0.99)	0.40 (0.07 to 0.97)
Inverse HR applied to the crizotinib OS curve (95% CI)	2.61 (1.01 to 23.81)	2.49 (1.03 to 14.49)

HR=hazard ratio; RPSFTM=rank preserving structural failure time method
Source: CS, Table 34

The final OS curves used in the company's first-line PROFILE 1001 scenario analysis are shown in

Figure 7. Mean OS in the company's first-line PROFILE 1001 scenario analysis model is 69.0 months for treatment with crizotinib and 25.8 months for treatment with pemetrexed+platinum, which yields an OS gain of 43.2 months.

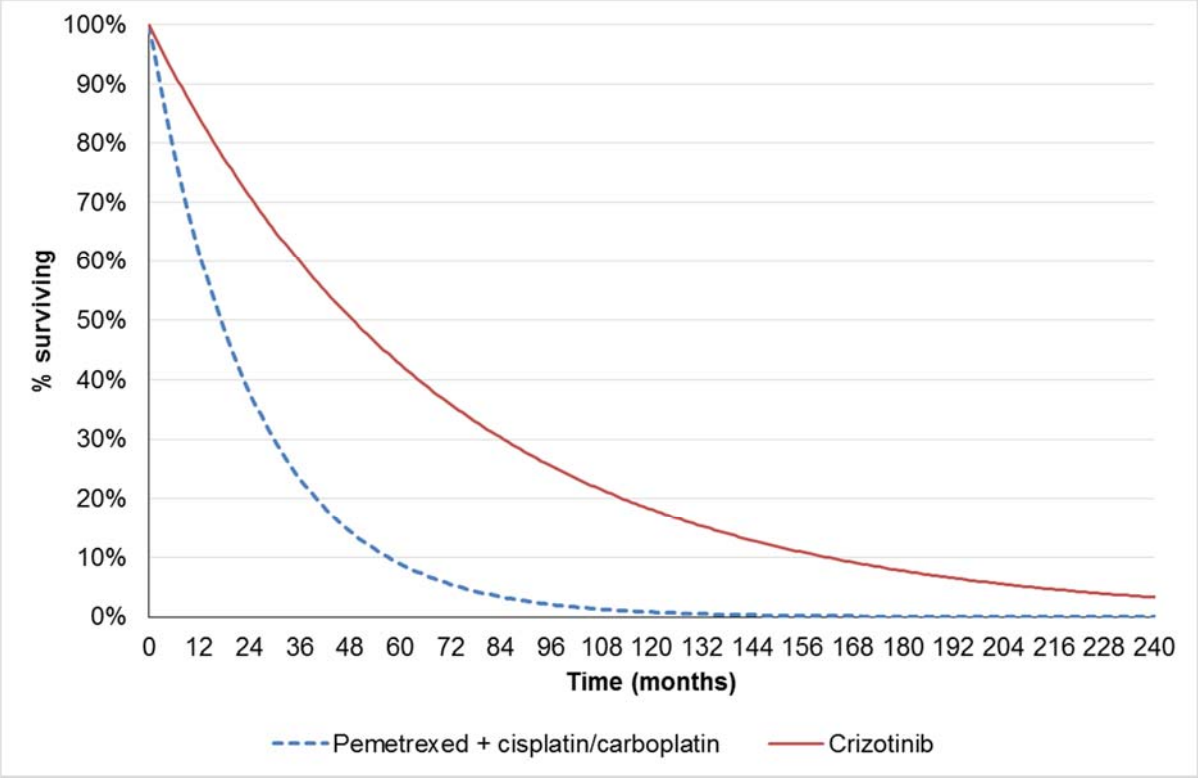

Figure 7 Company model first-line PROFILE 1001 scenario analysis OS

Source: company model

The final OS curves used in the company's subsequent-line PROFILE 1001 scenario analysis are shown in Figure 8. Mean OS in the company's subsequent-line PROFILE 1001 scenario analysis model is 69.0 months for treatment with crizotinib and 27.9 months for treatment with docetaxel, which yields an OS gain of 41.0 months.

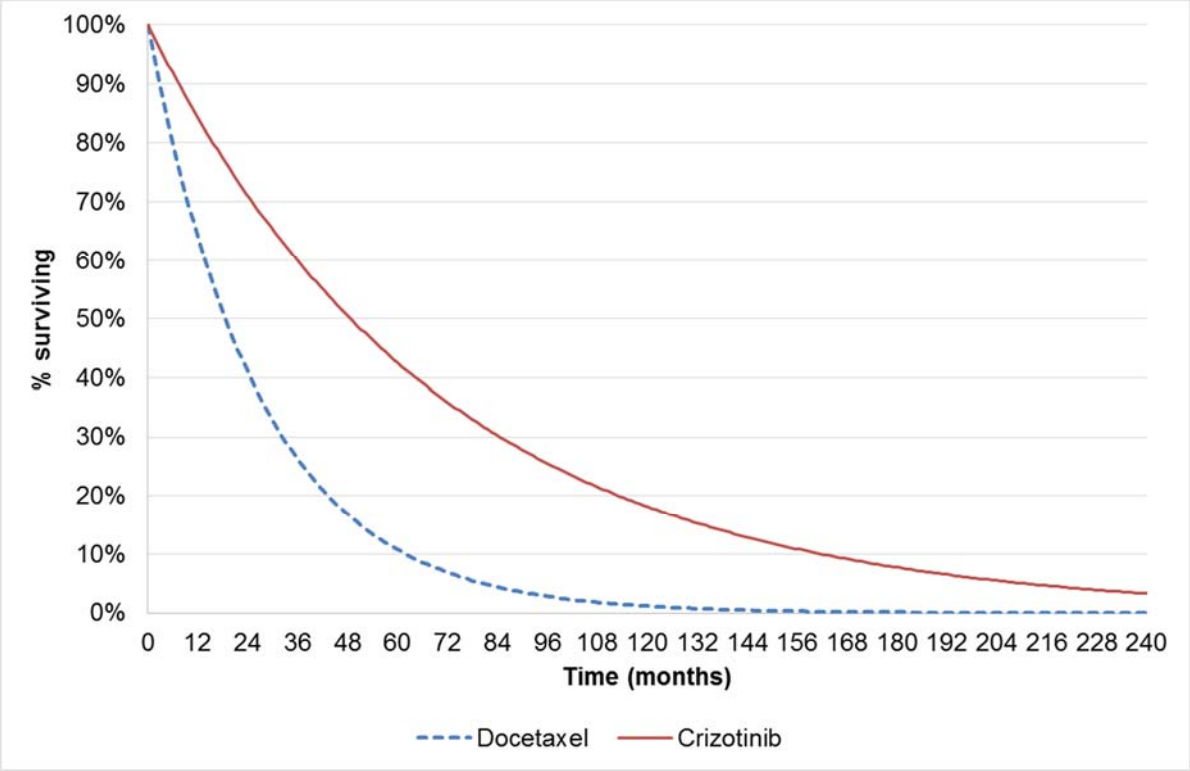

Figure 8 Company model subsequent-line PROFILE 1001 scenario analysis OS

Source: company model

Progression-free survival (comparators)

The company estimated PFS for treatment with pemetrexed+platinum therapy in the first-line setting using the inverse of the HR from the PROFILE 1014 PFS analysis (HR= [redacted] applied to the chosen exponential curve for treatment with crizotinib.

The company used the inverse of the crossover-adjusted HR from the pooled chemotherapy arm of the PROFILE 1007 trial (HR=2.05, CI: 1.57 to 2.70) to estimate PFS for treatment with docetaxel in the subsequent-line setting. Although the HR for the docetaxel subgroup was available from the PROFILE 1007 trial for PFS, the company used the HR from the pooled chemotherapy arm to maintain consistency with the modelling of OS. The company used the HR for the docetaxel subgroup in a scenario analysis (Table 23).

Table 23 PFS HRs from PROFILE 1007 used in the PROFILE 1001 scenario analysis (subsequent-line setting)

	PROFILE 1007 (chemotherapy)	PROFILE 1007 (docetaxel)
HR (95% CI)	0.49 (0.37 to 0.64)	0.30 (0.21 to 0.43)
Inverse HR applied to the crizotinib PFS curve (95% CI)	2.05 (1.57 to 2.70)	3.33 (2.33 to 4.76)

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival
Source: CS, Table 37

The final PFS curves used in the company's first-line PROFILE 1001 scenario analysis are shown in Figure 9. Mean PFS in the company's first-line PROFILE 1001 scenario analysis model is 34.3 months for treatment with crizotinib and 16.1 months for treatment with pemetrexed+platinum, which yields a PFS gain of 18.2 months.

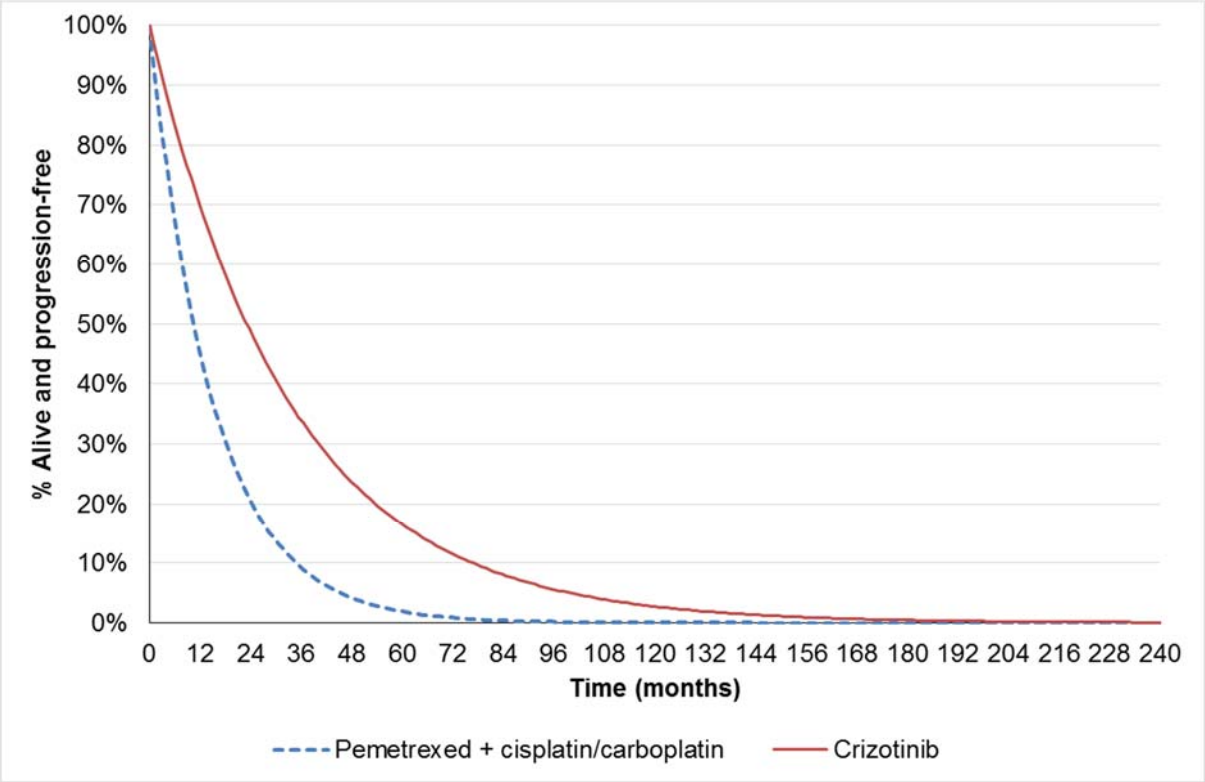

Figure 9 Company model first-line PROFILE 1001 scenario analysis PFS

Source: company model

The PFS curves used in the company's subsequent-line PROFILE 1001 study scenario analysis are shown in Figure 10. Mean PFS in the company's subsequent-line PROFILE 1001 study scenario analysis model is 34.3 months for treatment with crizotinib and 17.2 months for treatment with docetaxel, which yields a PFS gain of 17.1 months.

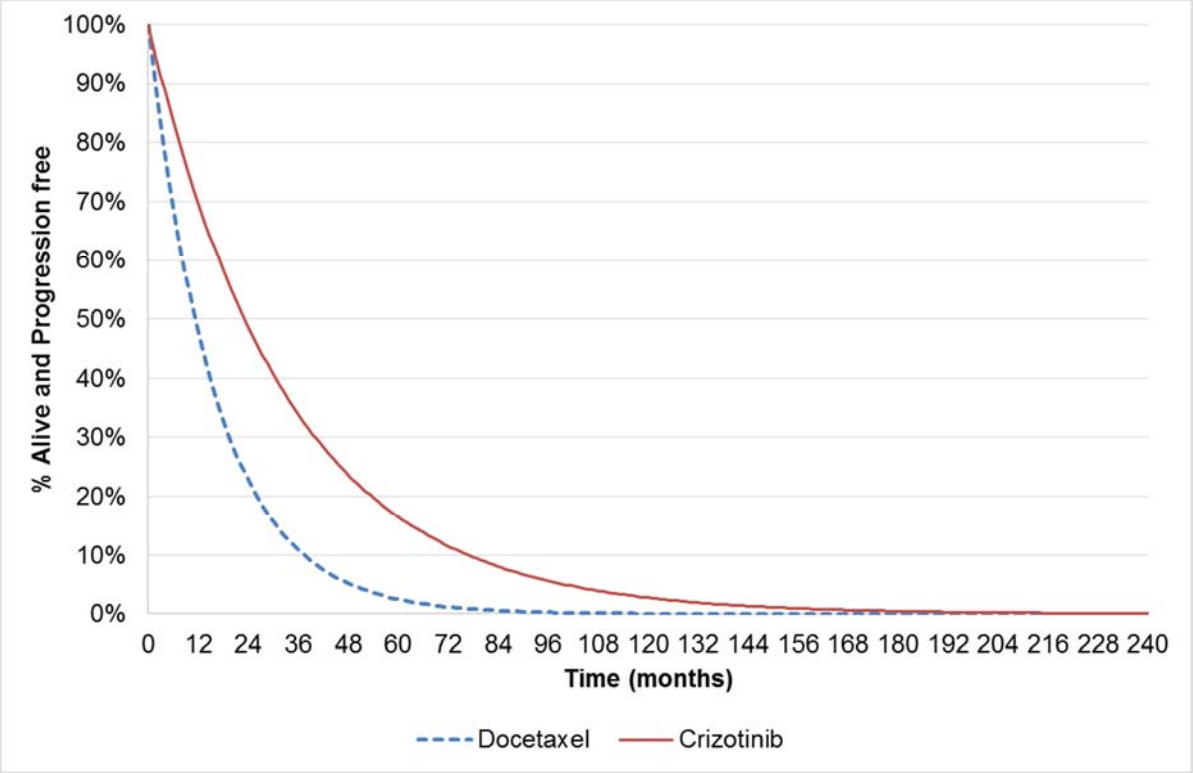

Figure 10 Company model subsequent-line PROFILE 1001 scenario analysis PFS

Source: company model

Time to treatment discontinuation (comparators)

A maximum of six cycles of treatment was assumed for treatment with pemetrexed+platinum therapy in the first-line setting. A maximum of three cycles of treatment was assumed for treatment with docetaxel in the subsequent-line setting.

Mean TTD in the company's first-line PROFILE 1001 scenario analysis model is 36.2 months for treatment with crizotinib and 3.8 months for treatment with pemetrexed+platinum.

Mean TTD in the company's subsequent-line PROFILE 1001 scenario analysis model is 36.2 months for treatment with crizotinib and 1.9 months for treatment with docetaxel.

5.4.6 Health-related quality of life

HRQoL data for treatment with crizotinib in patients with ROS1+ advanced NSCLC were not collected during the PROFILE 1001 study. Instead, the company used utility data collected from the PROFILE 1014 and PROFILE 1007 trials (these data were used in TA406 and TA422) on the assumption that HRQoL data from the ALK+ advanced NSCLC population would be an appropriate proxy for HRQoL for the ROS1+ advanced NSCLC population. Utility data were collected in the PROFILE 1014 and PROFILE 1007 trials using the EQ-5D questionnaire.

In the first-line model, PFS utility values were calculated using a mixed-effects analysis of the EQ-5D results from the PROFILE 1014 trial. The company calculated the mean first-line PFS utility value to be 0.81 for treatment with crizotinib and 0.72 for treatment with pemetrexed+platinum therapy. These PFS utility values are applied in the first-line model to all patients in the pre-progression state whilst receiving or following treatment, as well as to patients being treated with crizotinib beyond progression. The mean utility value used for the progressed state (treatment with docetaxel) in the first-line model is the same as the PFS utility value for treatment with docetaxel in the subsequent-line model. The utility value used in the model for patients who progress from docetaxel into third-line BSC is 0.473, which was taken from a paper by Nafees.[86]

Mean PFS utility values in the subsequent-line model were derived from a paper reporting patient-reported outcomes from the PROFILE 1007 trial.[87] The mean reported PFS utility value from the PROFILE 1007 trial was 0.82 for treatment with crizotinib and 0.66 for treatment with docetaxel. However, the company states that it is unlikely that HRQoL for PFS in subsequent-line treatment with crizotinib is higher than for first-line treatment with crizotinib, and as such has adjusted the utility value for PFS for crizotinib in the subsequent-line model to match the PFS utility in the first-line model (0.81). As in the first-line model, the subsequent-line PFS utility values are applied to all patients in the pre-progression state whilst receiving or following treatment, as well as to patients being treated with crizotinib beyond progression. Patients who progress (or discontinue treatment with crizotinib post-progression) are assumed to move into BSC with a utility value of 0.473.

The company notes that PFS utility values in both the first- and subsequent-line models for treatment with crizotinib are higher than those for the relevant comparators. The company justifies this by stating that treatment with crizotinib reduces symptoms of the disease more so than chemotherapy, and that it is associated with fewer and less severe side effects. A summary of all the utility values used in the first- and subsequent-line models is shown in Table 24

Utility values are taken directly from the PROFILE 1007 and PROFILE 1014 trials and have not been adjusted for AEs.

Table 24 Summary of utility values used for the cost effectiveness analysis in company model

State	Utility value: mean (SE)	95% CI
First-line model		
Treatment with crizotinib	0.81 (0.01)	(0.79 to 0.82)
Progression-free: pemetrexed+platinum therapy	0.72 (0.01)	(0.70 to 0.74)
Progressed (first time): docetaxel	0.66 (0.02)	(0.58 to 0.74)
Progressed (second time): BSC	0.47 (0.05)	(0.38 to 0.56)
Subsequent-line model:		
Treatment with crizotinib	0.81 (0.01)	(0.79 to 0.82)
Progression free: docetaxel	0.66 (0.02)	(0.58 to 0.74)
Progressed (first time): BSC	0.47 (0.05)	(0.38 to 0.56)

BSC=best supportive care; NSCLC=non-small cell lung cancer; SE=standard error
Source: adapted from CS, Table 40

5.4.7 Resources and costs

Drug acquisition costs

The company based resource use and unit costs for the economic models on several sources, including data from: PROFILE 1007 and PROFILE 1014 trials, national databases, previous technology appraisals of crizotinib in first- and subsequent-line ALK+ advanced NSCLC and clinical advice. Full details of the systematic review that was carried out to identify relevant cost and healthcare resource utilisation data are presented in Appendix I of the CS. The drug acquisition costs used in the company model are detailed in Table 25.

Table 25 Unit costs of interventions and comparators in the company models

Treatment	Unit	Unit cost	Source	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Crizotinib	60 x 200 mg tablets	£4,689.00 [redacted])	MIMS[88]	2 x 250 mg per day (30 days)	£4,689.00 [redacted]
	60 x 250 mg tablets	£4,689.00 [redacted])			
Pemetrexed	100 mg vial	£160.00		500 mg/m^2 = 500*1.73 = 866 mg (21 days)	£1,465.40 with wastage £1,385.40 without wastage
	500 mg vial	£800.00			
Cisplatin	10 mg (10 ml vial)	£1.99	eMIt[89]	75 mg/m^2 = 75*1.73 =130 mg (21 days)	£14.64 with wastage £10.97 without wastage
	50 mg (50 ml vial)	£6.48			
	100 mg (100 ml vial)	£8.45			
Carboplatin	50 mg (5 ml vial)	£3.25		Target AUC = 5, dose = 500 mg (21 days)[45]	£23.64 with wastage £22.66 without wastage
	150 mg (15 ml vial)	£7.49			
	450 mg (45 ml vial)	£20.39			
	600 mg (60 ml vial)	£27.89			
Docetaxel	20 mg (1 ml vial)	£3.85		75mg/m^2 = 75*1.80 =135 mg (21 days)	£20.59 with wastage £17.25 without wastage
	80 mg (4 ml vial)	£12.39			
	140 mg (7 ml vial)	£20.62			
	160 mg (8 ml vial)	£20.44			

PAS=patient access scheme; *with PAS
Source: adapted from CS, Table 41

Crizotinib costs in the first- and subsequent-line models are applied according to the proportion of patients on treatment in each cycle according to TTD data from the relevant trials (as used in TA406 and TA422).

Pemetrexed+platinum therapy costs in the first-line model are applied according to the proportion of patients on treatment in each cycle according to TTD data from the PROFILE 1014 trial (as used in TA406). The company has modelled concomitant platinum therapy in the base case using on the proportions observed in the PROFILE 1014 trial: cisplatin (54%) or carboplatin (46%) as per the investigator's choice. Alternative proportions are investigated in a sensitivity analysis.

Docetaxel costs in the subsequent-line model are applied on the assumption that treatment is received for a maximum of three cycles, based on a median PFS of 2.6 months in the PROFILE 1007 trial.

Dosing

Standard treatment with crizotinib is 500 mg daily (250 mg tablets twice a day) for all patients.

Dosing for pemetrexed, cisplatin and docetaxel is based on body surface area (BSA). The company has used the BSA from TA406 (1.73m^2) in the base case first-line model for treatment with pemetrexed and with cisplatin. It has used the BSA from TA422 (1.80m^2) in the base case subsequent-line model. In the scenario analysis using time-to-event data from PROFILE 1001, the company has assumed a BSA of 1.80m^2 for comparator treatments for both lines of treatment.

Dosing for carboplatin is based on a target area under the concentration versus time curve (AUC in mg/mL/min). No information on the dose of carboplatin was reported for the PROFILE 1007 or 1014 trials, so the company reviewed other NICE STAs to reach AUC estimates of 5 mg/mL/min or 6 mg/mL/min, which translate to doses of 500 mg or 750 mg respectively. The company has assumed a target AUC for carboplatin of 5 mg/mL/min in the model, which translates to a dose of 500 mg.

Wastage

The company has assumed drug wastage in the base case analysis for all treatments except for crizotinib.

Drug administration costs

The company has assumed a dispensing cost associated with 12 minutes of pharmacist time for crizotinib (£14.59, uplifted from £14.40 in PSSRU 2015[90] to 2016 prices using the Hospital and Community Health Service index), since it is an oral therapy that does not require hospital administration.

Cisplatin-containing regimens were assumed to incur a day-case administration appointment, whereas carboplatin-containing regimens and docetaxel monotherapy were assumed to incur an outpatient administration appointment. Drug administration costs for all treatments used in the company model are shown in Table 26.

Table 26 Drug administration costs in the company model for crizotinib and comparators

Treatment	Setting	Cost code	Description	Unit cost
Crizotinib	N/A	N/A	Dispensing cost (12 minutes pharmacist time)	£14.59
Pemetrexed plus cisplatin	Day case and regular day/night	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£406.63
Pemetrexed plus carboplatin	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Docetaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30

Source: CS, Table 42

Health state resource use and costs

The company has assumed that the health state and monitoring costs associated with progression-free (first- and subsequent-line models) and progressed disease (receiving therapy) states are the same. It has assumed that patients receiving BSC in the first- and second-line models use the same health state and monitoring resources, which are different from those in the progression-free and progressed (receiving therapy) states. Resource use assumptions were sourced from TA406 and TA296 (superseded by TA422). The costs associated with these health states are shown in Table 27.

Table 27 Health states and associated costs in the company model

Health state	Resources Required	Frequency per month (from TA406)	Unit cost	Reference
Patients in progression-free health state and patients in progressed disease health state receiving second-line treatment	Outpatient Visit	0.75	£151.12	NHS reference costs 2015-16 Outpatient Attendances Data - medical oncology (370) [91 91 91 91 89 89 93 92 90 90 78 78]
	GP visit	10% patients (1 visit)	£27.00	PSSRU 2016 - Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	20% patients (1 visit)	£69.20	NHS reference costs 2015-16 Nurse cancer relate adult face-to-face (N10AF)
	Complete Blood Count	0.75	£3.10	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS05)
	Biochemistry	0.75	£1.18	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS04)
	CT scan	30% patients (0.75 scans)	£132.19	NHS reference costs 2015-16 Direct Access: Pathology Services (RD26Z) [91 91 91 91 89 89 93 92 90 90 78 78]
	Chest X-ray	0.75	£30.26	NHS reference costs 2015-16 Direct Access Plain Film (DAPF)
Total cost per month (first- and subsequent-line treatment)			£185.53	
Patients in progressed disease health state receiving third-line treatment	Oncologist Visit	1 visit	£151.12	NHS reference costs 2015-16 Outpatient Attendances Data - medical oncology (370) [91 91 91 91 89 89 93 92 90 90 78 78]
	GP visits	28% patients	£27.00	PSSRU 2016 - Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	10% patients (1 visit)	£69.20	NHS reference costs 2015-16 Nurse cancer relate adult face-to-face (N10AF)
	Complete Blood Count	100% patients	£3.10	NHS reference costs 2015 -16 Direct Access: Pathology Services (DAPS05)
	Biochemistry	100% patients	£1.18	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS04)
	CT scan	5% patients (0.75 scans)	£132.19	NHS reference costs 2015-16 Direct Access: Pathology Services (RD26Z) [91 91 91 91 89 89 93 92 90 90 78 78]
	X-ray	30% patients (0.75 scans)	£30.26	NHS reference costs 2015-16 Direct Access Plain Film (DAPF)
Total cost per month, progressed disease			£181.65	

BSC=best supportive care; CT=computed tomography
Source: adapted from CS, Table 47

The model includes a one-off cost for palliative care in the 90 days before death. This cost of terminal care includes district nurse, nursing, residential and hospice care, and Marie Curie nursing (Table 28). The cost of terminal care is estimated to be £7,415 and is applied as a one-off cost at the point of death.

Table 28 Cost of palliative care in the company model

Cost	Unit cost	Reference	2015/16 Uplifted cost (PSSRU 2016)[92]
District nurse	£278	Georghiou and Bardsley[93]	£298
Nursing and residential care	£1,000		£1,106
Hospice care – inpatient	£550		£590
Hospice care – final 3 months of life	£4,500		£4,830
Marie Curie nursing service	£550		£590
Total cost			£7,415

Source: CS, Table 48

ROS1 testing

The company notes that the introduction of crizotinib to treat ROS1+ advanced NSCLC would require additional resource for ROS1 testing. The company has considered upfront testing (alongside ALK and EGFR testing) in the base case analysis and sequential testing (after patients have been found to be negative for ALK and EGFR rearrangements) in a scenario analysis. The company has assumed that there will be no impact of ROS1 testing on resource costs other than the purchase of the tests as the NHS already has the infrastructure in place to carry out the testing. It has also assumed that all patients who will be tested for ROS1 rearrangements have non-squamous NSCLC.

The company has used a reported prevalence of 1.8% for ROS1 rearrangements amongst patients with adenocarcinoma[9] and a prevalence of 93.9% for adenocarcinoma amongst patients with non-squamous NSCLC. This results in a calculated prevalence of 1.69% for ROS1 rearrangements amongst patients with non-squamous NSCLC.

Testing for ROS1 is modelled as IHC followed by confirmatory FISH. The company has used the reported specificity (83%) and sensitivity (100%) of the IHC test[94] to estimate the proportion of patients who would go on to receive the FISH test after the IHC test. It has assumed that 100% of patients receiving the FISH test would be diagnosed accurately.

The company base case analysis includes testing for ROS1 rearrangements upfront, meaning that all patients with non-squamous NSCLC would be tested using IHC. All patients with non-squamous NSCLC who test positive with IHC will then be tested with FISH. The company estimates that 18.69% of patients tested with IHC will test positive for ROS1 (1.69% who have ROS1 and 17% [100-83%] who test false positive). Patients who test positive using IHC will

then be tested with FISH, which then will result in 1.69% of patients originally tested testing positive for ROS1. The total estimated costs of up front testing for ROS1 rearrangements in the non-squamous NSCLC population is £4,288 per patient correctly diagnosed (Table 29).

Table 29 Company estimate of upfront ROS1 testing cost (base case)

Item	Cost per test	% of non-squamous patients receiving test	Total cost
IHC test	£50[95]	100%	£50
FISH test	£120[96]	1.69% (% ROS1) + 17% (% false positive IHC) = 18.7%	£120 * 18.7% = £22.44
		Total cost per testing	£50 + £22.44 = £72.44
		Total cost per ROS1+ patient diagnosed	£72.44 / 1.69% = £4,287.92

IHC= ImmunoHistoChemistry; FISH=fluorescence in situ hybridization
Source: adapted from CS, Table 53

Adverse events

In the base case analysis, the company has included resource use and costs in the model due to Grade 3 and Grade 4 AEs occurring in ≥5% of patients in the PROFILE 1007 and PROFILE 1014 trials. These AEs were elevated transaminases, neutropenia, anaemia, leukopenia, thrombocytopenia, and pulmonary embolism. In the scenario analysis using the results of the PROFILE 1001 study, hypophosphatemia was also included. Costs related to AEs are applied as a one-off cost in the first cycle of the model.

The resource use and costs associated with managing each AE used in the company model are given in Table 30.

Table 30 Cost of treating adverse events in company model

Adverse event	Resource required	Source	Unit cost	Total cost	Reference for unit cost
Anaemia	1.7 hospitalisation days	Consistent with TA296 (replaced by TA422) and TA406	£335.57 per day	£570.47	NHS reference costs 2015/16; Iron Deficiency Anaemia with CC Score 0-1 SA04L
Thrombocytopenia	2.0 hospitalisation days		£303.52 per day	£607.04	NHS reference costs 2015/16; Thrombocytopenia with CC Score 0-1 SA12K
Neutropenia	Managed by dose reduction		-	-	-
Leukopenia	Managed by dose reduction (assumption)		-	-	-
Elevated transaminases	Managed by dose reduction		-	-	-
Hypophosphatemia	1 hospitalisation day	Assumption	£287.19 per day	£287.19	NHS reference costs 2015/16; Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N
Pulmonary embolism	1 hospitalisation day	Assumption	£26.34 per day	£26.34	NHS reference costs 2015/16; Weighted average of Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4 (YR23B) and Anticoagulant Services (Total Outpatient Attendances)

CC=complication and comorbidity
Source: adapted from CS, Table 50

5.4.8 Cost effectiveness results

The company's base case estimates of total costs, life years gained (LYG), QALYs and ICERs per QALY gained for the comparison of the cost effectiveness of first-line treatment with crizotinib versus pemetrexed+platinum and subsequent-line treatment with crizotinib versus docetaxel monotherapy are shown in Table 31. The ERG reiterates that the company's base case estimates for first- and subsequent-line treatment with crizotinib use data from patients with ALK+ advanced NSCLC population as a proxy for data from patients with ROS1+ advanced NSCLC patients.

Base case analysis

In the first-line base case analysis, treatment with crizotinib generates incremental LYG (+2.39 years) and more benefits (+1.28 QALYs) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case ICER for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line base case analysis, treatment with crizotinib generates incremental LYG (+1.36 years) and more benefits (+0.93 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

PROFILE 1001 scenario analysis

In the first-line scenario analysis, treatment with crizotinib generates incremental LYG (+3.60 years) and more benefits (+1.95 QALYs) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case ICER for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line scenario analysis, treatment with crizotinib generates incremental LYG (+3.43 years) and more benefits (+1.95 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

Table 31 Company deterministic cost effectiveness results: base case and PROFILE 1001 study scenario analysis (with crizotinib PAS)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line							
Pemetrexed+platinum	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]
Base case: subsequent-line							
Docetaxel	£11,076	1.39	0.71				
Crizotinib	[redacted]	2.75	1.63	[redacted]	1.36	0.93	[redacted]
Scenario analysis (PROFILE 1001): first-line							
Pemetrexed+platinum	£22,570	2.15	1.29				
Crizotinib	[redacted]	5.75	3.25	[redacted]	3.60	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line							
Docetaxel	£12,706	2.32	1.29				
Crizotinib	[redacted]	5.75	3.24	[redacted]	3.43	1.95	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; PAS=patient access scheme; Inc=incremental; QALY=quality adjusted life year
Source: CS, Table 62-65

5.4.9 Sensitivity analyses

Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses to explore the sensitivity of model results to variations in the magnitude of various model inputs. The results from the first- and subsequent-line models in the base case and PROFILE 1001 scenario analysis are presented in Figures 40 to 43 of the CS.

Results from the company first-line base case model show that varying the TTD and OS parametric model coefficients for crizotinib has the biggest effect on the company's cost effectiveness results. Results from the subsequent-line base case model show that varying the HR for OS has the biggest effect on the company's cost effectiveness results, followed by varying the covariates for OS and PFS, and utility values for treatment with docetaxel and BSC.

Results from the company's first-line PROFILE 1001 study scenario analysis show that varying the HR for OS has the biggest effect on the company's cost effectiveness results, followed by varying the covariates for OS, PFS and TTD, and the utility value for BSC. Results from the subsequent-line PROFILE 1001 study scenario analysis model show that, as in the first-line scenario analysis, varying the HR for OS has the biggest effect on the company's cost effectiveness results, followed by varying the covariates for OS, PFS and TTD, and the utility value for BSC.

Probability sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained in the first- and subsequent-line base case and scenario analysis. The PSA was run for 10,000 iterations. Results from the PSA are shown in Table 32.

The probabilistic ICER per QALY gained in the company first-line base case for crizotinib versus pemetrexed+platinum is [redacted] (deterministic ICER = [redacted]. The probabilistic ICER per QALY gained in the company subsequent-line base case for crizotinib versus docetaxel is [redacted] (deterministic ICER = [redacted].

The probabilistic ICER per QALY gained in the company first-line PROFILE 1001 scenario analysis for crizotinib versus pemetrexed+platinum is [redacted] (deterministic ICER = [redacted]. The probabilistic ICER per QALY gained in the company subsequent-line PROFILE 1001 scenario analysis for crizotinib versus docetaxel is [redacted] (deterministic ICER = [redacted].

Table 32 Company probabilistic cost effectiveness results: base case and PROFILE 1001 study scenario analysis (with crizotinib PAS)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line (deterministic ICER = [redacted])							
Pemetrexed+platinum	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]
Base case: subsequent-line (deterministic ICER = [redacted])							
Docetaxel	£11,092	1.40	0.71				
Crizotinib	[redacted]	2.76	1.63	[redacted]	1.37	0.92	[redacted]
Scenario analysis (PROFILE 1001): first-line (deterministic ICER = [redacted])							
Pemetrexed+platinum	£22,913	2.41	1.39				
Crizotinib	[redacted]	5.82	3.34	[redacted]	3.42	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line (deterministic ICER = [redacted])							
Docetaxel	£13,378	2.83	1.47				
Crizotinib	[redacted]	5.82	3.33	[redacted]	2.99	1.86	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life year
Source: CS, Table 66, Table 67, Table 68, Table 69

5.4.10 Model validation and face validity check

The company undertook a number of steps to try to ensure the validity of its models:

- Comparison of outcomes with previous appraisals, and outcomes from trials and published literature
- Clinical expert validation of the results of survival modelling
- Quality control of the economic model by model developers on behalf of the company.

5.5 Detailed critique of the company's economic model

5.5.1 NICE Reference Case checklist

Table 33 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. Data from the ALK+ advanced NSCLC population was used as proxy data for ROS1+ advanced NSCLC patients in the base case analyses
Comparator(s)	Alternative therapies routinely used in the NHS	Partial. Pemetrexed+platinum therapy is the only comparator included in the cost effectiveness analysis for first-line treatment. Docetaxel monotherapy (based on a mix of pemetrexed or docetaxel monotherapy) is the only comparator included in the cost effectiveness analysis for subsequent-line treatment
Perspective costs	NHS and PSS	Partial. PSS costs were not fully considered in the CS
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. Time horizon of 20 years
Synthesis of evidence on outcomes	Systematic review	Yes. The company uses data from the PROFILE 1001 study and PROFILE 1007 and 1014 trials
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standard and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	Yes. Time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes. The company undertook a probabilistic sensitivity analysis

HRQoL=health-related quality of life; NSCLC=non-small cell lung cancer; PSS=Personal Social Services; QALY=quality adjusted life year

5.5.2 Drummond checklist

Table 34 Drummond critical appraisal checklist completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	Evidence of effectiveness based on data from the ALK+ advanced NSCLC population as a proxy for data for ROS1+ advanced NSCLC patients
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partial	Cost of treating some AEs may have been underestimated
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	The company undertook a probabilistic sensitivity analysis in the first- and subsequent-line base case analysis and scenario analysis. The model lacked the facility to change assumptions previously accepted by an Appraisal Committee
Did the presentation and discussion of study results include all issues of concern to users?	Partial	The company did not provide adequate rationale for some of the assumptions made

AEs=adverse events; ERG=Evidence Review Group; NSCLC=non-small cell lung cancer

5.6 ERG critique of the company's economic model

5.6.1 Fundamental issues in the economic analysis

There are several fundamental issues that prevent the ERG from providing a detailed critique of the submitted cost effectiveness models in this ERG report. The ERG's principal concern is that it has been unable to check and verify many of the inputs into the economic models submitted by the company. The ERG has been unable to verify whether the models appropriately address the decision problem set by NICE for two key reasons:

1. The CS relies heavily on the assumptions and modelling approaches used in three previous STAs (TA406, TA422 and TA296). The company has not provided sufficient justification in the CS for the application of these assumptions and approaches in the current appraisal, beyond the fact that they were previously accepted. The ERG considers that assumptions accepted in a previous STA should not be reused unquestioningly as the context in which those assumptions were preferred may have changed. In addition,

the ERG views this appraisal as being independent from previous appraisals of crizotinib in advanced NSCLC – it is neither an update nor a review – and therefore the ERG considers that the CS should be written as a stand-alone document.

For example, the Appraisal Committee in TA422 preferred one of the ERG's scenarios for modelling OS over the company's base case modelling. This scenario has been presented as the base case model for subsequent-line OS in this STA without any justification, other than that it was the preferred approach in TA422. In TA422 the ERG had to explore alternative scenarios for modelling OS because the company did not provide sufficient information about the crossover adjustment that was performed and, without the additional information, the ERG could not fully critique the method. The ERG does not consider it appropriate to simply assume that the method preferred in TA422 is the best possible method for estimating OS for subsequent-line treatment in an ALK+ NSCLC population especially when the Appraisal Committee preferred the previous ERG's method due to the lack of information provided by the company. The company could have provided the missing information in the current CS to allow the ERG to properly review the crossover-adjustment method, but they did not.

2. Even if the ERG were able to verify the assumptions made by the company, lack of model functionality would impede the ERG's ability to investigate the effects of specific key assumptions in the model.

   For example, in the base case analysis, the time-to-event estimates from the PROFILE 1014 trial that were used to model outcomes for first-line treatment were adjusted for baseline characteristics, as the baseline characteristics in the PROFILE 1014 trial were not considered to be representative of patients with ALK+ advanced NSCLC seen in NHS clinical practice. This approach was considered appropriate by the Appraisal Committee in TA406. However, the company has not built into the first-line model the same function for the associated PFS and TTD estimates, which means that the overall effect on the first-line base case ICER per QALY gained of removing the baseline-characteristics adjustment cannot be easily investigated.

The issues the ERG has had with verifying the model have been compounded by the company's submission of updated models during the appraisal process. This update was submitted as a result of a mistake identified by the company which it says has no impact on the ICER per QALY gained. However, the ERG is not able to say whether the company's

changes would impact the ICERs per QALY gained yielded as a result of the ERG's amendments to the model.

The ERG understands that NICE is currently undertaking a consultation process to develop a quality assurance checklist that will be used by ERGs to validate company models. The ERG agrees that quality assurance is an important aspect of the STA process and is necessary to allow Appraisal Committees to make informed decisions. The appraisal of crizotinib for ROS1+ advanced NSCLC includes two company models that cannot be fully quality assured for the reasons outlined above. This also means that the ERG cannot be confident that the results of any additional exploratory analyses are reliable. As a result, the critique and information provided in this ERG report is limited and the ERG is unable to provide ERG preferred base case ICERs per QALY gained.

5.6.2 Key company modelling assumptions

The company base case analysis is founded on the assumption that the outcomes of treatment with crizotinib in an ALK+ advanced NSCLC population are an appropriate proxy for the outcomes of treatment with crizotinib in a ROS1+ advanced NSCLC population. This assumption is discussed in Section 2.1. The company has included a scenario analysis that uses data from a ROS1+ advanced NSCLC population in the single-arm PROFILE 1001 study. The company claims that the results of this scenario analysis help to reduce uncertainty in decision making by demonstrating that crizotinib is also cost effective when the limited data available are used directly to model treatment for the ROS1+ advanced NSCLC population. The ERG has therefore examined the company's PROFILE 1001 study scenario analysis as well as the base case model in order to test the robustness of the company's cost effectiveness results.

The company has also assumed that 'pooled chemotherapy' is a suitable proxy for treatment with docetaxel in the subsequent-line model. This assumption has not been investigated in the cost effectiveness analysis by the ERG.

5.6.3 Major modelling issues

First- and subsequent-line treatments with crizotinib in an ALK+ advanced NSCLC population have been previously appraised by NICE (TA406, TA422 and TA296); therefore, much of the data and modelling included in the company base case analysis has been discussed in previous STAs (Table 35). The ERG has prioritised the critique of newly available data in this appraisal (updated OS from the PROFILE 1014 trial and data from the PROFILE 1001 study). However, this does not imply that the ERG is satisfied that inputs and approaches not covered in this critique are appropriate and properly implemented in the model.

Table 35 Previous appraisals featuring selected model inputs used in this STA

Model	Outcome	Previous appraisal
First-line base case	OS	Updated from TA406
	PFS	TA406
	TTD	TA406
	Utility	TA406
Subsequent-line base case	OS	TA422
	PFS	TA296 and TA422
	TTD	TA422
	Utility	TA406 and TA422
PROFILE 1001 scenario analysis	OS	New
	PFS	New
	TTD	New
	Utility	TA406 and TA422

PFS=progression-free survival; OS=overall survival; TTD=time-to-treatment discontinuation

Post-progression survival – first-line base case

The company's first-line base case model yields a substantial PPS benefit for treatment with crizotinib versus pemetrexed+platinum. Comparing PPS for treatment with crizotinib (29.6 months) and pemetrexed+platinum (10.4 months) results in a 19.2 month PPS gain for patients treated with crizotinib. This PPS gain is compared to a PFS gain of 9.5 months for treatment with crizotinib (16.8 months) versus pemetrexed+platinum (7.3 months). This means that the extra survival gained beyond progression constitutes 67% of total OS gain for treatment with crizotinib (Table 36). This suggests that the treatment effect is better after progression (and after patients have stopped treatment) than before progression and therefore that OS treatment effect is better than PFS treatment effect. The ERG does not consider this modelled outcome to be supported by the evidence from the trial nor by the literature.

Table 36 First-line base case: overall survival breakdown by health state

Health state	Crizotinib (months)	Pemetrexed+platinum (months)	Increment (months)	Increment
Pre-progression	16.8	7.3	9.5	33.3%
Post-progression	29.6	10.4	19.2	66.7%
Total	**46.4**	**17.7**	**28.7**	**100%**

Source: company model

There is evidence to suggest that it is plausible to assume (in the absence of robust evidence to the contrary) that the OS treatment effect might be expected to be similar to the PFS treatment effect in advanced NSCLC trials. As noted in section 4.3.2, the ERG in TA422 referred to an analysis by the FDA[78] which explored trial-level and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib). The results of this analysis suggest that it is not unreasonable to assume similarity between PFS and OS treatment effects in the absence of other evidence.

The ERG acknowledges that there may be some PPS benefit attributable to treatment with crizotinib, not least because a substantial proportion of patients in the PROFILE 1014 trial continued to receive crizotinib after progression due to 'symptomatic benefit' (mean length of post-progression treatment in the model is 1.4 months). However, given that the magnitude of OS gain is unknown in the PROFILE 1014 trial due to trial immaturity and patient crossover, the ERG considers it questionable to model a PPS gain that is substantially larger than PFS gain (which translates into a greater OS treatment effect than PFS treatment effect).

Post-progression survival – subsequent-line base case

The company's subsequent-line base case model also yields a substantial PPS benefit for patients treated with crizotinib, although the proportion of OS gain attributable to PPS gain is smaller in the subsequent-line base case model than in the first-line model. Post-progression survival in the subsequent-line model is 22.5 months for treatment with crizotinib versus 11.8 months for docetaxel. This means that patients in the subsequent-line setting who are treated with crizotinib are expected to survive twice as long after progression when compared to patients treated with docetaxel. Post-progression survival gain is estimated in the company model to be twice as long as PFS gain, meaning that 65% of OS gain is attributable in the model to survival gained after progression (

Table 37). Again, this implies that the treatment effect is better after progression than before progression (and that OS treatment effect is greater than PFS treatment effect).

Table 37 Subsequent-line base case: overall survival breakdown by health state

Health state	Crizotinib (months)	Docetaxel (months)	Increment (months)	Increment
Pre-progression	10.6	4.9	5.7	34.8%
Post-progression	22.5	11.8	10.6	65.2%
Total	**33.0**	**16.7**	**16.3**	**100.0%**

Source: company model

The ERG again acknowledges that some patients are treated with crizotinib beyond progression in the subsequent-line setting and that this may indicate some prolonged benefit beyond progression. The company models treatment beyond progression in the subsequent-line base case to be 5.4 months. Clinical advice to the ERG is that it is plausible that patients at this stage in their treatment might receive 2 to 3 months of treatment with crizotinib beyond progression because there are few other treatment options available; however, an average of 5.4 months of treatment beyond progression is unlikely.

PROFILE 1001 study scenario analysis

In the CS, the company has mainly used data from a different population (ALK+ advanced NSCLC) to the population of interest because the data available for treatment with crizotinib in a ROS1+ advanced NSCLC population are limited. The company concluded that it was preferable to use data from larger RCT trials, albeit with immature OS, in an ALK+ advanced NSCLC population (PROFILE 1014 and PROFILE 1007 trials) than to use data from a small, immature, single-arm study in a ROS1+ advanced NSCLC population (PROFILE 1001 study). The ERG acknowledges that, for modelling purposes, more data are better than less. However, it also notes that the uncertainty inherent in the model as a result of the use of a proxy population (the extent to which the populations are similar is unknown) cannot be quantified or otherwise described, whereas uncertainty originating from poor quality data is more straightforward to articulate.

Since there were very few patients treated in the first-line setting in the PROFILE 1001 study, the company decided it was appropriate to pool first- and subsequent-line results and use the same 'all-lines' data to model first-and subsequent-line treatment in its PROFILE 1001 scenario analysis. The ERG agrees that the pooling of data seems appropriate given there were only seven patients in the first-line setting; however, the ERG notes that this approach adds to the uncertainty of any results based on data from the PROFILE 1001 study.

The company has attempted to fit parametric models to the 'all-lines' time-to-event data to estimate OS, PFS and TTD in the ROS1+ advanced NSCLC population, but concedes that

none of the fitted models have good face validity as is shown by the OS data depicted in Figure 11. One reason for the lack of visual fit of the parametric models is the immaturity of the trial data. Almost 70% of OS data from the PROFILE 1001 study is censored; thus the censored information has a much greater influence on the calculation of curve parameters than does the information about events that have been observed.

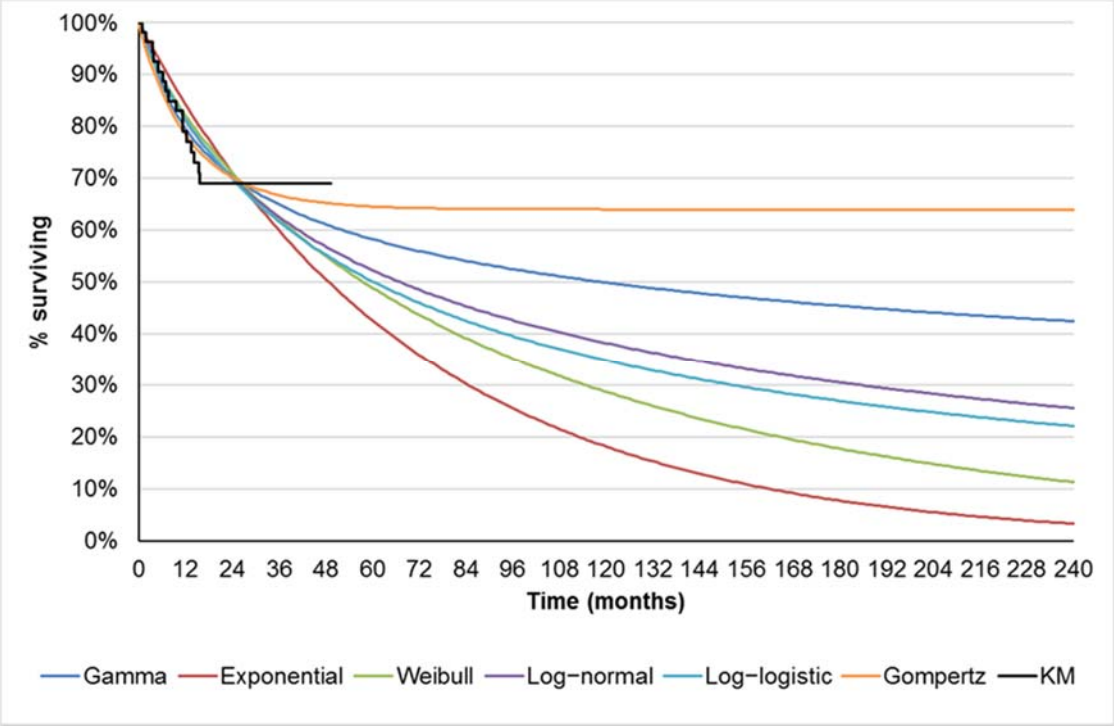

Figure 11 Company parametric curve fits to OS data from PROFILE 1001

Source: CS, Figure 24

As well as lacking face validity, the company's modelling of treatment with crizotinib from the PROFILE 1001 study results in very long survival projections in comparison to the base case analysis. Mean OS is 5.8 years in the company's PROFILE 1001 study scenario for treatment with crizotinib versus 3.9 years in the base case analysis. Mean PFS is estimated to be 2.9 years in the company's scenario versus 1.2 years in the base case analysis.

The company has created comparator time-to-event estimates by using HRs from the PROFILE 1014 and PROFILE 1007 trials. The OS HRs are based on RPSFTM crossover adjustments carried out by the company, which are critiqued in Section 4 of this report. The ERG does not consider these HRs to be appropriate, given that the modelling of crossover adjusted OS in the base case analysis results in implausible PPS estimates.

Progression-free utility values: first-line treatment

Although the EQ-5D scores from the PROFILE 1014 trial appear to show greater HRQoL benefit for treatment with crizotinib than for treatment with pemetrexed+platinum, the ERG is

concerned that the magnitude of that benefit is uncertain. This is due to the lack of long-term EQ-5D data for treatment with pemetrexed+platinum, the lack of a statistically significant difference between mean EQ-5D estimates for those cycles where data have been recorded and the potential influence of the open-label nature of the trial on patients' responses to the EQ-5D. The ERG has explored a range of cost effectiveness estimates bounded by the assumption of no HRQoL benefit for treatment with crizotinib. The ERG has also explored the impact of using a PFS utility value of 0.75 for treatment with pemetrexed+platinum. These analyses do not resolve the company's inconsistent use of data i.e., use of adjusted baseline characteristics for the time-to-event estimates and use of unadjusted utility values.

The ERG also notes that, although baseline EQ-5D values are similar in the two arms of the PROFILE 1014 trial, there is a substantial increase in the mean utility value (from 0.72 to 0.81) reported between baseline and cycle 2 in the crizotinib arm. This increase does not occur in the pemetrexed+platinum arm. The ERG is concerned that this sudden increase in utility in one arm and not the other may be explained to some extent by the open-label nature of the trial; that is, patients who know they are receiving the intervention may report feeling better than those receiving the comparator treatment. This concern is supported by the observation that cycle 2 is the only cycle in which there is a statistically significant difference ($p<0.05$) between mean EQ-5D values recorded in each arm of the PROFILE 1014 trial.

It is noted in the FAD for TA406 that the Appraisal Committee preferred the company's revised PFS utility estimate (0.75) for treatment with pemetrexed+platinum in the first-line setting, as it considered the 0.72 value used in the company's base case to be too low. The company in this STA has not explored the impact of using a PFS utility of 0.75 for treatment with pemetrexed+platinum in the first-line setting.

The ERG is also concerned that these utility values pertain to the unadjusted PROFILE 1014 trial population, whereas, in the first-line base case model, the time-to-event estimates have been adjusted to reflect the population observed in NHS clinical practice.

5.6.4 Minor modelling issues

Cost of pulmonary embolism

The company has estimated the cost of treating pulmonary embolism to be £26.34; this cost has likely been underestimated, as Hospital Episode Statistics[97] report mean time in hospital for pulmonary embolism to be 6 days. Also, no treatment costs are included in this estimate. NICE guidance on treating thromboembolism[98] indicates that patients should be initially treated for at least 5 days with a low molecular weight heparin (LMWH) and that a LMWH should be given for 6 months if a patient with active cancer develops a pulmonary embolism.

The impact of this underestimated cost on the size of the ICER per QALY gained is small, so the ERG has not amended the cost in the model.

Testing for ROS1 rearrangements

The company has assumed upfront testing in the base case analysis for both the first- and subsequent-line models. Clinical advice to the ERG is that only a small percentage of patients who are eligible to receive crizotinib as a subsequent-line treatment would not have already been tested for ALK and EGFR mutations earlier in their treatment pathway. The ERG therefore considers that it would be more appropriate to use the cost of sequential testing (ROS1 testing in EGFR- and ALK-negative population) in the subsequent-line setting. This has a small effect on the ICER per QALY gained.

The ERG notes that NHS laboratory services may offer a discount when testing for more than one mutation at the same time. The All Wales Genetic Laboratory list price to carry out FISH analysis (ALK) for lung cancer is £120 and the price for EGFR testing is £175 when undertaken in isolation; however, the cost to carry out ALK and EGFR tests at the same time is £250, which represents a 15% discount on the price of carrying out each of these tests individually. Therefore, it is plausible to assume that the upfront cost of carrying out FISH testing for ROS1 alongside other tests would be approximately £102 (£120 * 85%). This has a small effect on the ICER per QALY gained.

The final scope issued by NICE required that the company conduct a sensitivity analysis without the cost of the ROS1 diagnostic test. This sensitivity analysis has not been provided in the CS. However, the functionality exists in the company model to remove the cost of ROS1 testing. The ERG has also investigated the impact of removing the cost of ROS1 testing, which reduces the ICER per QALY gained in the first–line setting by [redacted] to [redacted] and reduces the ICER per QALY gained in the subsequent–line setting by [redacted] to [redacted].

5.6.5 ERG exploratory analyses

Overall survival: first-line treatment

As previously discussed, PPS gain in the company first-line base case model is implausibly large. This can be attributed to inappropriate estimates of either PFS or OS (or both). Given that OS in the PROFILE 1014 trial is both immature and confounded by crossover, whereas PFS is much more mature and should not be affected by crossover, the ERG has focused its exploratory analysis on the remodelling of OS.

The ERG notes that the company's RPSFTM method of adjusting for the impact of treatment switching is flawed and that, as such, the company's crossover-adjusted HR is unreliable. The crossover-adjusted HR is not used to model OS in the first-line base case analysis, but the data that were used to calculate that HR are used as the basis of parametric curve estimates. Hence, the company's modelling of OS in the first-line model is also flawed.

Without access to the individual patient data from the PROFILE 1014 trial, the ERG is not able to investigate whether there are more appropriate ways to adjust the data for crossover. Instead, the ERG has investigated two scenarios for OS to try to establish a range of plausible ICERs per QALY gained. It is important to note that these scenarios do not represent absolute bounds for the upper and lower limits of OS gain for crizotinib – OS gain could, in reality, be greater or less than is presented in the ERG's scenarios. However, the ERG considers the two scenarios to be useful in establishing a logical range of possible estimates of OS gain in the absence of robust data.

The first scenario is that the pre-progression treatment effect for treatment with crizotinib carries on after progression, so that the benefit patients experience does not diminish with time i.e., the PFS treatment effect is the same as the PPS treatment effect. As noted in Section 5.6.3, there is some evidence to suggest that this is a plausible assumption. This assumption is implemented in the model by applying the PFS HR to the modelled crizotinib OS estimates. The ERG notes that the PH assumption does not hold for PFS in the PROFILE 1014 trial, so the results of this scenario should be treated with caution.

The second scenario assumes that there is no benefit to treatment with crizotinib after progression, or that the treatment effect falls to zero on progression i.e., PPS is equal for both treatments and any gain in OS is attributable only to better survival before progression. This scenario is implemented in the model by adjusting the exponential OS curve for treatment with pemetrexed so that PPS is equal to PPS for treatment with crizotinib.

In both ERG scenarios (Figure 12), the OS estimates for treatment with crizotinib used to estimate OS for treatment with pemetrexed are unadjusted for crossover. The ERG prefers to accept the level of crossover (19.2%) rather than use the company's RPSFTM-adjusted curve, as the company's RPSFTM-adjusted curve for treatment with crizotinib in the first-line model estimates better survival for crizotinib than the unadjusted curve. The ERG has not seen the details of the company's crossover methods and therefore cannot comment on the approach.

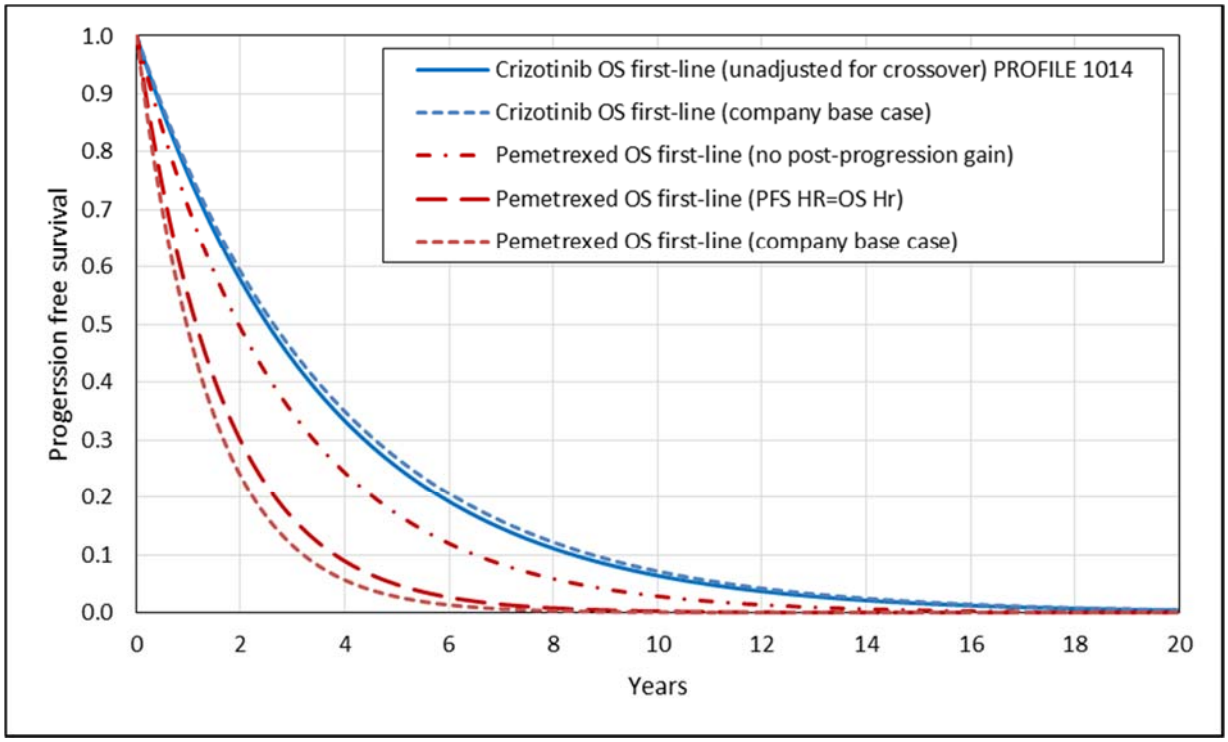

Figure 12 First-line OS: company base case and ERG scenarios (PROFILE 1014)

Source: company model; ERG calculations

Using the company's unadjusted modelling of OS in the first-line model and applying the PFS HR from the PROFILE 1014 trial to estimate OS for treatment with pemetrexed+platinum, the company's base case ICER per QALY gained increases by [redacted] to [redacted]. The company's base case ICER per QALY gained increases by [redacted] to [redacted] when equal PPS is assumed for both treatments.

Table 38 Cost effectiveness results of ERG exploratory OS modelling (first-line base case)

Modelling approach	Incremental cost	Incremental OS (months)	Incremental QALYs	ICER per QALY gained
Company base case (OS=RPSFT Wilcoxon)	[redacted]	28.70	1.28	[redacted]
Company model (OS=unadjusted for crossover)*	[redacted]	10.98	0.67	[redacted]

Scenario 1: OS treatment effect = PFS HR†	[redacted]	23.65	1.11	[redacted]
Scenario 2: OS treatment effect = no PPS gain†	[redacted]	9.55	0.62	[redacted]

OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year
Source: company model; ERG calculations
* this scenario removes the RPSFTM adjustment from both the crizotinib and pemetrexed+platinum OS estimates, which decreases incremental OS gain for crizotinib as a greater proportion of patients in the PROFILE 1014 trial switched from pemetrexed+platinum to crizotinib than from crizotinib to pemetrexed+platinum.
† these scenarios apply a treatment effect to crizotinib OS estimates (unadjusted for crossover) to estimate OS for pemetrexed+platinum.

Overall survival: subsequent-line treatment

The company has applied the PFS HR from the PROFILE 1007 trial to the RPSFTM-adjusted docetaxel OS curve in the subsequent-line base case analysis. The ERG is concerned that applying a HR to OS data that has already been adjusted for crossover somewhat defeats the point of trying to find a method that avoids the pitfalls of the RPSFTM approach.

The ERG has instead calculated the two OS scenarios (OS treatment effect=PFS HR and OS treatment effect=no PPS gain) as before but based on an exponential curve for treatment with crizotinib calculated from unadjusted OS estimates from the PROFILE 1007 trial (Figure 13). There is more substantial crossover from crizotinib to chemotherapy in the PROFILE 1007 trial than in the PROFILE 1014 trial; however, since patients are assumed to move to BSC once they stop treatment in the subsequent-line model, not adjusting for patients who receive further active treatment is an optimistic assumption for treatment with crizotinib.

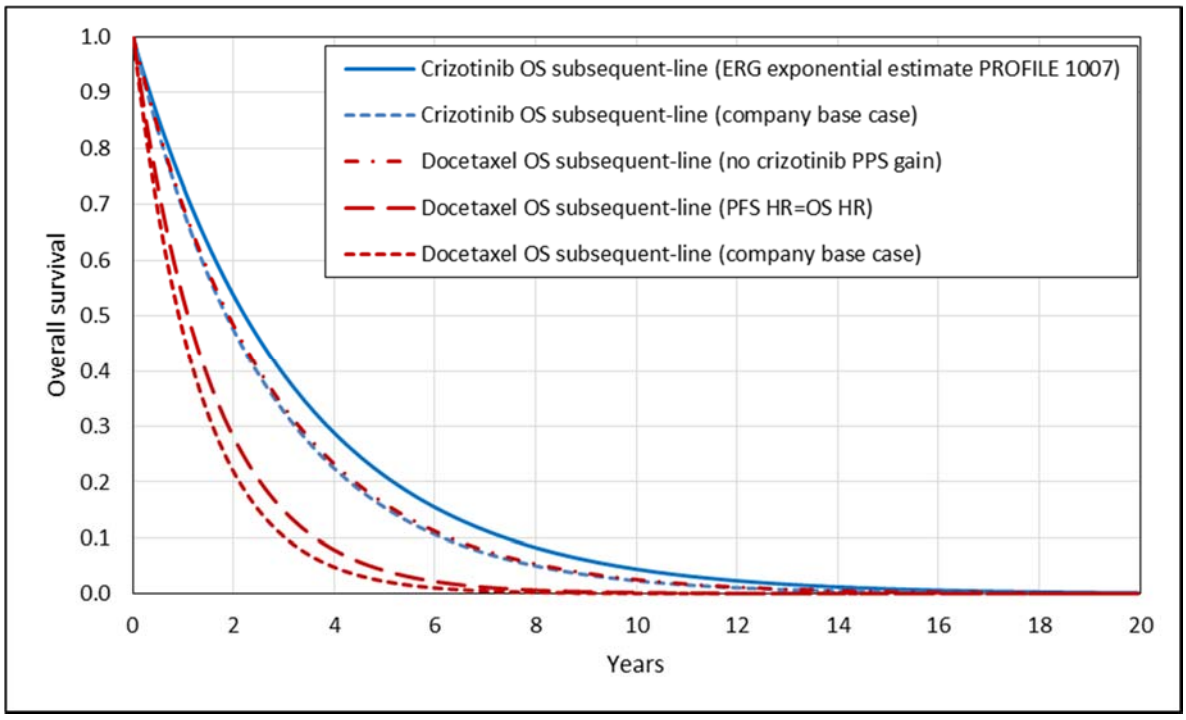

Figure 13 Subsequent-line OS: company base case and ERG scenarios (PROFILE 1007)

Source: company model; ERG calculations

Using unadjusted modelling of OS in the subsequent-line model and applying the PFS HR from the PROFILE 1007 trial to estimate OS for treatment with docetaxel, the base case ICER per QALY gained decreases by [redacted] to [redacted]. The base case ICER per QALY gained increases by [redacted] to [redacted] when equal PPS is assumed for both treatments.

Table 39 Cost effectiveness results of ERG exploratory OS modelling (subsequent-line base case)

Modelling approach	Incremental cost	Incremental OS (months)	Incremental QALYs	ICER per QALY gained
Company base case (OS=PFS HR based on RPSFT docetaxel estimate)	[redacted]	1.36	0.93	[redacted]
Scenario 1: OS treatment effect=PFS HR applied to unadjusted crizotinib	[redacted]	1.64	1.03	[redacted]
Scenario 2: OS treatment effect=no PPS gain	[redacted]	0.48	0.55	[redacted]

OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year
Source: company model; ERG calculations

PROFILE 1001 study scenario

The ERG does not consider the data from the PROFILE 1001 study to be sufficiently robust to provide reliable estimates of time-to-event outcomes for treatment with crizotinib in a ROS1+ advanced NSCLC population. The lack of a comparator arm in the PROFILE 1001 study is a particular concern, as it prevents robust conclusions about the comparative effectiveness of crizotinib in this population being drawn. Even if it were concluded that treatment with crizotinib results in different outcomes in a ROS1+ advanced NSCLC population versus an ALK+ advanced NSCLC population, it remains unknown whether patients receiving pemetrexed+platinum, docetaxel or any other treatment would also respond differently depending on whether they test positive for ROS1 or ALK rearrangements.

However, the ERG has remodelled the data from the PROFILE 1001 study in order to provide an alternative to the approach employed to by the company in its PROFILE 1001 scenario and investigate the sensitivity of the model to alternative assumptions. The ERG has explored the impact of different assumptions of treatment effect applied to the company's modelling of OS for treatment with crizotinib. It has also investigated the impact of modelling OS, PFS and TTD to improve face validity and to reduce mean OS.

Treatment effect

The company uses the RPSFTM (Wilcoxon)-adjusted HR from the PROFILE 1014 trial to estimate the treatment effect for OS for the ROS1+ advanced NSCLC population in the first-

line setting. The ERG has instead applied the same methods it applied to the updated OS data from the PROFILE 1014 trial: applying the PFS HR from the PROFILE 1014 trial to assume equal PPS for each treatment.

Applying the PFS HR from the PROFILE 1014 trial to the company's modelled OS estimates for treatment with crizotinib from the PROFILE 1001 study increases the ICER per QALY gained by [redacted] to [redacted] compared to the company's PROFILE 1001 scenario. Adjusting the OS curve for treatment with pemetrexed so that pemetrexed PPS equals crizotinib PPS increases the ICER per QALY gained by [redacted] to [redacted] compared to the company's PROFILE 1001 scenario.

The company has already used the PFS HR from the PROFILE 1014 trial to estimate PFS treatment effect for the PROFILE 1001 scenario, so the ERG has made no change to the modelling of PFS. The ERG has also made no change to the modelling of TTD, since the data are almost complete.

The company uses the PFS HR from the PROFILE 1007 trial in its PROFILE 1001 scenario for subsequent-line treatment. This yields an ICER per QALY gained of [redacted]. The ERG has also investigated the effect of assuming equal PPS for treatment with docetaxel and crizotinib, which represents the assumption that treatment effect falls to zero immediately on progression. Adjusting the OS curve for treatment with docetaxel so that docetaxel PPS equals crizotinib PPS increases the ICER per QALY gained by [redacted] to [redacted] compared to the company's PROFILE 1001 scenario.

The ERG has made no change to the modelling of PFS or TTD in the subsequent-line PROFILE 1001 scenario.

Crizotinib time-to-event estimates

The ERG has investigated the impact of remodelling OS, PFS and TTD from the PROFILE 1001 study by using 'all-lines' K-M data directly as far as possible and then appending an exponential tail to project out to the time horizon (Figure 14). Details of this method are given in Appendix 10.5. This method relies on the assumption that survival has settled into a long-term trend that is apparent in the data. However, the ERG cautions that, given the small size of the study and the immaturity of the data in the PROFILE 1001 study, this assumption is unlikely to hold for OS in particular. The cost effectiveness results based on any modelling of time-to-event data from the PROFILE 1001 study are subject to substantial uncertainty.

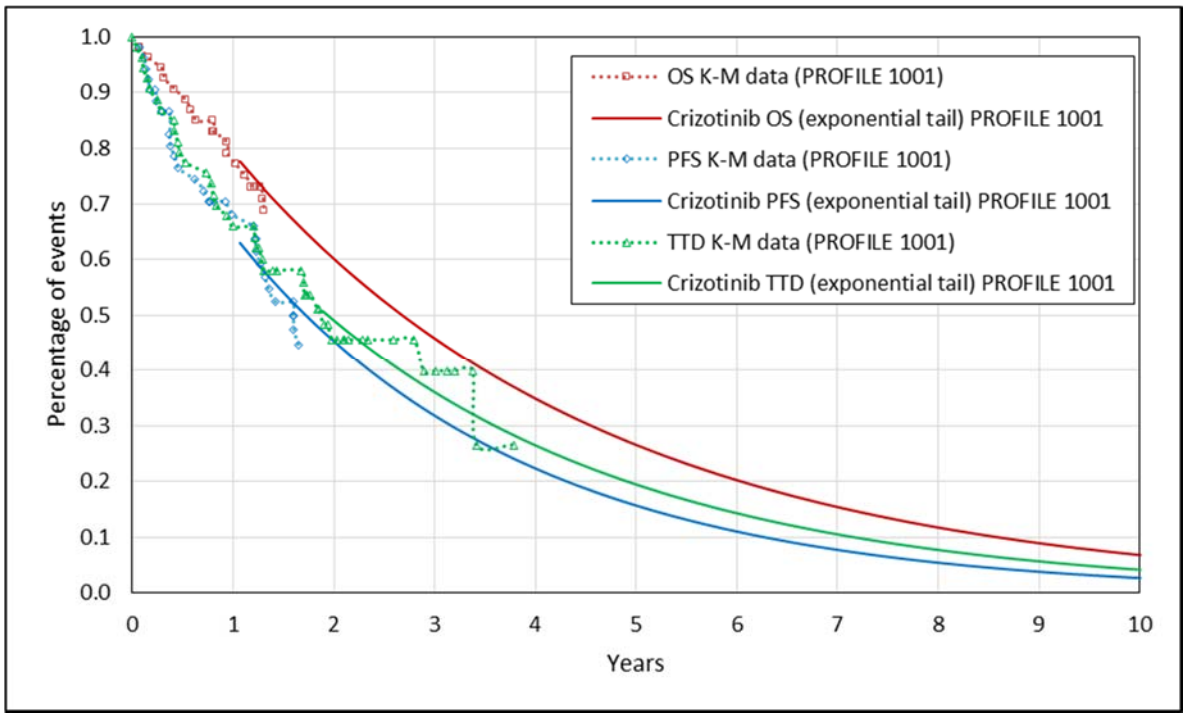

Figure 14 PROFILE 1001 'all-lines' ERG model: K-M data+exponential tail

Source: clarification B1; ERG calculations

Mean OS for treatment with crizotinib (first- and subsequent-line) is reduced from 69 months (5.8 years) in the company PROFILE 1001 scenario to 45.7 months (3.8 years) in the ERG model (Figure 15). Mean PFS for treatment with crizotinib (first- and subsequent-line) is reduced from 34.3 months (2.9 years) in the company scenario to 31.8 months (2.7 years) in the ERG model. Mean TTD for treatment with crizotinib (first- and subsequent-line) increases slightly from 35.7 months to 36.9 months, so mean time on treatment after progression is increased from 1.9 months to 5.1 months.

The ERG has estimated the treatment effect for OS and PFS in this scenario by applying the PFS HR from the 1014 trial in the first-line (Figure 15, Figure 16) and by applying the PFS HR from the 1007 trial in the subsequent-line (Figure 17 and Figure 18) to the 'all-lines' K-M data+exponential crizotinib model. The ERG has not amended TTD for pemetrexed+platinum and docetaxel in this scenario.

Mean OS gain for treatment with crizotinib versus pemetrexed in the first-line setting is reduced to 23.8 months (2.0 years) in the ERG PROFILE 1001 study scenario versus 43 months (3.6 years) in the company scenario. Mean PFS gain is reduced slightly from 18.2 months (1.5 years) in the company PROFILE 1001 study scenario to 17.4 months in the ERG scenario.

Compared to the company's PROFILE 1001 scenario first-line ICER, applying the ERG's remodelled PROFILE 1001 study data in the first-line setting increases the ICER per QALY gained by [redacted] to [redacted].

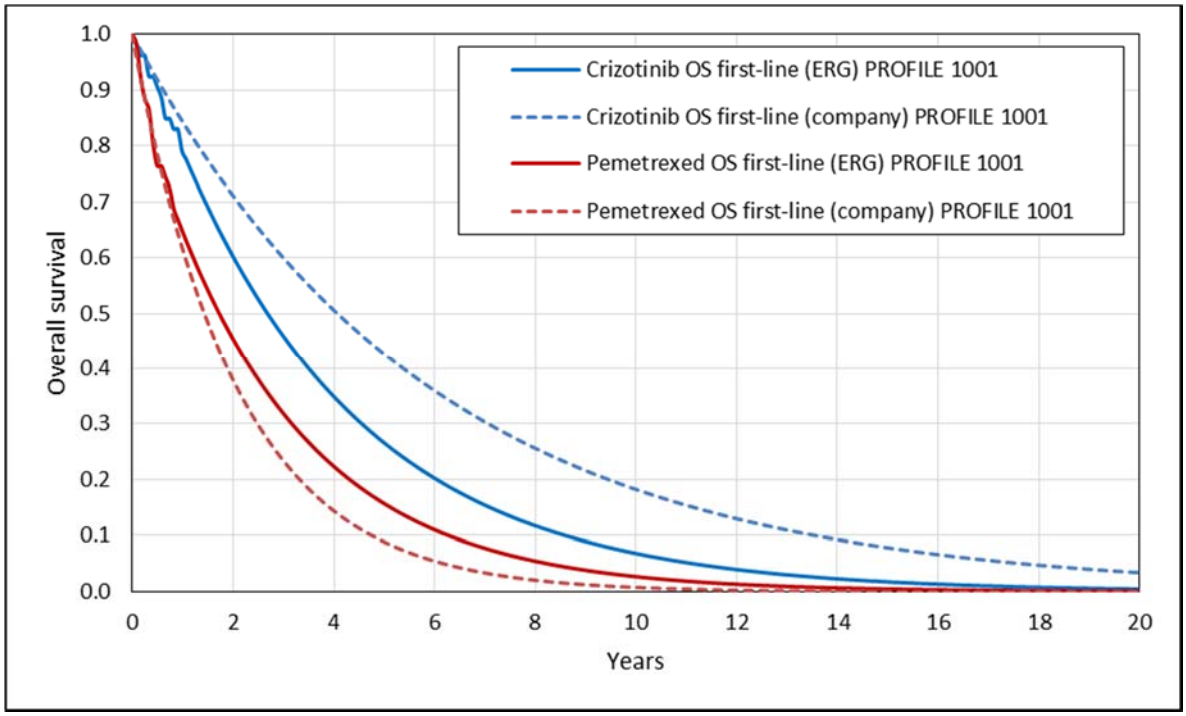

Figure 15 First-line OS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

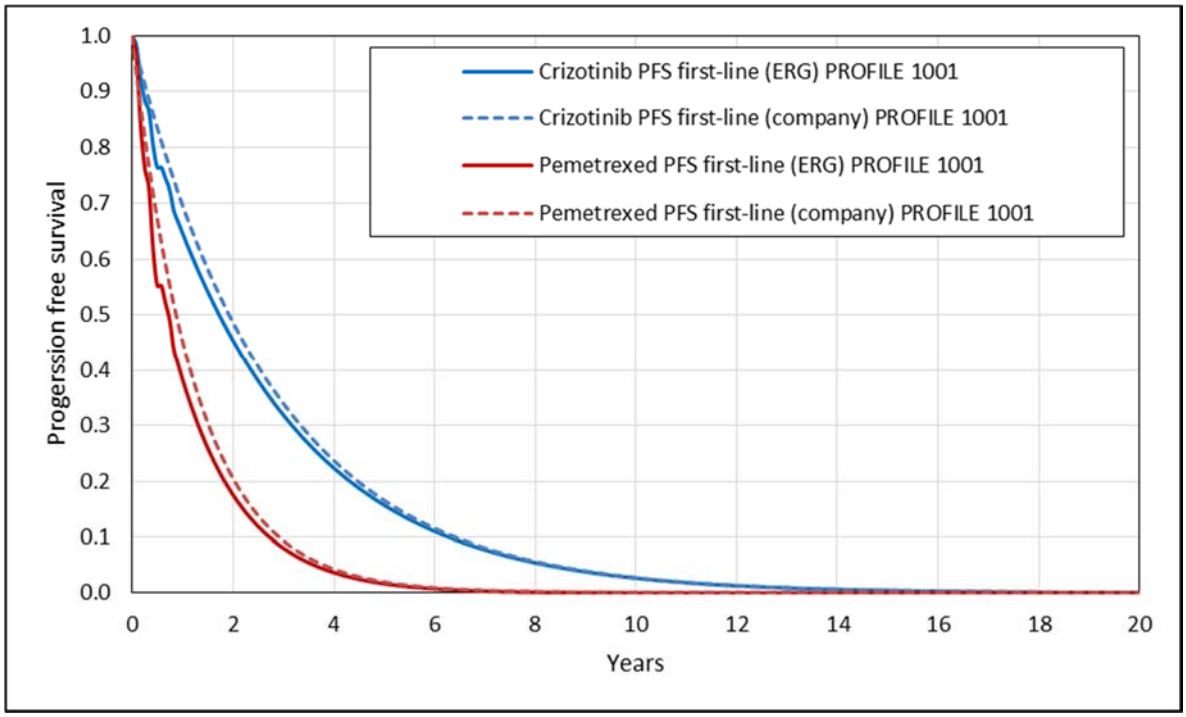

Figure 16 First-line PFS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

Mean OS gain for treatment with crizotinib versus docetaxel in the subsequent-line is reduced to 22.3 months (1.9 years) in the ERG PROFILE 1001 study scenario versus 41.1 months (3.4 years) in the company scenario. Mean PFS gain is reduced slightly from 17.1 months (1.4 years) in the company PROFILE 1001 study scenario to 16.3 months in the ERG scenario.

Compared to the company's PROFILE 1001 scenario subsequent-line ICER, applying the ERG's remodelled PROFILE 1001 study data in the subsequent-line model increases the ICER per QALY gained by [redacted] to [redacted].

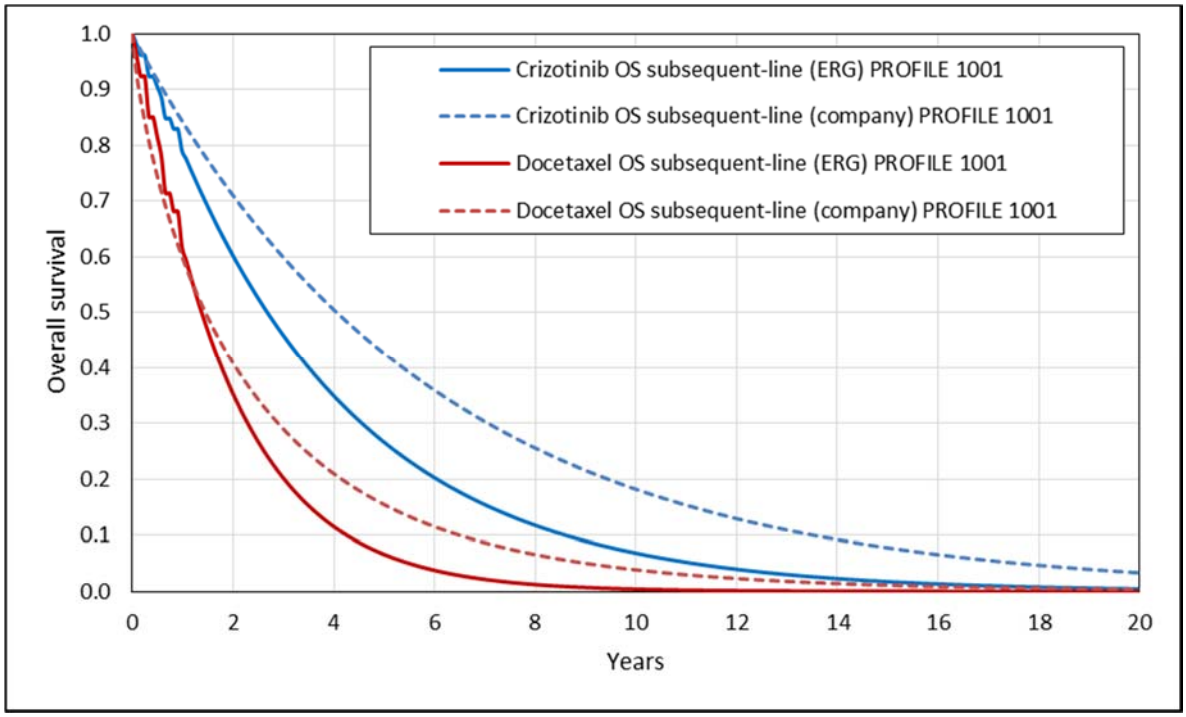

Figure 17 Subsequent-line OS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

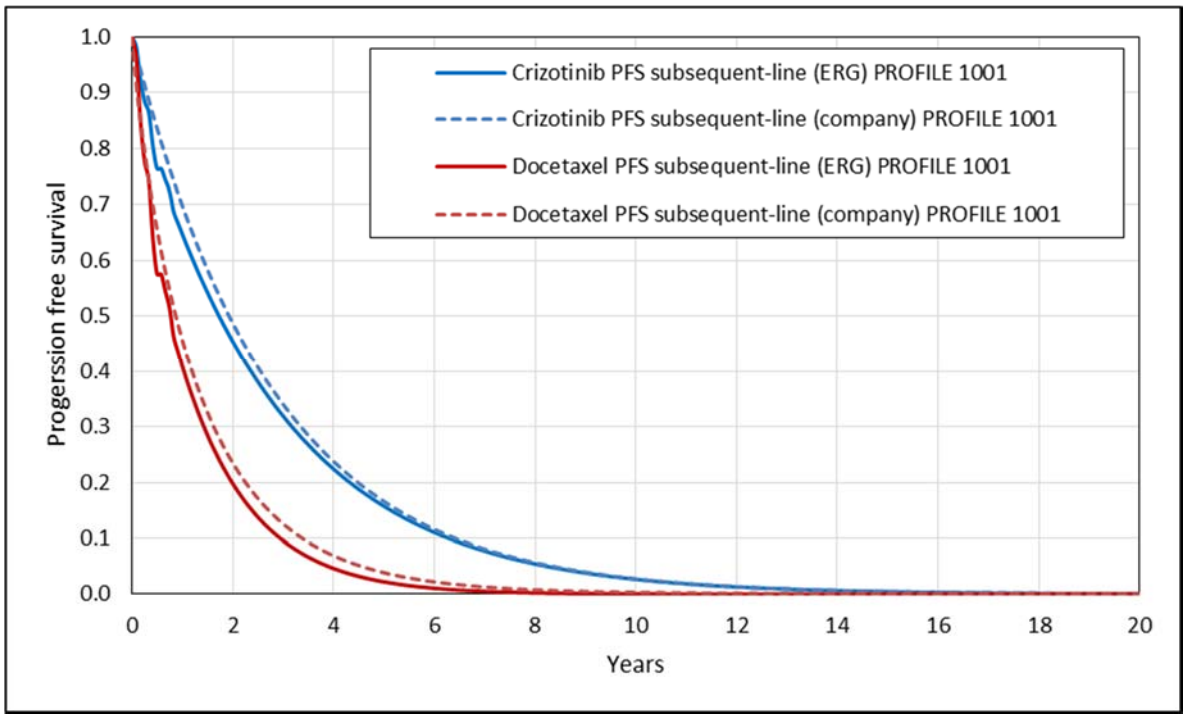

Figure 18 Subsequent-line PFS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

Progression-free utility values: first-line treatment

Given the lack of long-term EQ-5D data for treatment with pemetrexed+platinum, the lack of a statistically significant difference between mean EQ-5D estimates for those cycles where data have been recorded and the potential influence of the open-label nature of the trial on patients' responses to the EQ-5D, the ERG has explored the impact of assuming that there is no difference in PFS utility values between treatment with crizotinib and treatment with pemetrexed+platinum. The ERG has also explored the impact of using a PFS utility value of 0.75 for treatment with pemetrexed+platinum. These analyses do not resolve the company's inconsistent use of data i.e., use of adjusted baseline characteristics for the time-to-event estimates and use of unadjusted utility values.

If the PFS utility in both arms is assumed to be the same as the base case crizotinib PFS utility (0.81), the first-line base case ICER increases by [redacted] to [redacted] per QALY gained. If the PFS utility in both arms is assumed to be the same as the base case pemetrexed+platinum PFS utility (0.72), the first-line base case ICER increases by [redacted] to [redacted] per QALY gained. If the PFS utility for treatment with pemetrexed+platinum is assumed to be 0.75, the first-line base case ICER increases by [redacted] to [redacted] per QALY gained.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has made the following revisions to the company base case ICERs for treatment with crizotinib versus pemetrexed+platinum in the first-line setting and treatment with crizotinib versus docetaxel in the subsequent-line setting:

First-line treatment

Base case survival estimates:

- ERG OS treatment effect: use PFS HR from PROFILE 1014 trial [R1a]
- ERG OS treatment effect: no PPS gain [R1b]

PROFILE 1001 scenario survival estimates:

- ERG OS treatment effect: use PFS HR from PROFILE 1014 [R2a]
- ERG OS treatment effect: no PPS gain [R2b]
- ERG remodel crizotinib time-to-event: K-M data+exponential [R3]

PFS utility values:

- ERG PFS utility: crizotinib utility (0.81) for both treatments [R7a]
- ERG PFS utility: pemetrexed utility (0.72) for both treatments [R7b]
- ERG PFS utility: pemetrexed utility = 0.75 [R7c]

Subsequent-line treatment

Base case survival estimates:

- ERG OS treatment effect: apply PFS HR from PROFILE 1007 to unadjusted crizotinib estimate) [R4a]
- ERG OS treatment effect: no PPS gain [R4b]

PROFILE 1001 scenario survival estimates:

- ERG OS treatment effect: no PPS gain [R5]
- ERG remodel crizotinib time-to-event: K-M data+exponential [R6]

The ERG notes that the company's subsequent-line PROFILE 1001 analysis applies the PFS HR from the PROFILE 1007 trial to modelled crizotinib OS from the PROFILE 1001 study. The ERG has therefore not modelled the application of the PFS HR from the PROFILE 1007 trial as an exploratory scenario in the subsequent-line PROFILE 1001 analysis.

In both the first- and subsequent-line models, the ERG has only included changes that have a substantial impact on the size of the estimated ICER per QALY gained and has not included the effects of minor issues (Section 5.6.4).

In both the first- and subsequent-line models, the ERG has only included changes that have a substantial impact on the size of the estimated ICER per QALY gained and has not included the effects of minor issues (Section 5.6.4).

A summary of the individual effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with crizotinib versus pemetrexed+platinum in the first-line setting is shown in **Error! Reference source not found.**. A summary of the individual effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with crizotinib versus docetaxel in the subsequent-line setting is given in Table 42.

A summary of the individual effects of the ERG's model amendments on the company's PROFILE 1001 cost effectiveness results for the comparison of treatment with crizotinib versus pemetrexed+platinum in the first-line setting is given in Table 43. A summary of the individual effects of the ERG's model amendments on the company's PROFILE 1001 cost effectiveness results for the comparison of treatment with crizotinib versus docetaxel in the subsequent-line setting is shown in Table 45.

Given the fundamental uncertainties in this appraisal (Section 5.6.1), the ERG is not able to provide preferred base case ICERs per QALY gained. The ERG has instead provided a number of scenario combinations that explore the sensitivity of the company's models to alternative methods of estimating OS and utility values for PFS. These scenarios are shown in **Error! Reference source not found.** and Table 44 for the first-line model.

Table 40 Base case cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG revisions

ERG revisions	Crizotinib			Pemetrexed			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company updated base case (from 24 November 2017)	[redacted]	3.86	2.13	£23,267	1.47	0.84	[redacted]	2.39	1.28	[redacted]
R1a) OS treatment effect: use PFS HR from 1014	[redacted]	3.70	2.06	£23,777	1.73	0.96	[redacted]	1.97	1.11	[redacted]
R1b) OS treatment effect: no PPS gain	[redacted]	3.70	2.06	£25,848	2.91	1.44	[redacted]	0.80	0.62	[redacted]
R7a) PFS utility: crizotinib utility (0.81) for both*	[redacted]	3.86	2.13	£23,267	1.47	0.90	[redacted]	2.39	1.23	[redacted]
R7b) PFS utility: pemetrexed utility (0.72) for both*	[redacted]	3.86	2.00	£23,267	1.47	0.84	[redacted]	2.39	1.15	[redacted]
R7c) PFS utility: pemetrexed utility = 0.75*	[redacted]	3.86	2.13	£23,267	1.47	0.86	[redacted]	2.39	1.26	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

*When applied individually, PFS utility scenarios should be applied to the company base case model including the company's modelling of OS (adjusted for crossover using RPSFTM Wilcoxon)

Table 41 Base case cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG scenarios

Model scenarios			Crizotinib			Pemetrexed			Incremental			ICER
			Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company updated base case (from 24 November 2017)			[redacted]	3.86	2.13	£23,267	1.47	0.84	[redacted]	2.39	1.28	[redacted]
R1a, R7a	OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	3.70	2.06	£23,777	1.73	1.01	[redacted]	1.97	1.05	[redacted]
R1a, R7b		PFS utility=0.72 for both	[redacted]	3.70	1.94	£23,777	1.73	0.96	[redacted]	1.97	0.98	[redacted]
R1a, R7c		PFS utility=0.75 for pemetrexed	[redacted]	3.70	2.06	£23,777	1.73	0.98	[redacted]	1.97	1.09	[redacted]
R1b, R7a	OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	3.70	2.06	£25,848	2.91	1.50	[redacted]	0.80	0.57	[redacted]
R1b, R7b		PFS utility=0.72 for both	[redacted]	3.70	1.94	£25,848	2.91	1.44	[redacted]	0.80	0.49	[redacted]
R1b, R7c		PFS utility=0.75 for pemetrexed	[redacted]	3.70	2.06	£25,848	2.91	1.46	[redacted]	0.80	0.60	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 42 Base case cost effectiveness results for crizotinib (PAS) versus docetaxel (subsequent-line): ERG revisions

Model scenario and ERG revisions	Crizotinib			Docetaxel			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company base case	[redacted]	**2.75**	**1.63**	**£11,076**	**1.39**	**0.71**	[redacted]	**1.36**	**0.93**	[redacted]
R4a) OS treatment effect: apply PFS HR to unadjusted crizotinib estimate	[redacted]	3.29	1.84	£11,520	1.65	0.82	[redacted]	1.64	1.03	[redacted]
R4b) OS treatment effect: no PPS treatment effect	[redacted]	3.29	1.84	£13,428	2.81	1.29	[redacted]	0.48	0.55	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 43 PROFILE 1001 scenario cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG revisions

ERG revisions	Crizotinib			Pemetrexed			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company PROFILE 1001 scenario	[redacted]	**5.75**	**3.25**	**£22,570**	**2.15**	**1.29**	[redacted]	**3.60**	**1.95**	[redacted]
R2a) OS treatment effect: use PFS HR from 1014	[redacted]	5.75	3.25	£23,662	2.74	1.54	[redacted]	3.01	1.71	[redacted]
R2b) OS treatment effect: no PPS gain	[redacted]	5.75	3.25	£26,110	4.24	2.11	[redacted]	1.52	1.13	[redacted]
R3) Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	3.81	2.56	£21,979	1.83	1.13	[redacted]	1.98	1.43	[redacted]
R7a) PFS utility: crizotinib utility (0.81) for both	[redacted]	5.75	3.25	£22,570	2.15	1.41	[redacted]	3.60	1.84	[redacted]
R7b) PFS utility: pemetrexed utility (0.72) for both	[redacted]	5.75	3.00	£22,570	2.15	1.29	[redacted]	3.60	1.70	[redacted]
R7c) PFS utility: pemetrexed utility = 0.75	[redacted]	5.75	3.25	£22,570	2.15	1.33	[redacted]	3.60	1.91	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 44 PROFILE 1001 cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG scenarios

Model scenarios			Crizotinib			Pemetrexed			Incremental			ICER
			Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company PROFILE 1001 scenario			[redacted]	**5.75**	**3.25**	**£22,570**	**2.15**	**1.29**	[redacted]	**3.60**	**1.95**	[redacted]
R2a, R7a	OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	5.75	3.25	£23,662	2.74	1.65	[redacted]	3.01	1.59	[redacted]
R2a, R7b		PFS utility=0.72 for both	[redacted]	5.75	3.00	£23,662	2.74	1.54	[redacted]	3.01	1.46	[redacted]
R2a, R7c		PFS utility=0.75 for pemetrexed	[redacted]	5.75	3.25	£23,662	2.74	1.58	[redacted]	3.01	1.67	[redacted]
R2b, R7a	OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	5.75	3.25	£26,110	4.24	2.23	[redacted]	1.52	1.02	[redacted]
R2b, R7b		PFS utility=0.72 for both	[redacted]	5.75	3.00	£26,110	4.24	2.11	[redacted]	1.52	0.89	[redacted]
R2b, R7c		PFS utility=0.75 for pemetrexed	[redacted]	5.75	3.25	£26,110	4.24	2.15	[redacted]	1.51	1.09	[redacted]
R3, R7a	Remodel crizotinib time-to-event: K-M data+ exponential	PFS utility=0.81 for both	[redacted]	3.81	2.56	£21,979	1.83	1.24	[redacted]	1.98	1.33	[redacted]
R3, R7b		PFS utility=0.72 for both	[redacted]	3.81	2.31	£21,979	1.83	1.13	[redacted]	1.98	1.18	[redacted]
R3, R7c		PFS utility=0.75 for pemetrexed	[redacted]	3.81	2.56	£21,979	1.83	1.17	[redacted]	1.98	1.40	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 45 PROFILE 1001 scenario cost effectiveness results for crizotinib (PAS) versus docetaxel (subsequent-line): ERG revisions

ERG revisions	Crizotinib			Docetaxel			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company PROFILE 1001 scenario*	[redacted]	**5.75**	**3.24**	**£12,706**	**2.32**	**1.29**	[redacted]	**3.43**	**1.95**	[redacted]
R5) OS treatment effect: no PPS gain	[redacted]	5.75	3.24	£15,606	4.24	2.03	[redacted]	1.51	1.21	[redacted]
R6) Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	3.81	2.55	£12,080	1.95	1.11	[redacted]	1.86	1.45	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression free survival; PPS=post-progression survival; QALY=quality adjusted life year

*Please note: the company PROFILE 1001 study scenario represents PFS HR from PROFILE 1007 to PROFILE 1001 data

6.1 Conclusions of the cost effectiveness section

The various revisions implemented by the ERG in the company models for the comparison of treatment with crizotinib versus pemetrexed+platinum in the first-line setting and crizotinib versus docetaxel in the subsequent-line setting yield a mixture of effects. Incremental costs and incremental benefits both increase and decrease depending on the individual revision or combination of revisions (scenarios).

The resulting ICERs per QALY gained in the first-line base case vary from [redacted] (using pemetrexed+platinum PFS utility of 0.75) to [redacted] (assuming no PPS treatment effect and a PFS utility of 0.72 for both treatments). The resulting ICERs per QALY gained in the subsequent-line base case vary from [redacted] (docetaxel OS=applying PFS HR to unadjusted crizotinib OS estimates) to [redacted] (assuming no PPS treatment effect).

The resulting ICERs per QALY gained in the first-line PROFILE 1001 scenario vary from [redacted] (using pemetrexed+platinum PFS utility of 0.75) to [redacted] (assuming no PPS treatment effect and a PFS utility of 0.72 for both treatments). The resulting ICERs per QALY gained in the subsequent-line PROFILE 1001 scenario vary from [redacted] (remodel crizotinib time-to-event: K-M data+ exponential) to [redacted] (assuming no PPS treatment effect).

7 END OF LIFE

The NICE End of Life criteria, and the data presented by the company to show that these criteria have been met, are presented in Table 46.

Table 46 Company summary of evidence for End of Life consideration

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	There is a paucity of estimates of OS with current chemotherapy in the ROS1+ advanced NSCLC population specifically. There is no conclusive evidence that ROS1-positivity is a better prognostic factor for survival, compared to unselected NSCLC. Based on opinion from 12 leading clinical experts from the UK, the PFS in chemotherapy-treated ROS1+ patients is similar to the PFS in chemotherapy-treated ALK+ patients. As there are limited data on OS for ROS1+ advanced NSCLC patients, data from ALK+ NSCLC have been used as supportive evidence, due to the similarities between patients with ALK and ROS1. Estimates for median OS in ALK+ patients range from 6 to 22 months, with median OS in the chemotherapy arm of PROFILE 1007 reaching 21.9 months at the final analysis. Based on the available evidence and support from 12 UK leading clinical experts, the life expectancy of ROS1+ advanced NSCLC patients is expected to be less than 24 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS was not reached in PROFILE 1001, with only 30.2% of patients having died at the time of PFS analysis (30th November 2014). At this point, median PFS was 19.3 months, therefore this is expected to be the minimum value for OS. In the previous appraisal of crizotinib as a subsequent-line therapy for ALK+ NSCLC, it was acknowledged that PFS is considered a conservative indicator of OS for targeted therapies: *"[The Committee] discussed comments by the manufacturer that it is biologically plausible that the overall survival to PFS ratio would be higher with targeted therapy than with chemotherapy. The clinical specialists confirmed that in some patients there was a dramatic response to treatment and that targeted therapies such as crizotinib could reduce tumour size to below that at the beginning of therapy. Therefore, at progression, the size of the tumour could still be smaller than at the beginning of therapy and as a result, benefit would continue into the progressed disease stage. The Committee was persuaded by this evidence."*[99] Crizotinib demonstrated clear benefits in terms of tumour response in PROFILE 1001, which, based on the NICE Committee's previous considerations, is supportive of a continued survival benefit with crizotinib into progressed disease. As such, the observed PFS with crizotinib should be considered an absolute minimum estimate of OS. In both the first-line and the subsequent-line settings, NICE has accepted an extension of life of more than three months in ALK+ advanced NSCLC patients receiving crizotinib compared to standard care. The model predicts an extension to life associated with crizotinib in ROS1+ patients of 2.39 years compared to pemetrexed plus platinum therapy and 1.36 years compared to docetaxel therapy, which therefore meets the NICE criteria for end-of-life.

Source: CS, Table 25

7.1 Short life expectancy

The evidence for life expectancy in the ROS1+ advanced NSCLC population is uncertain, particularly given the lack of comparator data available from the PROFILE 1001 study.

The Appraisal Committee in TA406 considered that life expectancy in the ALK+ advanced NSCLC population in the first-line setting was likely to be less than 24 months and that the short life expectancy criterion was met. This consideration was made taking into account the company's revised model that used an earlier data cut from the PROFILE 1014 trial than is used in this appraisal. This consideration was made based on estimates of OS with adjusted baseline characteristics.

The Appraisal Committee in TA422 noted that there was some uncertainty around life expectancy in the ALK+ advanced NSCLC population in the subsequent-line setting, but considered that, on balance, it was likely to be less than 24 months and that the short life expectancy criterion was met.

7.2 Extension to life

The evidence for extension to life in the ROS1+ advanced NSCLC population is uncertain, particularly given the lack of a comparator to crizotinib in the PROFILE 1001 study.

The Appraisal Committee in TA406 considered that it could be sufficiently confident that treatment with crizotinib in the first-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population, although the size of the OS benefit was unclear. It concluded that the extension to life criterion was met.

The Appraisal Committee in TA422 considered that treatment with crizotinib in the subsequent-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population. The Appraisal Committee concluded that the extension to life criterion was met. However, the ERG notes that the NHS standard of care for this group of patients has recently changed and is now docetaxel+nintedanib (which has not been included as a comparator in this appraisal).

8 OVERALL CONCLUSIONS

8.1 Clinical effectiveness

The ERG considers that the company has addressed the decision problem **only** if it is considered that outcome data from patients with ALK+ advanced NSCLC can be used as a proxy for the outcome data of patients with ROS1+ advanced NSCLC. The ERG considers that the evidence (PROFILE 1001 study, PROFILE 1007 and PROFILE 1014 trials) presented by the company was generally of good quality. The ERG notes that the OS data available for patients treated with ROS1+ advanced NSCLC or patients with ALK+ advanced NSCLC are immature.

8.2 Cost effectiveness

The company base case analysis is founded on the assumption that the outcomes of treatment with crizotinib in an ALK+ advanced NSCLC population are an appropriate proxy for the outcomes of treatment with crizotinib in a ROS1+ advanced NSCLC population. The scenario analysis for the ROS1+ advanced NSCLC population is based on a small, immature, single-arm study (PROFILE 1001) and any modelling of this data will likely be subject to substantial uncertainty.

The ERG's revised ICERs per QALY gained vary greatly depending on which of its revisions are taken into account. The ICERs per QALY gained for treatment with crizotinib versus pemetrexed+platinum in the first-line base case vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus docetaxel in the subsequent-line base case vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus pemetrexed+platinum in the first-line PROFILE 1001 scenario vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus docetaxel in the subsequent-line PROFILE 1001 scenario vary from [redacted] to [redacted].

8.3 Implications for research

There are currently no comparative studies evaluating the use of crizotinib in ROS1+ advanced NSCLC patients and it is unlikely that such studies will become available due to the perceived lack of clinical equipoise and the small number of patients with ROS1+ advanced NSCLC. An international, multicentre, prospective single-arm cohort study with appropriate long duration of follow-up could shed more light on the effectiveness of crizotinib and particularly the impact of crizotinib on the OS of patients with ROS1+ advanced NSCLC. An international registry would be a useful alternative for collecting data on this patient population.

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10 APPENDICES

10.1 Analysis populations of the included study and trials

Table 47 Analysis populations of the included study and trials

PROFILE 1001	PROFILE 1014	PROFILE 1007
Response analysis (ORR, DR, TTR, DCR): RE population (n=53) – all patients in the SA population who had an adequate baseline disease assessment Patients also needed to meet one of the two following criteria: 1. Had at least one post-baseline disease assessment at least six weeks from first dose of crizotinib or 2. Withdrew from the study or experienced progressive disease/death at any time on study *Safety analysis (PFS, TTP, TTF, OS, AEs, patient characteristics):* SA population (n=53) – included all enrolled patients who received at least one dose of crizotinib	*Primary analysis (and secondary efficacy analyses):* ITT population (n=343) – included all patients who were randomised to study treatment at the initial randomisation *Safety analyses:* AT population (n=340) – included all patients who received at least one dose of study treatment assigned to them at the initial randomisation *Analysis of PROs:* PRO evaluable population - included all patients from the ITT population who had also completed a baseline PRO assessment and at least one postbaseline PRO	[redacted]

AT=as treated; DCR=disease control rate; DR=duration of response; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; RE=response evaluable; SA=safety analysis; TTF=time to treatment failure; TTP=time to progression; TTR=time to tumour response
Source: CS, Table 12; TA406 CS, Table 18; CS Appendix L Table 76

10.2 Primary outcomes of the included study and trials

Table 48 Primary outcomes of the included study and trials: definitions, assessment measures and statistical analysis methodology

	PROFILE 1001	**PROFILE 1014**	**PROFILE 1007**
Primary outcome	ORR, defined as the percentage of patients with confirmed CR or PR according to RECIST (v1.0 for ROS1+ cohort [n=50]; v1.1 for ALK- cohort [n=3])	PFS, defined as the time from randomisation to RECIST (v1.1)-defined progression (as assessed by IRR) or death	PFS, defined as the time from randomisation to RECIST (v1.0)-defined progression (as assessed by IRR) or to death
Assessment measures	Tumour assessments were performed every 8 weeks in the ROS1+ cohort, and every 6 weeks in the ALK- cohort until RECIST-defined disease progression. Once a patient had completed 15 cycles, tumour assessments reduced to every 16 weeks in the ROS1+ cohort or every 12 weeks in the ALK- cohort, until after 24 cycles in the ROS1+ cohort or 35 cycles in the ALK- cohort. After 24 cycles, tumour assessment was performed every 24 weeks	Tumour assessments were performed every 6 weeks during treatment and at post-treatment follow-up visits (again, scheduled for every 6 weeks) until RECIST-defined progression, as assessed by IRR	Disease assessments were performed at 6-week intervals, i.e. every other cycle, beginning on Day 1 of Cycle 3
Statistical analysis	The point estimate of ORR was provided alongside corresponding 2-sided 95% CIs using the exact method based on the F-distribution	PFS was analysed using the K-M method. 2-sided log-rank tests stratified according to baseline stratification factors were used for between-group comparisons of PFS, with stratified Cox regression models applied to estimate HRs	PFS was summarised using the K-M method and displayed graphically. The median event time for each treatment arm and corresponding 2-sided 95% CI for the median was provided for PFS. A stratified 1-sided log-rank test was used to compare PFS between the two treatment arms. A Cox regression model, stratified for baseline stratification factors, was fitted. The estimated HR and 2-sided 95% CI were provided

ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; HR=hazard ratio; IRR=independent radiology review; K-M=Kaplan-Meier; ORR=objective response rate; PFS=progression-free survival; PR=partial response; RECIST=response evaluation criteria in solid tumours

Source: CS, Table 8, Table 10 and Table 13; TA406 CS, Table 15 and Table 19; CS Appendix L; PROFILE 1007 protocol

10.3 Assessment of proportional hazards

The ERG has assessed the validity of the OS and PFS PH assumptions for the PROFILE 1014 and PROFILE 1007 trials by plotting the cumulative hazard associated with crizotinib treatment versus the cumulative hazard associated with chemotherapy treatment (H-H plot) for each outcome, together with the constant PH trend line. If the PH assumption is valid for these data, the data points should lie close to the trend line and be evenly distributed either side of it. The trend line should also pass through the origin of the graph.

10.3.1 PROFILE 1014

The H-H plot for PFS data from the PROFILE 1014 trial is provided in Figure 19. The data deviate from the linear trend line, and the estimated constant for a linear relationship is statistically significantly different from zero (0.093, 95% CI: 0.077 to 0.109). The graph suggests that the assumption of PH does not hold for PFS data from the PROFILE 1014 trial.

PFS

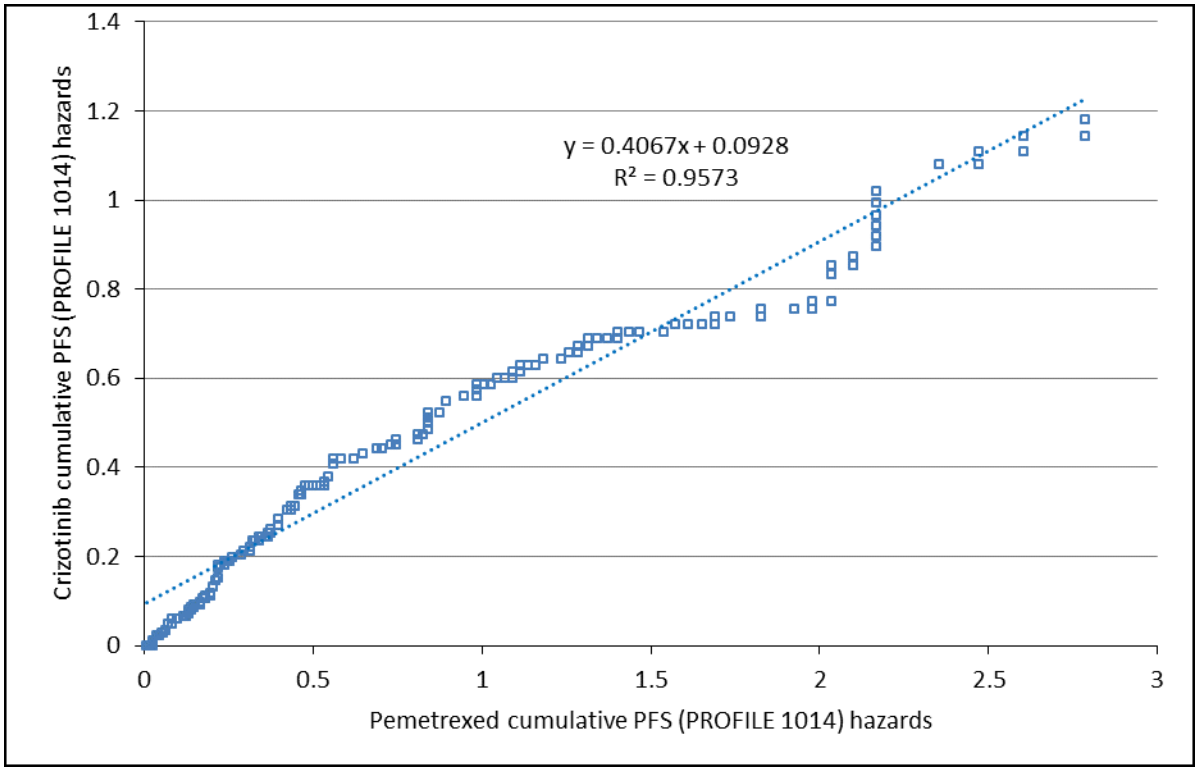


Figure 19 H-H plot for the PROFILE 1014 trial PFS data

PFS=progression-free survival

Unadjusted OS

The H-H plot for unadjusted OS data from the PROFILE 1014 trial is provided in Figure 20. Generally, the data points are reasonably distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (-0.016, 95% CI: -0.024 to -0.009), but considers that this may be due to features of the data in the earliest stages of follow-up. Consequently, the ERG is of the opinion that the PH assumption may hold for unadjusted OS data from the PROFILE 1014 trial.

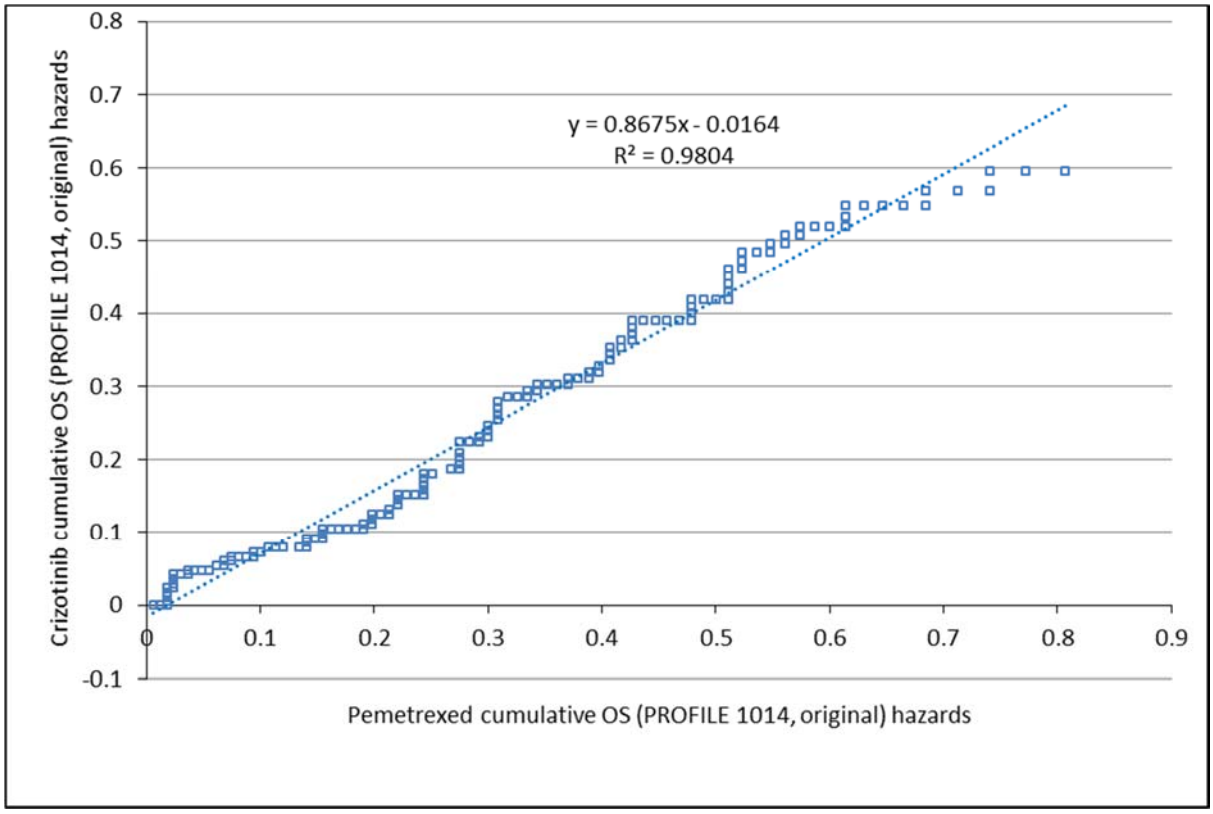


Figure 20 H-H plot for the PROFILE 1014 trial unadjusted OS data

OS=overall survival

RPSFT-adjusted (log-rank test) OS

The H-H plot for RPSFT-adjusted (log-rank test) OS data from the PROFILE 1014 trial is provided in Figure 21. Apart from some systematic deviation in the earliest stages of follow up, the data are reasonably well distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (0.017, 95% CI: 0.015 to 0.019), but considers that this may be due to early features of the data. The ERG concludes that the PH assumption may hold for RPSFT-adjusted (log-rank test) OS data from the PROFILE 1014 trial.

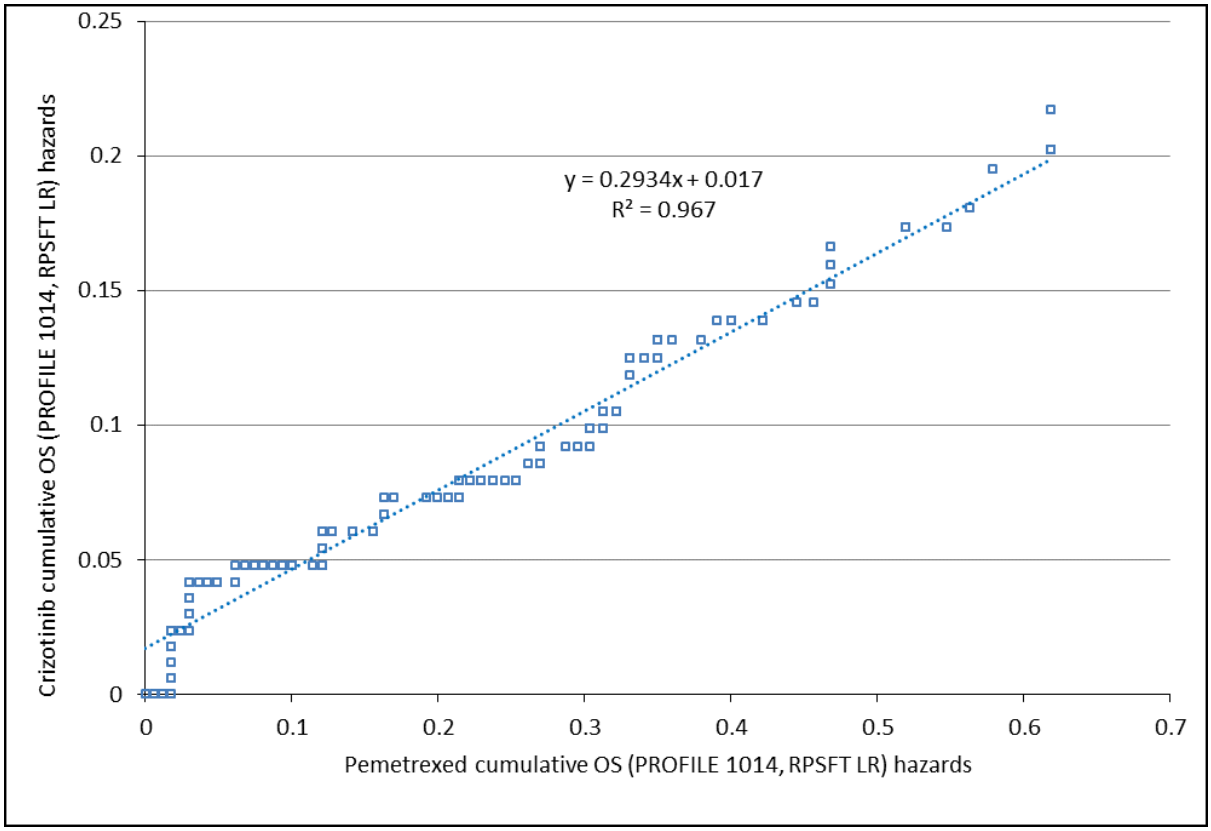


Figure 21 H-H plot for the PROFILE 1014 trial RPSFT-adjusted (log-rank test) OS data

LR=log-rank; OS=overall survival; RPSFT=rank-preserving structural failure time

RPSFT-adjusted (Wilcoxon test) OS

The H-H plot for RPSFT-adjusted (Wilcoxon test) OS data from the PROFILE 1014 trial is provided in Figure 21. Apart from some systematic deviation in the earliest stages of follow up, the data are reasonably well distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (0.011, 95% CI: 0.005 to 0.015), but considers that this may be due to early features of the data, and that the PH assumption may hold for RPSFTM-adjusted (Wilcoxon test) OS data from the PROFILE 1014 trial.

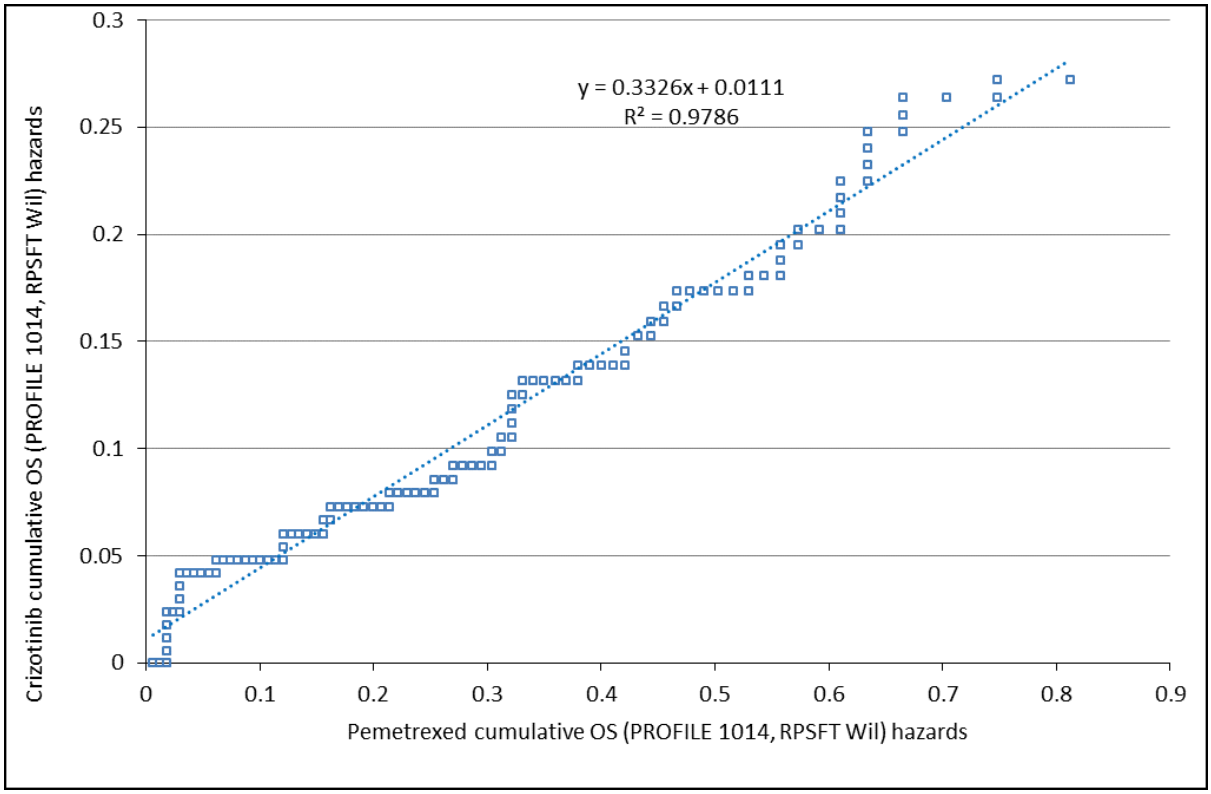


Figure 22 H-H plot for the PROFILE 1014 trial RPSFTM-adjusted (Wilcoxon test) OS data

OS=overall survival; RPSFT=rank-preserving structural failure time model

10.3.2 PROFILE 1007

PFS

The H-H plot for PFS data from the PROFILE 1007 trial is provided in Figure 23. The data deviate from the linear trend line, and the estimated constant for a linear relationship is statistically significantly different from zero (-0.114, 95% CI: -0.133 to -0.094). The graph suggests that the assumption of PH does not hold for PFS data from the PROFILE 1007 trial.

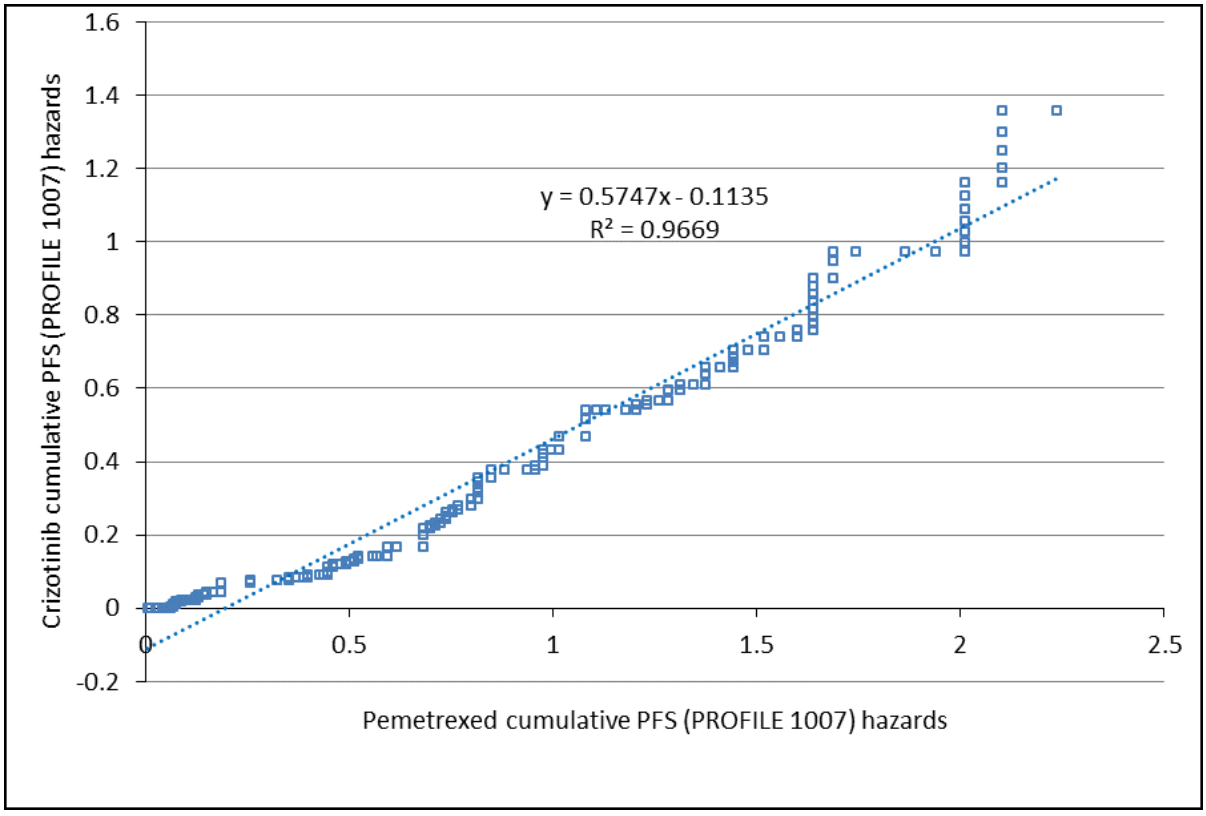
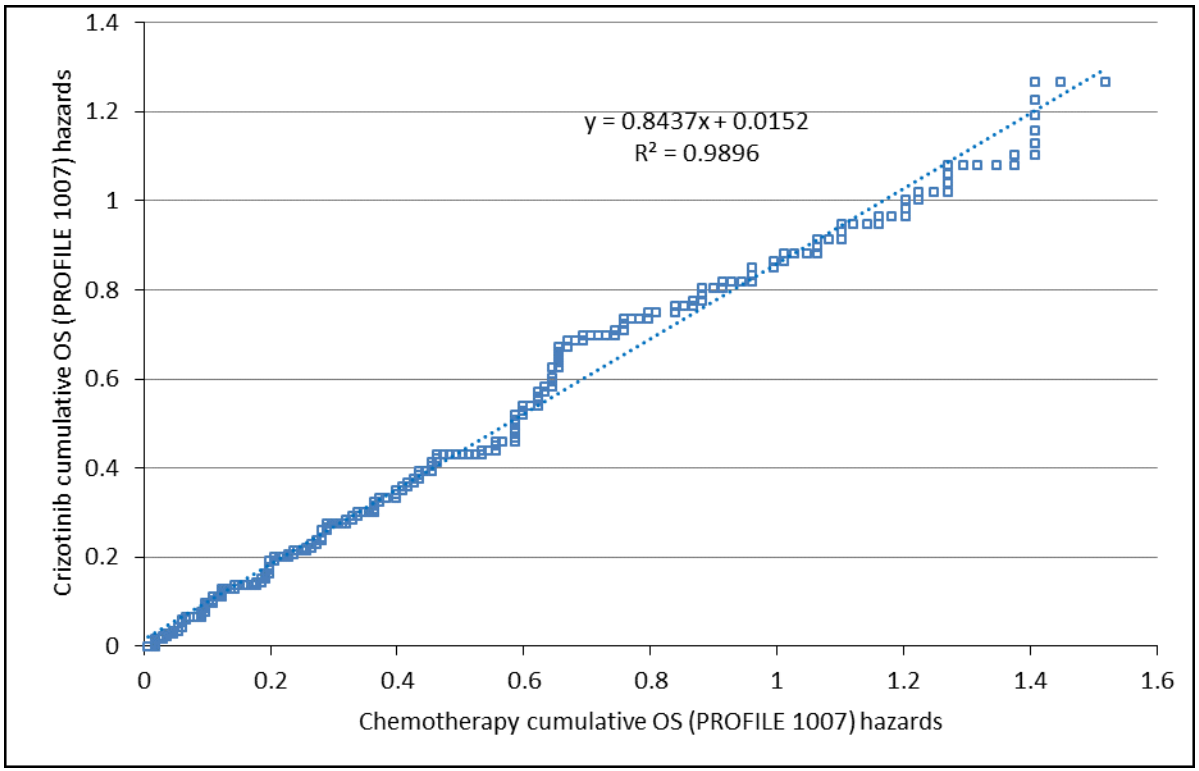


Figure 23 H-H plot for the PROFILE 1007 trial PFS data

PFS=progression-free survival

Unadjusted OS

The H-H plot for OS data from the PROFILE 1007 trial is provided in Figure 23. The data are reasonably well distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (0.015, 95% CI: 0.008 to 0.023), but generally there is not strong evidence to suggest that the PH assumption is violated. The ERG considers that the assumption of PH may hold for unadjusted OS data from the PROFILE 1007 trial.



OS=overall survival

10.4 ERG assessment of statistical approach used to analyse data from the included study and trials

Table 49 ERG assessment of statistical approach used to analyse data from the included study and trials

	PROFILE 1001	**PROFILE 1014**	**PROFILE 1007**
Sample size calculation	The sample size calculation is presented in Table 13 of the CS. The ERG is satisfied that this sample size calculation was pre-specified in the supplemental TSAP (p7-8).	The sample size calculation is presented in Table 19 of the TA406 CS. The ERG is satisfied that this sample size calculation was pre-specified in the TSAP (p9).	The sample size calculation is presented in Table 75 of Appendix L of the CS. The ERG is satisfied that this sample size calculation was pre-specified in the TSAP (p8).
Protocol amendments	Protocol amendments were listed in the final protocol (p2-5). All protocol amendments were made before the time of data cut-off (30th November 2014), and so were unlikely to have been driven by the results of the trial.	Protocol amendments were listed in the final protocol (p2-5). All but the last two of the protocol amendments were made before the time of data cut-off [redacted], and so were unlikely to have been driven by the results of the trial. The final protocol amendment specified post-hoc analyses to evaluate treatment activity in patients with or without brain metastases, and post-hoc analyses of PFS, ORR, OS and AEs by type of chemotherapy. The ERG is satisfied that the methods of analysis presented in the amended TSAP were appropriate.	Protocol amendments were listed in the final protocol (p2-5). All protocol amendments were made before the time of data cut-off (31st August 2015), and so were unlikely to have been driven by the results of the trial.
Subgroup analyses	Subgroup analyses were pre-specified for ORR according to baseline characteristics in the TSAP (p23). Results of subgroup analyses are presented in Appendix E of the CS.	Subgroup analyses were pre-specified for PFS, ORR, and OS according to baseline characteristics in the TSAP (p17). Results of subgroup analyses are presented in the CSR (p147, p383-400, p639).	Pre-planned subgroup analyses for PFS, ORR, and OS are available in the TSAP (p15). Results of subgroup analyses are presented in the preliminary CSR for PFS (p90) and the final CSR for OS (p110). The results of subgroup analyses for ORR have not been made available to the ERG.

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Sensitivity analyses	Although the primary analysis of ORR was based on derived tumour assessment (investigator assessment), IRR was also carried out in the ROS1+ cohort (n=50). IRR was not performed for tumour scans from the three ALK- NSCLC patients who were retrospectively found to be ROS1+ due to differences in RECIST versions used and treatment cycle lengths. The ERG is satisfied that the additional efficacy analysis based on IRR were pre-planned in the supplemental TSAP (p19-20). A summary of the results of this additional efficacy analysis is available in the CS (p58), but full results have not been made available to the ERG.	Pre-planned sensitivity analyses of the primary endpoint are available in the TSAP (p21-22). Results of sensitivity analyses for PFS are presented in the CSR (p148).	Pre-planned sensitivity analyses of the primary endpoint are available in the TSAP (p19). Results of sensitivity analyses for PFS are presented in the preliminary CSR (pp90-91).
Safety analysis	Included the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory parameters. AEs were classified and graded according to the CTCAE v3.0. In accordance with the plan for analysis of AEs outlined in the supplemental TSAP (pp18-19), many different summaries of AEs are provided as summary tables and as narrative descriptions in the CSR (Section 12).	Included the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory parameters. AEs were classified and graded according to the CTCAE v4.0. In accordance with the plan for analysis of AEs outlined in the TSAP (pp26-32), many different summaries of AEs are provided as summary tables and as narrative descriptions in the CSR (Section 12).	Included the type, incidence, severity, seriousness and relationship to study medications of AEs and any laboratory abnormalities. AEs were classified and graded according to the CTCAE v4.0. In accordance with the plan for analysis of AEs outlined in the TSAP (pp23-28), many different summaries of AEs are provided as summary tables and as narrative descriptions in the CSR (Section 12).

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Analysis of PROs	N/A	PROs were assessed using the EORTC QLQ-C30, the lung cancer specific module (QLQ-LC13), the EQ-5D questionnaire, and the VSAQ-ALK. Patients completed the self-administered EORTC QLQ-C30, QLQ-LC13, VSAQ-ALK, and EQ-5D questionnaires on Day 1 of each cycle until EOT/withdrawal, and prior to any testing, treatment, or discussion with the physician or site personnel. The EORTC QLQ-C30 and QLQ-LC13 were also to be administered on Day 7 and Day 15 of Cycle 1. Detailed statistical methodology of PROs is presented in the TSAP (pp32-34). The ERG is satisfied that the methodology used to analyse PROs was appropriate, and that all results are reported in the CSR (pp163-179).	PROs were assessed using the EORTC QLQ-C30, the lung cancer specific module (QLQ-LC13), the EQ-5D questionnaire, and the VSAQ-ALK. Patients completed the self-administered questionnaires at baseline, Day 1 of every cycle, at the EOT or withdrawal, and prior to any testing, treatment, or discussion with the physician or clinic personnel. Detailed statistical methodology of PROs is presented in the TSAP (pp28-31). The ERG is satisfied that the methodology used to analyse PROs was appropriate, and that all results are reported in the preliminary CSR (pp106-118) and the final CSR (pp114-117).

AEs=adverse events; ALK=anaplastic lymphoma kinase; CS=company submission; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; EORTC=European Organisation for Research on the Treatment of Cancer; ERG=evidence review group; EOT=end of treatment; EQ-5D=EuroQol-5D; IRR=independent radiology review; N/A=not applicable; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; QLQ-LC13=EORTC lung cancer-specific quality of life questionnaire; QLQ-C30=Quality of Life Questionnaire-Core 30; RECIST=Response Evaluation Criteria on Solid Tumours; TSAP=trial statistical analysis plan; VSAQ-ALK=Visual Symptom Assessment Questionnaire-ALK

Source: CS, Table 9, Table 13; TA406 CS, Table 17; CS Appendix L, Table 75; PROFILE 1001 CSR; PROFILE 1014 CSR; PROFILE 1007 CSR; ERG comment

10.5 ERG PROFILE 1001 time-to-event modelling

The ERG's investigated projecting time-to-event data based on using the K-M data directly from the PROFILE 1001 study and appending a parametric projection based on the trend identified in the latter part of the dataset. This method assumes that time-to-event data are sufficiently mature to have settled into a long term trend and that this trend can be identified in the data. The data in the PROFILE 1001 study are immature and based on a small sample (n=53), so the results of the ERG's remodelling should be treated with caution.

Given the paucity of data in the PROFILE 1001 study, an exponential curve was fitted to minimise parameter assumptions. The face validity of the exponential fit can be assessed by cumulative hazard plots (Figure 24, Figure 25, Figure 26), since an exponential cumulative hazard results in a straight line when plotted against time. The exponential curve has good face validity for OS and TTD, but is a less good fit for PFS.

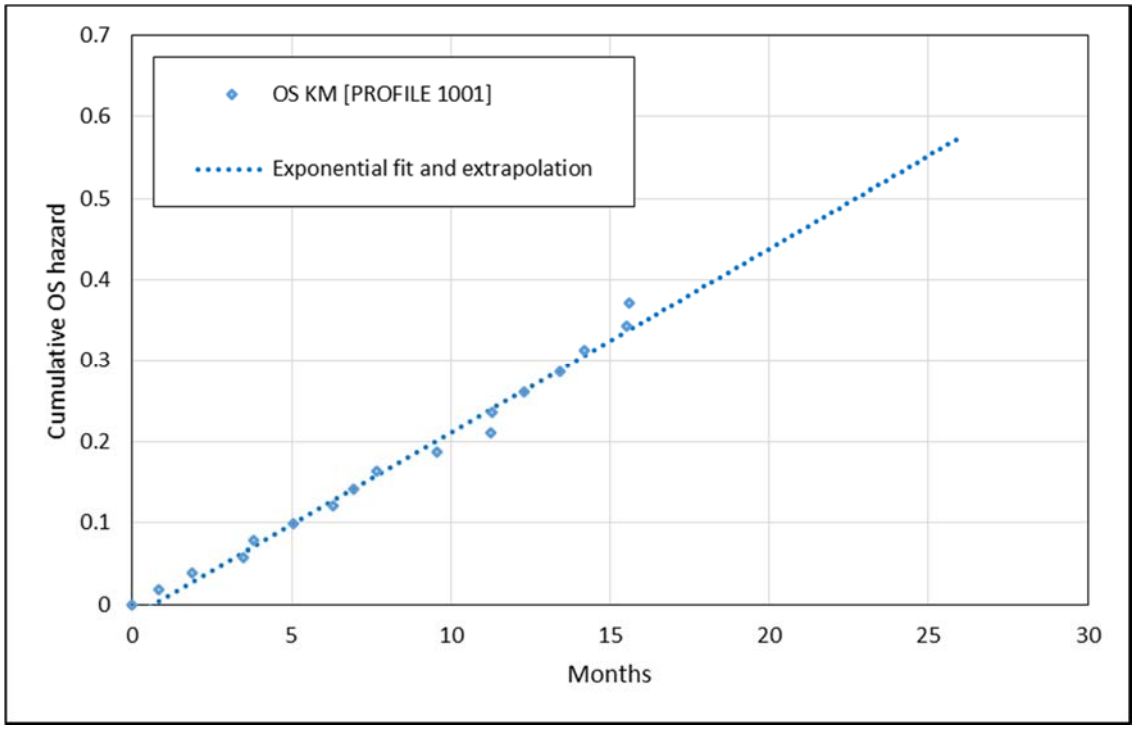


Figure 24 Cumulative OS hazard and ERG fitted exponential model: PROFILE 1001

KM=Kaplan-Meier; OS=overall survival

Figure 25 Cumulative TTD hazard and ERG fitted exponential model: PROFILE 1001

KM=Kaplan-Meier; TTD=time-to-treatment discontinuation

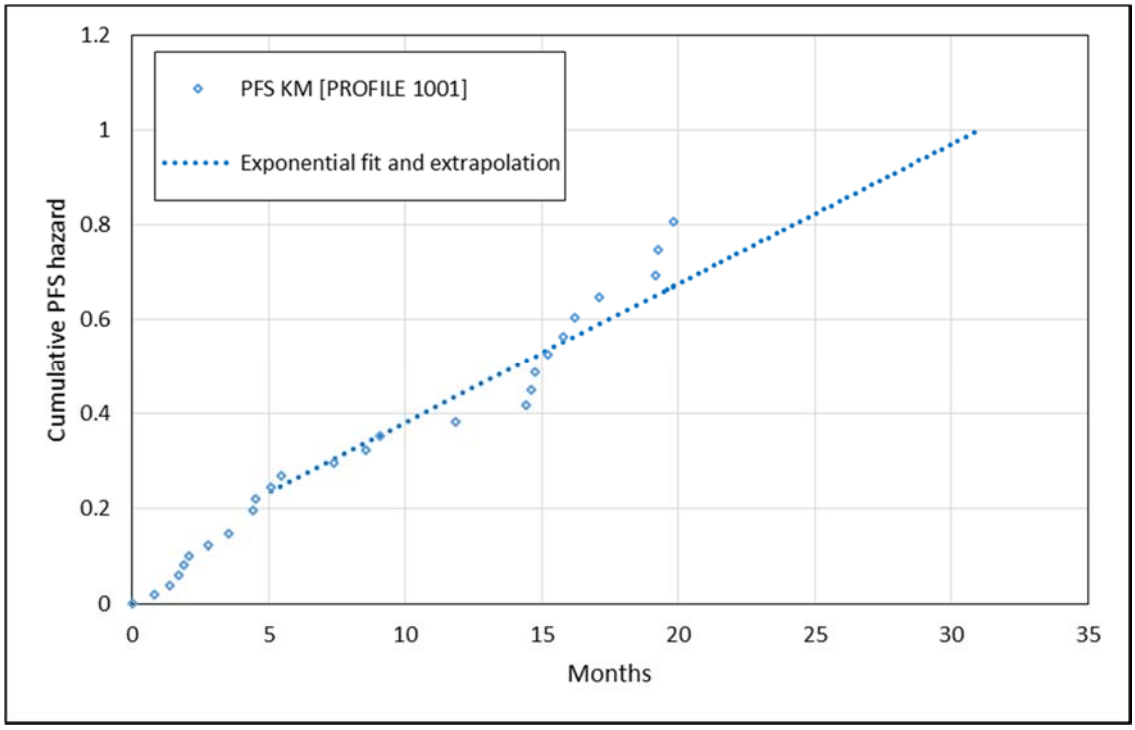


Figure 26 Cumulative PFS hazard and ERG fitted exponential model: PROFILE 1001

KM=Kaplan-Meier; PFS=progression free survival

10.6 ERG Revisions to company's model

All revisions are activated by a logic switch. Logic switches are indicated by named range variables Mod_*number* where *number* = 1 to 8. A menu of revisions and Mod names appears below and on the 'Base case results' worksheet in the ERG amended model.

Instructions for modifying the updated company model (received 1 November 2017)

1. Populate the following named switch values in the 'Base case results' sheet

Name	Switch	Details	Switch options					
			1		2		3	
			Revision #	*Revision*	*Revision #*	*Revision*	*Revision #*	*Revision*
Mod_1	0	ERG first line OS [PROFILE 1014]	R1a)	PFS HR	R1b)	PPS=PPS		
Mod_2	0	ERG first-line OS treatment effect [PROFILE 1001]	R2a)	PFS HR	R2b)	PPS=PPS		
Mod_3	0	ERG first-line remodel crizotinib [PROFILE 1001]	R3)	KM+exponential				
Mod_4	0	ERG subsequent-line OS [PROFILE 1007]	R4a)	PFS HR (applied to ERG crizotinib)	R4b)	PPS=PPS (applied to ERG crizotinib)		
Mod_5	0	ERG subsequent-line OS treatment effect [PROFILE 1001]	R5	PPS=PPS				
Mod_6	0	ERG subsequent-line remodel crizotinib [PROFILE 1001]	R6)	KM+exponential				
Mod_7	0	ERG first line PFS utility	R7a)	0.81	R7b)	0.72	R7c)	Pemetrexed = 0.75
Mod_8	0	ERG subsequent-line PFS utility	R8a)	-0.03 crizotinib	R8b)	+0.03 docetaxel		

2. Move all sheets from *ID1098_ ERG additional model data.xlsx* into the model

3. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below

- paste formulae into the cells referred to in the ‘Cells’ column in the table below

For individual revisions:

R1, R4, R7 and R8: Please set the model to base case (in Model controls! sheet)

R1: Please set the PROFILE 1014 crossover adjustment to “Unadjusted” (Model controls! J118)

R2, R3, R5 and R6: Please set the model to PROFILE 1001 scenario (in Model controls! sheet)

For scenarios/combined revisions:

If scenario contains R1 or R4: Please set the model to base case (in Model controls! sheet)

If scenario contains R1: Please set the PROFILE 1014 crossover adjustment to “Unadjusted” (Model controls! J118)

If scenario contains R2, R3, R5 or R6: Please set the model to PROFILE 1001 scenario (in Model controls! sheet)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R1 ERG first line OS [1014] R2 ERG first-line OS treatment effect [1001] R3 ERG first-line remodel crizotinib [1001]	Mod_1 Mod_2 Mod_3	OS (1L)	Q88:Q2358	Pemetrexed+platinum =IF(con_survival_ALK="No",OFFSET(Q87,1,VLOOKUP(con_OS_model_pem,Lists_parametric_models,2,FALSE),),IF(con_updated_1014_data="No",X88,Y88))*IF(AND(Mod_1=0,Mod_2=0,Mod_3=0),1,0)+'ERG first-line'!E11*IF(AND(Mod_1=1,Mod_2=0,Mod_3=0),1,0)+'ERG first-line'!F11*IF(AND(Mod_1=2,Mod_2=0,Mod_3=0),1,0)+'ERG first-line'!H11*IF(AND(Mod_1=0,Mod_2=1,Mod_3=0),1,0)+'ERG first-line'!I11*IF(AND(Mod_1=0,Mod_2=2,Mod_3=0),1,0)+'ERG first-line'!K11*IF(AND(Mod_1=0,Mod_2=0,Mod_3=1),1,0)
R3 ERG first-line remodel crizotinib [1001]	Mod_3	OS (1L)	E88:E2358	Crizotinib =IF(con_survival_ALK="No",OFFSET(E87,1,VLOOKUP(con_OS_model_criz,Lists_parametric_models,2,FALSE),),IF(con_updated_1014_data="No",L88,M88))*IF(Mod_3=0,1,0)+'ERG first-line'!J11*IF(Mod_3=1,1,0)
R3 ERG first-line remodel crizotinib [1001]	Mod_3	PFS (1L)	E85:E2355	Crizotinib =IF(con_survival_ALK="No",OFFSET(E84,1,VLOOKUP(con_PFS_model_criz,Lists_parametric_models,2,FALSE),),L85)*IF(Mod_3=0,1,0)+'ERG first-line'!L11*IF(Mod_3=1,1,0)
R3 ERG first-line remodel crizotinib [1001]	Mod_3	PFS (1L)	Q85:Q2355	Pemetrexed+platinum =IF(con_survival_ALK="No",OFFSET(Q84,1,VLOOKUP(con_PFS_model_pem,Lists_parametric_models,2,FALSE),),X85)*IF(Mod_3=0,1,0)+'ERG first-line'!M11*IF(Mod_3=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R3 ERG first-line remodel crizotinib [1001]	Mod_3	TOT (1L)	E60:E2330	Crizotinib =IF(con_survival_ALK="No",OFFSET(E59,1,VLOOKUP(con_TTF_model_criz,Lists_parametric_models,2,FALSE),),L60)*IF(Mod_3=0,1,0)+'ERG first-line'!N11*IF(Mod_3=1,1,0)
R4 ERG subsequent-line OS [1007] R6 ERG subsequent-line remodel crizotinib [1001]	Mod_4 Mod_6	OS (subsequent-line)	E90:E2360	Crizotinib =IF(con_survival_ALK="No",OFFSET(E89,1,VLOOKUP(con_OS_model_criz,Lists_parametric_models,2,FALSE),),L90)*IF(AND(Mod_4=0,Mod_6=0),1,0)+'ERG subsequent-line'!D11*IF(AND(OR(Mod_4=1,Mod_4=2),Mod_6=0),1,0)+'ERG subsequent-line'!J11*IF(AND(Mod_4=0,Mod_6=1),1,0)
R4 ERG subsequent-line OS [1007] R5 ERG subsequent-line OS treatment effect [1001] R6 ERG subsequent-line remodel crizotinib [1001]	Mod_4 Mod_5 Mod_6	OS (subsequent-line)	P90:P2360	Docetaxel =IF(con_survival_ALK="No",OFFSET(P89,1,VLOOKUP(con_OS_model_doc,Lists_parametric_models,2,FALSE),),W90)*IF(AND(Mod_4=0,Mod_5=0,Mod_6=0),1,0)+'ERG subsequent-line'!E11*IF(AND(Mod_4=1,Mod_5=0,Mod_6=0),1,)+'ERG subsequent-line'!F11*IF(AND(Mod_4=2,Mod_5=0,Mod_6=0),1,0)+'ERG subsequent-line'!I11*IF(AND(Mod_4=0,Mod_5=1,Mod_6=0),1,0)+'ERG subsequent-line'!K11*IF(AND(Mod_4=0,Mod_5=0,Mod_6=1),1,0)
R6 ERG subsequent-line remodel crizotinib [1001]	Mod_6	PFS (subsequent-line)	E87:E2357	Crizotinib =IF(con_survival_ALK="No",OFFSET(E86,1,VLOOKUP(con_PFS_model_criz,Lists_parametric_models,2,FALSE),),L87)*IF(Mod_6=0,1,0)+'ERG subsequent-line'!L11*IF(Mod_6=1,1,0)
R6 ERG subsequent-line remodel crizotinib [1001]	Mod_6	PFS (subsequent-line)	P87:P2357	Docetaxel =IF(con_survival_ALK="No",OFFSET(P86,1,VLOOKUP(con_PFS_model_doc,Lists_parametric_models,2,FALSE),),W87)*IF(Mod_6=0,1,0)+'ERG subsequent-line'!M11*IF(Mod_6=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R6 ERG subsequent-line remodel crizotinib [1001]	Mod_6	TOT (subsequent-line)	E60:E2330	Crizotinib =IF(con_survival_ALK="No",OFFSET(E59,1,VLOOKUP(con_TTF_model_criz,Lists_parametric_models,2,FALSE),),L60)*IF(Mod_6=0,1,0)+'ERG subsequent-line'!N11*IF(Mod_6=1,1,0)
R7 ERG first line PFS utility	Mod_7	Utilities	C33	Crizotinib =VLOOKUP(D33,$D$13:$E$14,2,FALSE)*IF(Mod_7<>2,1,0)+C15*IF(Mod_7=2,1,0)
R7 ERG first line PFS utility	Mod_7	Utilities	C34	Pemetrexed+platinum =VLOOKUP(D34,$D$15:$E$15,2,FALSE) *IF(AND(Mod_7<>1,Mod_7<>3),1,0)+C13*IF(Mod_7=1,1,0)+0.75*IF(Mod_7=3,1,0)
R8 ERG subsequent-line PFS utility	Mod_8	Utilities	C38	Crizotinib =VLOOKUP(D38,$D$23:$E$24,2,FALSE)*IF(Mod_8<>1,1,0)+(C23-0.03)*IF(Mod_8=1,1,0)
R8 ERG subsequent-line PFS utility	Mod_8	Utilities	C39	Docetaxel =VLOOKUP(D39,$D$25:$E$25,2,FALSE)*IF(Mod_8<2,1,0)+(C25+0.03)*IF(Mod_8=2,1,0)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRiG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by 5pm on Thursday 23 November 2017 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 Wording Changes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The licensed indication stated is not factually accurate. On pages 10 and 11: "Crizotinib is licensed in Europe for the treatment of patients with	Please change 'patients' to 'adults' "Crizotinib is licensed in Europe for the treatment of adults with ROS1+ advanced NSCLC"	Pfizer please request that the exact wording from the SmPC is used	The suggested change will be made in the updated ERG report.

ROS1+ advanced NSCLC" Wording in the summary of product characteristics (SmPC) is 'adults' with ROS1-positive advanced NSCLC.			
The rationale for why subsequent-line patients will decrease needs additional explanation On pages 10 and 38: "However, the company anticipates that the number of patients treated at subsequent-line will reduce over time as patients with ROS1+ advanced NSCLC will be identified when they first present with NSCLC symptoms."	Please add at end of this sentence: "However, the company anticipates that the number of patients treated at subsequent-line will reduce over time as patients with ROS1+ advanced NSCLC will be identified when they first present with NSCLC symptoms, and treated with crizotinib in the first-line."	The sentence currently used does not fully explain why crizotinib use in the 2nd and later lines will decrease.	The suggested sentence will be added in the updated ERG report.
No evidence is given to support the statements that docetaxel+nintedanib is the NHS standard of care On page 11: "Treatment with docetaxel+nintedanib in the subsequent care setting is the NHS standard of care for patients with tumours of	The ERG should please either add the evidence that this statement is based on, or the statement should be removed.	Statements on what therapy is the standard of care should always we accompanied with the evidence that this conclusion is based on, which may be clinical advice or prescribing data. NICE guidance states "Nintedanib in combination with docetaxel is recommended, within its marketing authorisation, **as an**	This is not a factual error. No change required.

adenocarcinoma histology." On page 21: "the NHS standard of care for treatment of patients with advanced NSCLC of adenocarcinoma histology has recently changed and is now docetaxel+nintedanib." On page 42: "However, the ERG considers that docetaxel+nintedanib is standard of care for patients with tumours of adenocarcinoma histology"		**option** for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy, only if the company provides nintedanib with the discount agreed in the patient access scheme." Furthermore, the ERG report (page 40), it is also stated that "Clinical advice to the ERG is that docetaxel monotherapy is also used to treat patients who are not fit enough for treatment with docetaxel+nintedanib."	
The wording "clinical effectiveness" is misleading here, as this section relates to using the ALK data as a proxy for ROS1 in the CS for comparative effectiveness analyses On page 12: "Clinical effectiveness analyses presented in the CS are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for	Please change "Clinical effectiveness analyses" to "Comparative effectiveness analyses" or "Relative effectiveness analyses"	The term "Clinical effectiveness" is later used in the ERG report in describing data from PROFILE 1001. Therefore, the ERG is not using this term to only relate to relative effectiveness. Pfizer would please suggest that this statement is changed to avoid any ambiguity.	The updated ERG report will state: Page 12 <u>Comparative effectiveness analyses presented in the CS are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for data from ROS1+ advanced NSCLC</u>

data from ROS1+ advanced NSCLC patients." On page 36: "Clinical effectiveness analyses presented are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for ROS1+ advanced NSCLC patients.".			patients. Page 36 Comparative effectiveness analyses presented are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for ROS1+ advanced NSCLC patients.
Insufficient justification to support the stament regarding the concerns about the generalisability of the clinical data to UK patients On page 14, 23 and 54: There are concerns regarding the generalisability of the clinical data to patients who are treated in clinical practice in the UK On page 14: "However, the patients recruited to the trial [PROFILE 1014] are not generally representative of patients with ALK+ advanced NSCLC who are treated in clinical practice in the UK as they	Please change the statement on page 14 and page 23 so that it agrees with the final conclusions of the Committee in TA406, that the patients' characteristics in PROFILE 1014 reflected people with ALK-positive NSCLC in England and that the adjustments made to the trial population based on Davis et al. 2015 (in the economic analysis) were considered to be conservative. Please remove the statement on page 54	In the guidance for crizotinib in first-line ALK-positive NSCLC, the Committee concluded that: "The Committee heard from the company and the clinical experts that the patients' characteristics in PROFILE 1014 reflected people with ALK-positive NSCLC in England, and so the Committee concluded that PROFILE 1014 was suitable for its decision making." Similarly, the Committee from the first-line crizotinib ALK-positive NSCLC appraisal noted: "The Committee was aware that the data from PROFILE 1014 were adjusted so that the trial	Clinical advice to the ERG is that patients recruited to the PROFILE 1014 trial are generally representative of patients treated in the NHS. In the updated ERG report, the statement on p14 will be changed to: The ERG considers the PROFILE 1014 trial to be a good quality trial. Clinical advice to the ERG is that the patients recruited to the trial are generally representative of patients with ALK+ advanced NSCLC who

have different baseline patient characteristics." On page 23: "There are concerns about the generalisability of the adjusted results of the PROFILE 1014 trial." Further explanation and justification for this statement is required, as it disagrees with the conclusions of the Committee in TA406. On page 54: "The estimates presented in the clinical effectiveness section of the CS (and in this ERG report) have not been adjusted to account for any differences in the patient characteristics of the PROFILE 1014 trial population and the population that would be treated in NHS clinical practice. Therefore, results from the PROFILE 1014 trial should be interpreted with caution due to the uncertainty surrounding the generalisability of these results to the ALK+ advanced NSCLC patient population, and therefore to the ROS1+ advanced patient		population reflected the patient population in a retrospective cohort study (Davis et al. 2015; see section 4.11), and considered this to be a conservative assumption" Furthermore, later in the current ERG report (page 23), the following statement can be found: "Clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS"	are treated in clinical practice in the UK. However, the ERG notes that adjustments were made to the trial population based on characteristics of patients from a retrospective cohort study from the US and Canada. A previous Appraisal Committee considered the adjustments to be conservative. No change to be made to text on p23. This statement refers to the adjusted results of the PROFILE 1014 trial. The ERG has concerns about the generalisability of the adjusted results to patients treated in the NHS. P54 The text in the updated ERG report will be changed to: The estimates presented

population, that would be treated in NHS clinical practice." The differences that the ERG believe exist between the PROFILE 1014 study and the population seen in clinical practice have not been explained and disagree with the conclusions of the Committee in TA406, as well as other statements in the ERG report.			in the clinical effectiveness section of the CS (and in this ERG report) have not been adjusted to account for any differences in the patient characteristics between the PROFILE 1014 trial population and the US and Canada cohort population that the company used. However, clinical advice to the ERG is that patients recruited to the PROFILE 1014 trial are generally representative of patients treated in the NHS and therefore the ERG questions the adjustment made based on a retrospective cohort study from the US and Canada. The ERG notes that a previous Appraisal Committee considered the adjustment to be conservative.
The ERG states that there are no useful OS data from either the ALK or ROS1 population,	Alter the wording on page 15 and 43 to avoid the phrase ' no useful OS data'. The ERG could please describe the data as	There is some OS data and although this is not mature, it does not mean that it is not useful. The	The updated ERG report will be amended to:

however albeit immature, the OS data is useful for decision making. On pages 15 and 43: "This means that there are no useful OS data from either the population specified in the decision problem…" Pfizer do not think this wording is appropriate On page 37: "This means that there are no OS data for patients with ROS1+ advanced NSCLC who have been treated with crizotinib." This statement is factually inaccurate, as there is still information available on OS, even if the median has not been reached.	'limited' or 'immature'. Please correct the statement on page 37 so that it states that there is no *median* OS data.	median duration of follow-up for OS in PROFILE 1001 was 25.4 months. The knowledge that the median duration has not been reached at this time point still provides useful OS data relevant to the decision problem. OS data also exists in supporting studies for the ROS1 population, including the EUCROSS and OX-ONC studies (see Table 8, Appendix D of the CS). These supporting studies were not used in the economic model but provide additional information to support the clinical effectiveness evidence from PROFILE 1001. HTA decisions have to be made on the basis of the evidence available and therefore the OS data that exists, despite being immature, is still useful for the decision-making process, even though it may not be optimal.	Page 15 and Page 43 <u>This means that there are no conclusive OS data for patients with ROS1+ advanced NSCLC who have been treated with crizotinib.</u> Page 37 <u>This means that there are no median OS data for patients with ROS1+ advanced NSCLC who have been treated with crizotinib.</u>
The recommendation for up-front testing is also supported independently, by clinical expert publications.	Please change sentence to: "The company states that a working group of pathologists, sponsored by Pfizer Ltd, recommended that the preferred approach to testing for ROS1 positivity is carried out at the same time as other molecular tests	As noted on page 25 of the CS, it is highlighted that up-front testing is also independently recommended by expert publications: "Patients with advanced non-	The updated ERG report will be amended to: <u>The company states that a working group of pathologists, sponsored by Pfizer Ltd,</u>

On page 33: "The company states that a working group of pathologists, sponsored by Pfizer Ltd, recommended that testing for ROS1 positivity is carried out at the same time as other molecular tests." This is also included in published recommendations, as outlined in the CS. This should be added.	and that this approach is also included in published expert recommendations."	squamous NSCLC should be tested upfront for ROS1-positivity, alongside EGFR and ALK testing.[61]" The reference for this is noted below. 61. Bubendorf L, Buttner R, Al-Dayel F, et al. Testing for ROS1 in non-small cell lung cancer: a review with recommendations. *Virchows Arch* 2016;469:489-503.	recommended that the preferred approach to testing for ROS1 positivity is carried out at the same time as other molecular tests and that this approach is also included in published expert recommendations.

Issue 2 Confidential Marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The date of future updates to PROFILE 1001 is CiC On pages 12, 42 and 64: "the company does not intend to carry out further updates of OS until [redacted]." [redacted] should be marked as commercial in confidence	Please mark [redacted] with blue highlighting and underlined, to indicate that this is commercial in confidence	Pfizer has not announced this future data cut yet and therefore wishes to keep this information confidential at the current time.	The suggested change will be made in the updated ERG report.
These data are published and can therefore be unmarked as CiC	Please remove blue confidential highlighting from 151 (86.8) and 23 (13.2) for the category age for PROFILE 1007	These numbers are in the Shaw *et al.* (2013) publication and therefore are publicly available	The suggested change will be made in the updated ERG report.

In Table 9: Category years for the chemotherapy arm of PROFILE 1007 are marked as commercial in confidence			
These data have not been published and are therefore deemed CiC On page 63: The response rates for the two patients retrospectively determined to be ROS1-negative should be marked as CiC.	[redacted] and [redacted], for the patients retrospectively determined to be ROS1-negative should please be underlined and highlighted in blue to indicate that this is commercial in confidence	These values have not yet been published and concern individual responses to treatment in the two ROS1-negative patients from PROFILE 1001. Therefore, Pfizer request that this is treated as commercial in confidence.	The suggested change will be made in the updated ERG report.
The unadjusted HR for PROFILE 1007 have been published and are therefore not CiC In Table 14: The unadjusted OS HR for PROFILE 1007 by treatment received should not be marked as CiC	Please remove confidential highlighting from 0.901 (0.667 to 1.216; p=0.25) and 0.791 (0.563 to 1.111; p=0.09) for OS HR.	These numbers are published in Shaw *et al.* (2016). Crizotinib vs chemotherapy in ALK+ advanced non-small cell lung cancer (NSCLC): final survival results from PROFILE 1007, presented at ASCO, June 3–7, 2016.	The suggested change will be made in the updated ERG report.

Issue 3 Incorrect Statements or Numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Clarifying that end-of-life criteria was met in both first- and subsequent-line appraisals On page 12: "The Appraisal Committee in TA422 and TA406 considered that treatment with crizotinib in the subsequent-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population. The Appraisal Committee concluded that the extension to life criterion was met." TA406 was the appraisal in first-line, not subsequent-line	Please change statement to: "The Appraisal Committee in TA406 and TA422 considered that treatment with crizotinib in the first-line and the subsequent-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population. The Appraisal Committee concluded that the extension to life criterion was met."	End-of-life criteria was met for both appraisals, TA406 and TA422, therefore this relates to both lines of therapy, first- and subsequent-line treatment with crizotinib. The sentence as it currently stands is not factually accurate.	In the updated ERG report, the text on p12 will be changed to: The Appraisal Committee in TA406 and TA422 considered that treatment with crizotinib in the first-line and the subsequent-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population. The Appraisal Committee concluded that the extension to life criterion was met.
Providing clarity on the exact grade of vision disorders, which were Grade 1 or 2 only On page 13: "The most frequently occurring AEs of any grade were vision disorders; these were generally	Please change sentence to: "The most frequently occurring AEs of any grade were vision disorders; these were all Grade 1 or Grade 2."	The use of the word 'generally' incorrectly indicates that there were a small number of Grade 3 or Grade 4 vision disorders, which is a factual inaccuracy.	In the updated ERG Report, the text will be changed to: The most frequently occurring AEs of any grade were vision disorders; these were all Grade 1 or Grade 2

Grade 1 or Grade 2." All vision disorders were Grade 1 or 2; there were no Grade 3 or 4 vision disorders (as stated in the text on page 71 of the CS).			The text in Section 4.5 of the updated ERG Report will also be amended to reflect this change.
Providing clarity on the type of Grade 4 AEs reported On page 13: "No Grade 4 AEs were recorded." This statement is not factually accurate, as there were 6 cases of pulmonary embolism that were Grade 4 (as stated in the footnote of Table 20 on page 73 of the CS).	Please change sentence to: "The only Grade 4 AEs recorded were 6 cases of pulmonary embolism, none of which were classed as treatment-related."	The statement in the ERG report is factually incorrect.	In the updated ERG report, the text on p13 will be changed to: <u>The only Grade 4 AEs recorded were 6 cases of pulmonary embolism, none of which were classed as treatment-related.</u> The text in Section 4.5 of the updated ERG Report will also be amended to reflect this change.
The percentage value for crossover (updated data cut for PROFILE 1014) is incorrect On page 13: "Patient crossover from pemetrexed+platinum to crizotinib was 63.7%." This value is factually incorrect - it should be 84.2%, as given in the Table 15 of the CS	Please change this value to 84.2% This correction was provided in the addendum.	The value of 84.2% was reported in the Mok et al. 2017 oral presentation presented at ESMO 2017 as referenced in Table 15 of the CS (Mok TS, Kim D-W, Wu Y-L, et al. Crizotinib in advanced ROS1-rearranged non-small cell lung cancer (NSCLC): updated results from PROFILE 1001. ESMO Congress (2017). 2017;Oral Presentation. ULR: http://oncologypro.esmo.org/Meeting-	The suggested correction will be made in the updated ERG report.

		Resources/ESMO-2017-Congress/Overall-Survival-OS-for-First-Line-Crizotinib-Versus-Chemotherapy-in-ALK-Lung-Cancer-Updated-Results-from-PROFILE-1014)	
The percentage value for crossover (PROFILE 1007) is incorrect On page 13, Table 13: "Patient crossover from chemotherapy to crizotinib was 86.8%." This value is incorrect – it should be 88.5%, as given in the Table 15 of the CS	Please change this value to 88.5% This correction was provided in the addendum.	The value of 88.5% was reported in the Shaw et al. 2016 poster (PROFILE 1007) presented at ASCO, as referenced in Table 15 of the CS (Shaw AT, Jänne PA, Besse B, et al. Crizotinib vs Chemotherapy in ALK+ Advanced Non-Small Cell Lung Cancer (NSCLC): Final Survival Results From PROFILE 1007. Presented at ASCO 2016 2016b.)	This correction will be made in the updated ERG report.
Percentage of patients previously treated with pemetrexed+platinum in the first line setting for PROFILE 1001 is incorrect On page 14: "Of the patients with previously treated disease, only 63.5% had received the NHS standard of care in the first-line setting, i.e., pemetrexed+platinum	Please change the value to 37.0%	The value used by the ERG is incorrect. Pfizer are not sure where the ERG have derived this value of 63.5% from.	The suggested correction will be made in the updated ERG report.

chemotherapy." As this relates to PROFILE 1001 trial, then this value is factually incorrect. In the response to clarification questions, we provided the information that 32.1% of the total PROFILE 1001 ROS1 population had received prior pemetrexed plus platinum as first-line therapy. This would equate to 37.0% of the 46 patients who had received prior treatment.			
There is insufficient evidence to support the statement that patients in PROFILE 1001 are 'older' compared to patients in PROPILE 1007 and PROFILE 1014 Page 38: "The ERG notes that, compared with patients in the PROFILE 1014 and PROFILE 1007 trials, patients recruited to the PROFILE 1001 study were older ..." Pfizer do not think there is sufficient evidence to justify the statement on patients in	Please remove the statement regarding patients in PROFILE 1001 being older than patients in PROFILE 1007 and 1014. The following statement (found on page 54 of the ERG report) should also be added to page 38: "The ERG did not note any important differences in baseline characteristics between the treatment arms of the PROFILE 1014 and PROFILE 1007 trials."	In PROFILE 1001, the mean age was 55 years. In PROFILE 1007 and PROFILE 1014, the mean age was 49-51 and 52-54, respectively (see Table 11 in the CS). These differences are not large enough to make the conclusion that PROFILE 1001 patients were 'older'. Later in the ERG report (page 53) it is also stated that: "The ERG did not note any important differences in baseline characteristics between the treatment arms of the PROFILE 1014 and PROFILE 1007 trials." Furthermore, the ERG report (page 23,	This is not a factual error, but a matter of opinion. No change required.

PROFILE 1001 being 'older' than patients in PROFILE 1007 and PROFILE 1014.		54, and 81) states: "clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS"	
The percentage used to quote the maturity of the updated data cut for PROFILE 1014 is incorrect On page 42: "Data for OS are also presented (44.3% mature)" This value is incorrect – it should be 41.3% for crizotinib and 47.4% for chemotherapy. The OS based on the updated analysis of PROFILE 1014 as reported by Mok et al. 2017 (ESMO Oral Presentation) was included in the addendum/corrections sent to NICE and the ERG on 30th October 2017. The Mok et al. 2017 presentations slides were	Please change this value to "41.3% mature for crizotinib and 47.4% mature for chemotherapy"	These values were reported in the Mok et al. 2017 ESMO Oral Presentation. (Mok TS, Kim D-W, Wu Y-L, et al. Crizotinib in advanced ROS1-rearranged non-small cell lung cancer (NSCLC): updated results from PROFILE 1001. ESMO Congress (2017). 2017;Oral Presentation. ULR: http://oncologypro.esmo.org/Meeting-Resources/ESMO-2017-Congress/Overall-Survival-OS-for-First-Line-Crizotinib-Versus-Chemotherapy-in-ALK-Lung-Cancer-Updated-Results-from-PROFILE-1014)	The 44.3% in the ERG report is the average value of 41.3% and 47.4%. No change required.

not added to the reference pack when the corrections to the CS were made.			
Incorrect value reported in CS and therefore ERG report In Table 9: Median time since first diagnosis in PROFILE 1001 is "not reported"	Please amend to 1.16 years (0.0–11.2)	Pfizer please suggest correcting the value as per the publicly available ROS1-positive NSCLC EPAR. The correct value was not reported in the original CS.	The ERG will add the 1.16 years in the updated ERG report.
Correcting the N numbers for PROFILE 1014 and PROFILE 1007 In Table 13: The N numbers for PROFILE 1007 and PROFILE 1014 are incorrect	The N number for PROFILE 1014 should please be corrected to 343. The N number for PROFILE 1007 should please be corrected to 347.	The N numbers for PROFILE 1007 and PROFILE 1014 have been confused. The change ensures that the correct N numbers are reported for each trial, as in the CS.	The suggested corrections will be made in the updated ERG report.
Correcting the number of patients who crossed-over in PROFILE 1007 In Table 13: The patient numbers for crossover in PROFILE 1007 are incorrect	The number of patients who crossed-over in PROFILE 1007 in the crizotinib arm is 65/173 (37.6%). This correction was provided in the addendum.	The correct numbers for patients who crossed-over to either crizotinib or chemotherapy were reported in Table 15 of the CS. The values were reported in the Shaw et al. 2016 poster presented at ASCO (Shaw AT, Jänne PA, Besse B, et al. Crizotinib vs Chemotherapy in ALK+ Advanced Non-Small Cell Lung Cancer (NSCLC): Final Survival Results From PROFILE 1007. Presented at ASCO 2016 2016b.	The suggested correction will be made in the updated ERG report.

The crossover adjusted HR reported for OS is incorrect. It would seem that the PFS HR has been used (as per accepted ERG scenario from TA422), instead of reporting the HR from directly from the PROFILE 1007 trial In Table 13: The crossover adjusted HR for OS for PROFILE 1007 is incorrect On page 68: The crossover adjusted HR for OS for PROFILE 1007 is incorrect	The crossover adjusted HR for OS for PROFILE 1007 should please be changed to 0.383 (0.283 to 0.518). This correction was provided in the addendum.	The HR quoted in the ERG's table 13 is the HR which was used in the economic modelling (accepted ERG scenario from TA422). This is the HR for PFS from PROFILE 1007 and subsequently used in the economic modelling for TA422 (and adopted in this submission). The previous ERG's rationale for this was that the PFS HR was assumed to be more robust than the crossover adjusted HR for OS (PROFILE 1007). As Table 13 reports a summary of the key efficacy results, it is therefore factually accurate to report here the crossover adjusted HR ***exactly*** as it is reported in PROFILE 1007 (adjusted using RPSFTM, based on the stratified log-rank test).	The HR presented in Table 13 of the ERG report was derived from the information available to the ERG at the time that the ERG report was submitted to NICE. The company provided the crossover-adjusted HR for OS after the ERG report had been submitted to NICE, with no information as to which method of crossover adjustment was used to generate the HR, and no explanation as to why the confidence intervals for the HR do not match the confidence intervals for the crossover-adjusted OS HR in TA422. The ERG considered it inappropriate to update the HR without understanding the underpinning methodology.
Providing clarity, the statement around PFS should state that it relates to crizotinib. On page 66: The ERG does not state that	The sentence should please state: "Median PFS data **for crizotinib** were not similar…"	To make sure that it is clear that this refers to median PFS for crizotinib, as stated in the CS.	The text in the updated ERG report will be amended as suggested.

the median PFS data reported are for crizotinib only when comparing across all three PROFILE studies			
Providing clarity that Pfizer did not provide an alternative crossover adjusted HR for PROFILE 1007, but rather provided a corrected value (as per above correction relating to Table 13). On page 69: The ERG state that the company provide an alternative crossover adjusted OS HR for PROFILE 1007, and notes that this does not match the RPSFTM-adjusted OS HR presented by the company in TA422.	The ERG should please state that this is the adjusted HR from the final OS analysis from PROFILE 1007, adjusted using RPSFTM, based on the stratified log-rank test.	This is not an alternative HR, but the clinical crossover adjusted HR using RPSFTM, based on the stratified log-rank test. The reference for this HR is Shaw *et al.* (2016). Crizotinib vs chemotherapy in ALK+ advanced non-small cell lung cancer (NSCLC): final survival results from PROFILE 1007, presented at ASCO, June 3–7, 2016.	The text in the updated ERG report will be changed to: The company provide a crossover adjusted OS HR for PROFILE 1007, and notes that this does not match the RPSFTM-adjusted OS HR presented by the company in TA422. As noted earlier in this document, the HR was provided by the company after the ERG report had been submitted to NICE, without explanation of the methods used in its calculation. No explanation was provided as to why the confidence intervals for the HR do not match the confidence intervals for the crossover-adjusted OS HR in TA422. The ERG considered it inappropriate to update the HR without understanding the underpinning calculations.

			The ERG was unable to find the HR in the Shaw 2016 conference abstract.
Providing clarity on the type of Grade 4 AEs reported, none of which were treatment-related On page 77: The ERG incorrectly reports that no Grade 4 AEs were recorded during the PROFILE 1001 study.	The statement should please be amended to state: "No treatment-related Grade 4 AEs were recorded during the PROFILE 1001 study".	In PROFILE 1001, there are six reports of Grade 4 pulmonary embolism, although none were treatment-related.	The suggested text will be included in the updated ERG report.
Providing clarity on why no patients in PROFILE 1007 were treated with docetaxel+nintedanib (as it was not available at the time) On page 81: The ERG state that no patients in the study PROFILE 1007 were treated with docetaxel+nintedanib	The following should please be added to the statement: "This is because docetaxel+nintedanib was not available to patients when this trial started recruitment."	Docetaxel+nintedanib was approved by the EMA in 2014. The PROFILE 1007 study started recruitment in 2009 and therefore the docetaxel+nintedanib combination therapy was not licensed at the time of PROFILE 1007 recruitment. The wording in the ERG report should be updated to explain the reason why no patients in PROFILE 1007 were treated with docetaxel+nintedanib.	This is not a factual error. No change required.

Issue 4 Incorrect reporting of pemetrexed plus platinum time on treatment methodology in the base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Providing clarity that in the base	Pfizer please request the statement on page	The statement is factually	The text in the updated

case, treatment with pemetrexed+platinum is not "capped" at six cycles. Instead, the time on treatment curve is used (as per TA406), which is not "capped" at six-cycles. On page 84 the ERG states: "Treatment is administered in the base case model for a maximum of six cycles." When referring to the duration of treatment for pemetrexed + platinum. On page 90: "Mean TTD in the company first-line base case model is 16.4 months for treatment with crizotinib and 3.8 months (maximum six cycles) for treatment with pemetrexed+platinum." Table 19, Page 86: "Stratified gompertz (independent) 6-cycles only"	84 to be amended to "Treatment is administered in the base case model based on the time on treatment curves from TA406. Treatment is administered in the PROFILE1001 analysis for a maximum of six cycles" Pfizer please request the statement on page 90 to be amended to: "Mean TTD in the company first-line base case model is 16.4 months for treatment with crizotinib and 3.8 months for treatment with pemetrexed+platinum." Pfizer please request the statement "6 cycles only" to be removed	inaccurate	ERG report will be changed to: P84 <u>Treatment is administered in the base case model based on the time on treatment curves from TA406</u> P90 <u>Mean TTD in the company first-line base case model is 16.4 months for treatment with crizotinib and 3.8 months for treatment with pemetrexed+platinum</u> Table 19 will be amended accordingly.

Issue 5 Updated base case 1st line TTD and PFS curves

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pfizer identified a cut and paste error relating to the base case first-line curves (TTD and PFS) that were presented in the CS. This was alerted to NICE, who requested an addendum alongside our response to the ERG report. 1st line base case curves Table 19, page 86: States stratified generalised gamma used for comparator PFS curve in base case (first line). And Stratified gompertz (independent) used for TTD curve in base case (first line). Page 89: "Fully stratified generalised gamma curves are used to estimate PFS in the first-line setting for this appraisal; the curves have been adjusted according to the baseline characteristics of the patients in the Davis study."	Please make amendments to the ERG report in line with the addendum provided alongside this proforma.	The ERG are correct in the statement in regards to the curves presented in the original company submission However, Pfizer would like to note that an addendum was submitted on 23/11/2017 where the following curves were updated to reflect the true Committee processes from TA406: <u>TTD</u> Crizotinib: Exponential (fully stratified model) Pemetrexed: Gompertz (fully stratified model) <u>PFS</u> Crizotinib: Log-normal (fully stratified model) Pemetrexed: Gamma (fully stratified model) The updated curves had minimal impact on the results.	The updated ERG report will reflect the updated PFS and TTD curves in the company's first-line model. The updated ERG report will also include the updated results of the ERG's exploratory analyses to take into account first-line base case presented in the company's addendum.

On page 90: "Fully stratified (independent) gompertz curves are used to estimate TTD in the first-line setting for this appraisal, which have been adjusted to take account of the baseline characteristics of the patients in the Davis study."			

Issue 6 Incorrect confidence intervals around the docetaxel utility

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Identified error relating to the confidence intervals for docetaxel utility (both health states) Table 24 on page 103: ERG report the confidence intervals for docetaxel (both health states) from PROFILE1007 as 0.61 to 0.70 which are incorrect	Pfizer please request the confidence intervals in Table 24 to be amended to 0.58 to 0.74	The confidence intervals are factually inaccurate This does not have an impact on the results at the confidence intervals are correct in the model.	This is an error in the CS. The confidence intervals reported in Table 24 of the ERG report are taken from Table 40 of the CS. The updated ERG report will include the suggested change.

Issue 7 Incorrect statement on functionality in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Providing clarity that the baseline-characteristics adjustment can be removed within the model On page 116: "However, the company has not built into the first-line model the same function for the associated PFS and TTD estimates, which means that the overall effect on the first-line base case ICER per QALY gained of removing the baseline-characteristics adjustment cannot be easily investigated."	Pfizer please this statement to be removed from the ERG report as it is not factually correct.	The statement incorrectly suggests that the functionality to remove the baseline characteristic adjustment for TTD and PFS is not available in the model. The ERG can remove the adjustment by changing the patient characteristics in Cells C6:D12 in Sheet "ALK+ 1L TTD" (for TTD) and C9:D15 in Sheet "ALK+ 1L PFS" (for PFS) in the same way as OS.	This is not a factual error. The ERG is aware that the model could be manually amended to remove the effect of the adjustment of baseline characteristics. The ERG's comment relates to the fact that, although these adjustments can be removed easily for OS using a switch in the Controls sheet, that switch does not extend to the rest of the time-to-event estimates. This adds extra complexity when reviewing the model.

Issue 8 Incorrect statement around impact on ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Providing clarity that typos previously identified and communicated to NICE have no impact on the ICER per QALY gained	Pfizer please request this state is amended to: "This update was submitted as a result of typos identified by the company which it says have **no impact** on the ICER per	The statement incorrectly suggests that there was a change in the results caused by the correction of the identified typos The only typo identified in the	The text in the updated ERG report will be changed to: This update was submitted as a result of a mistake identified by the company which it says has no impact on the ICER per QALY

One page 116 "This update was submitted as a result of mistakes identified by the company which it says have little impact on the ICER per QALY gained"	QALY gained"	model was to the Markov Trace diagrams. This has no impact on the results in the economic model.	gained

Issue 9 Incorrect reporting of data sources

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>Providing clarity for the correct data sources relating to subsequent line PFS and utility
Table 35, Page 118
<table>
<tr><th>Model</th><th>Outcome</th><th>Previous appraisal</th></tr>
<tr><td rowspan="3">First-line base case</td><td>OS</td><td>Updated from TA406</td></tr>
<tr><td>PFS</td><td>TA406</td></tr>
<tr><td>TTD</td><td>TA406</td></tr>
<tr><td>Utility</td><td>TA406</td></tr>
<tr><td rowspan="4">Subsequent-line base case</td><td>OS</td><td>TA422</td></tr>
<tr><td>PFS</td><td>TA296 (precursor to TA422)</td></tr>
<tr><td>TTD</td><td>TA422</td></tr>
<tr><td>Utility</td><td>TA422</td></tr>
</table>
</td>
<td>Pfizer requested the table is amended to:
<table>
<tr><th>Model</th><th>Outcome</th><th>Previous appraisal</th></tr>
<tr><td rowspan="4">First-line base case</td><td>OS</td><td>Updated from TA406</td></tr>
<tr><td>PFS</td><td>TA406</td></tr>
<tr><td>TTD</td><td>TA406</td></tr>
<tr><td>Utility</td><td>TA406</td></tr>
<tr><td rowspan="4">Subsequent-line base case</td><td>OS</td><td>TA422</td></tr>
<tr><td>PFS</td><td>TA296 and TA422</td></tr>
<tr><td>TTD</td><td>TA422</td></tr>
<tr><td>Utility</td><td>TA406 and TA422</td></tr>
<tr><td rowspan="3">PROFILE 1001 scenario</td><td>OS</td><td>New</td></tr>
<tr><td>PFS</td><td>New</td></tr>
<tr><td>TTD</td><td>New</td></tr>
</table>
</td>
<td>Some information in the table is not factually correct.</td>
<td>Table 35 will be amended as suggested in the updated ERG report.</td>
</tr>
</table>

PROFILE 1001 scenario analysis	OS	New	analysis	Utility	TA406 and TA422		
	PFS	New					
	TTD	New					
	Utility	TA406 and TA422					
This table incorrectly reports the sources for PFS (subsequent line) and utility (subsequent line)							

Issue 10 Incorrect trial referenced

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Providing clarity for the correct reference (PROFILE 1007) On page 127, Figure 13. In the legend of the graph, the crizotinib OS curve is labelled as the 'ERG exponential estimate PROFILE 1014'.	Pfizer please request the legend to be amended to: "ERG exponential estimate PROFILE 1007"	Factual inaccuracy. As this is referring to subsequent line should be PROFILE1007	In the updated ERG report, the legend for Figure 13 will be changed as suggested

Issue 11 ERG states the company presents a scenario which was not included in the model or company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Providing clarity that Pfizer did not undertake this scenario analysis for PROFILE 1001	Pfizer please request this statement to be removed from the ERG report as it is not factually correct.	The statement is factually incorrect Pfizer have not explored this	This is not a factual error. The company's subsequent-line PROFILE 1001 analysis applies

On page 136 The ERG states: "The ERG notes that the company PROFILE 1001 study scenario applies the PFS HR from the PROFILE 1007 trial to crizotinib OS, so the ERG has not modelled this method as an exploratory scenario."		scenario in the PROFILE1001 analysis	the PFS HR from the PROFILE 1007 trial to estimate OS transition probabilities for the comparator (docetaxel). For clarity, the text in the updated ERG report will be changed to read: The ERG notes that the company's subsequent-line PROFILE 1001 analysis applies the PFS HR from the PROFILE 1007 trial to modelled crizotinib OS from the PROFILE 1001 study. The ERG has therefore not modelled the application of the PFS HR from the PROFILE 1007 trial as an exploratory scenario in the subsequent-line PROFILE 1001 analysis.

Issue 12 ERG has included an exploratory analysis for utility in the second-line setting to account for baseline differences between the treatment arms of PROFILE 1001

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Providing clarity that baseline differences were accounted for in relation to PROFILE 1007	Pfizer please request that the ERG removes these statements, and similar statements.	The statement is factually incorrect as Pfizer did already adjust for baseline utility in their	In the updated ERG report, the following changes will be made: Page 24 Section 1.10:

utility values On page 123, the ERG states: "The Appraisal Committee in TA422 observed that mean baseline utility was different for the crizotinib and pooled chemotherapy arms in the PROFILE 1007 trial and noted that the company had not adjusted for this difference."	Pfizer also please request the scenarios where the ERG attempt to adjusted for this by subtracting 0.03 from the crizotinib utility and adding 0.03 to the docetaxel utility are also removed from the ERG report.	analysis. The primary paper (Blackhall et al, 2014) outlining the methods used states: *"Repeated measures mixed-effects analyses were performed to compare between-treatment EQ-5D index on treatment scores, the EORTC QLQ C-30 and LC-13 item and domain scores, and EQ-5D VAS change from baseline scores so as to adjust for correlation between data collected across multiple data points for an individual.* ***Baseline scores were included as control variables within the regression model.*** *No adjustments were made for multiplicity of testing."* Blackhall et al. 2014. Patient-Reported Outcomes and Quality of Life in PROFILE 1007: A Randomized Trial of Crizotinib Compared with Chemotherapy in Previously Treated Patients with ALK-Positive Advanced Non–Small-Cell Lung Cancer. J Thorac Oncol. 9: 1625–1633) Therefore, as baseline utility has	~~The ERG has also explored the impact of using different PFS utility values in the subsequent-line model, this time to explore the impact of adjusting for differences in baseline EQ-5D values in the PROFILE 1007 trial. The ERG has investigated two scenarios for subsequent-line PFS utility: a decrease of 0.03 in the PFS utility for treatment with crizotinib; and an increase of 0.03 in the PFS utility for treatment with docetaxel.~~ Page 25, Section 1.10.1 The resulting ICERs per QALY gained in the subsequent-line base case when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted]. The resulting ICERs per QALY gained in the subsequent-line PROFILE 1001 scenario when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted]. Page 119 Section 5.6.3: ~~Progression-free utility values: subsequent-line treatment~~ ~~The Appraisal Committee in TA422~~

		already been adjusted for, it is incorrect for the ERG to make any further adjustments in the exploratory analyses.	~~observed that mean baseline utility was different for the crizotinib and pooled chemotherapy arms in the PROFILE 1007 trial and noted that the company had not adjusted for this difference. The difference in mean baseline utility (0.03) in the PROFILE 1007 trial was not statistically significant. However, the ERG considers that a 0.03 difference in the point estimate of utility can have an impact on the size of the resulting ICERs per QALY gained when different utility values are applied to different treatments.~~ Page 131, Section 5.6.5: ~~**Progression free utility values: subsequent line**~~ ~~The ERG has investigated the impact of adjusting PFS utility values in the subsequent-line model to account for the difference in the baseline EQ-5D point estimates from the PROFILE 1007 trial.~~ ~~Removing 0.03 from the PFS utility estimate for treatment with crizotinib increases the subsequent-line base case ICER by £[redacted] per QALY gained to £[redacted]. Adding 0.03 to the PFS utility estimate for treatment with docetaxel increases the subsequent-line base case ICER by £[redacted] per QALY gained to £[redacted]~~ Page 132, Section 6:

			~~PFS utility values:~~ ~~• ERG PFS utility: subtract 0.03 from crizotinib [R8a]~~ ~~• ERG PFS utility: add 0.03 to docetaxel [R8b]~~ Relevant rows removed in Table 43 Table 44 removed Relevant rows removed in Table 47 Table 48 removed Page 141, Section 6: The resulting ICERs per QALY gained in the first-line base case vary from [redacted] (using pemetrexed+platinum PFS utility of 0.75) to [redacted] (assuming no PPS treatment effect and a PFS utility of 0.72 for both treatments). The resulting ICERs per QALY gained in the subsequent-line base case vary from [redacted] (docetaxel OS=applying PFS HR to unadjusted crizotinib OS estimates) to [redacted] (assuming no PPS treatment effect ~~and a decreased PFS utility [-0.03] for crizotinib~~). The resulting ICERs per QALY gained in the first-line PROFILE 1001 scenario vary from [redacted] (using pemetrexed+platinum PFS utility of 0.75) to [redacted] (assuming no PPS treatment effect and a PFS utility of 0.72 for both treatments). The resulting

			ICERs per QALY gained in the subsequent-line PROFILE 1001 scenario vary from [redacted] (~~an increased PFS utility [+0.03] for docetaxel~~ remodel crizotinib time-to-event: K-M data+ exponential) to [redacted] (assuming no PPS treatment effect ~~and a decreased PFS utility [-0.03] for crizotinib~~). Page 144 Section 8.2 The ICERs per QALY gained for treatment with crizotinib versus docetaxel in the subsequent-line base case vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus pemetrexed+platinum in the first-line PROFILE 1001 scenario vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus docetaxel in the subsequent-line PROFILE 1001 scenario vary from [redacted] to [redacted].