NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing presents:

- 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.

Key issues for consideration

Decision problem

- Is it appropriate to generalise to people with squamous cell carcinoma the prognosis, treatment pathway, treatment costs and the benefits for people with adenocarcinoma?
- The NICE scope did not include pemetrexed maintenance therapy as a comparator, however, it is available on the Cancer Drugs Fund.
  - Is there evidence for pemetrexed maintenance therapy in an ALK+ population?
  - Should this appraisal include pemetrexed maintenance therapy as a comparator?

Clinical effectiveness

- The protocol of PROFILE 1014 permitted patients to continue crizotinib after disease progression. Is this realistic for the NHS?
- PROFILE 1014 defined progression on radiographic criteria and not symptomatic criteria.
  - How do clinicians determine progression?
  - Are the progression (free survival) estimates from PROFILE 1014 generalisable to the clinical practice?
- Is it appropriate to generalise PROFILE 1014 results to:
  - Other people receiving chemotherapy (the ERG considered that the death rate in PROFILE 1014 was low)
  - People who cannot take platinum chemotherapy, and were excluded?
  - People who may also be EGFR+ in addition to ALK+?
- Is it appropriate to assume proportional hazards (as the company does) when estimating progression free survival and overall survival?
  - If not, what models would better reflect the data?
- Can the estimates of overall survival be considered reliable in the presence of extensive crossover, immature data and the imbalance of post-progression follow-up therapies?
  - Is it reasonable for the company to have adjusted the results related to survival from PROFILE 1014 to reflect the less-healthy UK population?
  - The company adjusted for cross-over (from chemotherapy to crizotinib) using a 2-stage model controlling for covariates. Which method is the best to adjust for cross-over between treatments in this appraisal?

Cost effectiveness

- The company weights the proportion of cisplatin and carboplatin accompanying pemetrexed a blended comparator. The company assumed that 54% of patients receive cisplatin and 46% receive carboplatin in combination with pemetrexed in the chemotherapy group (the comparator). Are they equally effective? Is this appropriate in this appraisal? Does this reflect UK practice?

- Is it appropriate to assume that all people receive second-line therapy after progression and that this therapy is docetaxel?
  - Is it appropriate to assume that the mean duration of second-line treatment was the same for regardless of whether 1st line therapy was with crizotinib or chemotherapy?
- Is it appropriate to assume that third-line therapy is 'best supportive care'?
- The ERG has concerns that the company calculates costs and QALYs of crizotinib from the key trial; that is, when the trial ends, treatment ends even if the patient hasn't progressed (is the patient is 'censored'). In 'real life' treatment would continue to or beyond progression. What is the Committee's view on this?
- Are the ERG's preferred base-case corrections and assumptions appropriate? These include:
  - Applying drug wastage for people who die part way through a cycle of treatment in both crizotinib and chemotherapy group
  - Removing transition utilities
  - Using an alternative utility for people who have not progressed but have completed chemotherapy treatment
  - Assuming that 25% of people are treated with cisplatin and 75% were treated with carboplatin for chemotherapy
  - Using alternative higher cost for ALK testing
  - Using per cycle drug administration costs for crizotinib
- The company used a generalised Gamma curve to estimate progression free survival and a Weibull curve to estimate OS for both crizotinib and chemotherapy. Is this appropriate?
  - The ERG's preferred base-case model used independent parametric models with separate covariates for prognostic factors for each treatment group. Is this appropriate?
  - The ERG selected the most appropriate curve based on the lowest Akaike information criterion (AIC). Is this appropriate? The ERG selected:
    - the log-normal curve for crizotinib and the Gamma curve for chemotherapy for PFS

- ◊ the Gamma curve for crizotinib and the exponential curve for chemotherapy for OS.

- Does crizotinib meet the end-of-life criteria?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of crizotinib within its marketing authorisation for previously untreated, anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with untreated, ALK-positive, advanced NSCLC.	People with untreated, non-squamous ALK-positive, advanced NSCLC.	The majority of patients (~98%) with ALK-positive NSCLC have non-squamous NSCLC	The population was narrower than the final NICE scope because it only considered people with non-squamous NSCLC. Because the ALK-positive mutation in people with squamous NSCLC is rare, the ERG considered that the company's approach was appropriate. The company did not consider the population with non-squamous or squamous tumours for people in whom treatment with platinum chemotherapy was not appropriate.
Intervention	Crizotinib	Crizotinib	–	The company's approach agreed with the final NICE scope.
Comparators	For people with non-squamous tumour histology:	For people with non-squamous NSCLC: • Pemetrexed in	–	The comparator was in line with the final NICE scope. However, the company

	• Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin)	combination with platinum chemotherapy (cisplatin or carboplatin)		considered cisplatin and carboplatin chemotherapy as a single comparator because they had similar PFS. The ERG noted that cisplatin and carboplatin have different toxicities. The ERG's clinical experts advised that 30% of people with NSCLC receive cisplatin chemotherapy, and 70% of people receive carboplatin chemotherapy. In PROFILE 1014, 53% of patients received cisplatin chemotherapy and 47% received carboplatin chemotherapy. The ERG stated that this may not represent clinical practice in the UK.
	For people with squamous tumour histology: • A third-generation drug (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin)	For people with squamous NSCLC: • Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin) in scenario analysis	Approximately 0.08% of people with squamous NSCLC have an ALK-positive mutation. Therefore, the company extrapolated from clinical data on from non-squamous patients in scenarios analysis.	The ERG considered the company's approach as reasonable.

	For people with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate: • Single-agent chemotherapy with a third-generation drug	Not addressed	The population represents <2% of people with ALK-positive NSCLC. Because of the absence of clinical data in the squamous population, the company considered that a cost-effectiveness analysis as unfeasible.	The ERG considered the company's approach as reasonable.
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	–	The outcomes agree with the outcomes listed in the final NICE scope.
Other considerations	The use of crizotinib is conditional on the presence of ALK mutation. The economic modelling should include the costs associated with diagnostic testing for ALK mutation in people with advanced NSCLC who would not otherwise have been tested. A sensitivity	The economic analysis is consistent with the final scope, presenting results as incremental cost-effectiveness ratios (ICERs), valuing health benefits in terms of QALYs and using an appropriate time horizon of 15 years. The base case analysis applies the	–	Treatments given after disease progression impact overall survival estimates. PROFILE 1014 included a number of second-line treatments which may not reflect current UK practice.

	analysis should be provided without the cost of the diagnostic test.	cost of ALK-testing in the crizotinib arm.		
NSCLC: non small cell lung cancer; ALK: anaplastic lymphoma kinase; PFS: progression free survival				

2 The technology and the treatment pathway

2.1 Lung cancer falls into 2 histological categories: non-small-cell lung cancers, which account for 85–90% of all lung cancers, and small-cell lung cancers. Non-small-cell lung cancer may be grouped by tumour histology into squamous cell carcinoma, adenocarcinoma and large-cell carcinoma, with the latter 2 being collectively referred to as 'non-squamous' lung cancer. Some non-small-cell lung cancers are associated with chromosomal alterations described as anaplastic lymphoma kinase (ALK) fusion genes. ALK fusion genes occur between the tyrosine kinase portion of the ALK gene and other genes. They are believed to be involved in the growth of tumours, and differ from epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations.

2.2 Crizotinib (Xalkori, Pfizer) is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase and its oncogenic variants (that is, ALK fusion events and selected ALK mutations). Crizotinib has a marketing authorisation in the UK for 'the first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).' It also has marketing authorisation 'for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)'

2.3 The summary of product characteristics lists the following as the most common adverse reactions associated with crizotinib treatment: visual disorder, diarrhoea, nausea, vomiting, constipation, oedema, fatigue, decreased appetite, neutropenia, elevated aminotransferases, anaemia, leukopenia, neuropathy, dysgeusia, dizziness, bradycardia, abdominal pain and rash. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 Current treatment options include:

- Chemotherapy with docetaxel, gemcitabine, paclitaxel or vinorelbine plus a platinum-based drug (carboplatin or cisplatin) for advanced NSCLC (NICE clinical guideline 121).
- Pemetrexed in combination with cisplatin, for cancer with adenocarcinoma or large-cell carcinoma histology (NICE technology appraisal guidance 181).

2.5 There are 2 types of targeted treatments for NSCLC: those for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations, and those for ALK-positive NSCLC. The EGFR-TK targeted treatments may not be relevant for the ALK-positive population. There is one ALK-positive targeted treatment, crizotinib, which has a marketing authorisation for previously treated ALK-positive advanced NSCLC. NICE technology appraisal 296 does not recommend crizotinib second-line for 'for treating adults with previously treated anaplastic-lymphoma-kinase-positive advanced non-small-cell lung cancer', but has been available via the Cancer Drugs Fund.

2.6 The recommended dosage of crizotinib is 250 mg twice daily. The list price of crizotinib is £4,689 for 60 capsules (excluding VAT; 'British national formulary' [BNF] online, accessed February 2016). The company has agreed a patient access scheme (discount) with the Department of Health. [redacted] The level of the discount is commercial in confidence.

Table 2 Technology

	Crizotinib	**Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin)**
Marketing authorisation	Crizotinib is indicated for first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer	Pemetrexed in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly

	(NSCLC).	squamous cell histology Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy
Dosing and administration method	Oral Dosing frequency: 250 mg twice daily (total of 500 mg daily). Monitoring (including tests) over and above standard care needed in some circumstances[1].	Dosing frequency: 500 mg/m^2 body surface area, administered as a 10-minute intravenous infusion on the first day of each 21-day cycle. Monitoring (including tests) undertaken to minimise toxicity. Patients treated with pemetrexed should also receive folic acid and vitamin B12 supplements.
Cost information	A confidential patient access scheme (PAS) was agreed with the Department of Health. With the PAS, 60 capsules of crizotinib 200 mg (or 250 mg) costs £[redacted] (excluding VAT; Calculated by NICE technical team) Without the PAS, 60 capsules of 200 mg (or 250 mg) crizotinib costs £4,689 (excluding VAT; 'British national formulary' [BNF] online, accessed February 2016). Mean cost of treatment (without the PAS)[2]: £51,579.00; assuming the median duration of treatment is 11 cycles of 30 days	The cost of pemetrexed is £800 for a 500-mg vial (excluding VAT, 'British national formulary' 57th edition). The cost per patient, assuming an average of four treatment cycles, is approximately £6,400. Mean cost of treatment[2]: £8,806.54 assuming median duration of 6 cycles of 21 days.

See summary of product characteristics for details on adverse reactions and contraindications.

[1]See table 5, page 27 of the company's submission for further information on monitoring

[2]Source table 55, page 159 of the company's submission for further information about the calculation

3 Comments from consultees

3.1 Comments from patient and profession groups were received from the British Thoracic Society (BTS), the Royal College of Pathologists (RCPath) and the Roy Castle Lung Cancer Foundation (RCLCF).

3.2 The RCLCF stated that people with advanced or metastatic NSCLC have no curative treatment options. It stated that people with NSCLC have poor overall outcomes and have a significant unmet medical need. Extending and improving the quality of life is significant to people with NSCLC and their families.

3.3 The RCLCF note that because crizotinib is taken orally, patients spend less time in hospital and avoid intravenous cannulation. The BTS stated that crizotinib is a highly effective therapy for people with ALK–positive advanced NSCLC and is desirable in terms of side effects and quality of life compared with platinum chemotherapy. The RCLCF stated that common side effects include visual disturbances, nausea, vomiting, diarrhoea and constipation.

3.4 The BTS stated that different test centres use different methods, standards and quality assurance processes to test for ALK. It stated that the proportion of successful ALK tests varies across the UK because some centres use immunohistochemistry or fluorescence in situ hybridisation (FISH) to confirm positive results, and some use different testing criteria (such as the proportion of viable tumour cells for the test).

3.5 The BTS noted that mainly people with good performance status (0–1) are included in clinical trials of NSCLC, and not people with advanced NSCLC (performance status 2–3). The BTS noted that crizotinib could be effective against other mutations (such as ROS-1) in advanced NSCLC. The RCPath noted that the evidence shows people with greater immunostaining of PD-L1 have a better response to crizotinib, and that a companion diagnostic (such as 28-8 pharmDx) could be needed. It stated

that if a companion diagnostic test were needed, additional training for pathologists would be needed, and costs of the test taken into account.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company undertook 2 systematic reviews to identify randomised controlled trials (RCTs) and non-RCT data for people with advanced or metastatic ALK-positive NSCLC.

4.2 PROFILE 1014 is an open-label, ongoing, randomised study in 343 previously untreated adults with confirmed ALK-positive, non-squamous, and advanced NSCLC. Patients were randomised in a 1:1 ratio to either crizotinib 250 mg twice daily or chemotherapy (that is, pemetrexed 500 mg/m^2 body surface area [BSA] with either cisplatin 75 mg/m^2 BSA or carboplatin target area under the curve [AUC] of 5 to 6 mg/mL/min every 3 weeks for a maximum of 6 cycles. The company stated that PROFILE 1014 is closed to enrolment and continue follow-up until median overall survival is reached.

4.3 In PROFILE 1014, results were analysed at a pre-specified number of events (229 progression free-survival events, which corresponded to a 50% reduction in time to progression) of disease progression which occurred. The data cut-off was 30 November 2013. Crizotinib improved both progression free survival (PFS) and objective response rates compared with chemotherapy (Table 3). The company noted that because less than half of the patients died in both the crizotinib and chemotherapy groups, the median overall survival (OS) was not reached at the pre-specified cut-off date. The company also noted that because a high proportion of patient's randomised to chemotherapy switched (that is, crossed-over) to crizotinib, that estimates of the relative effect of crizotinib to chemotherapy underestimated the true effect when analysed by intention-to-treat. The company used several methods to adjust for

crossover to estimate overall survival (rank-preserving structural failure time [RPSFT], 2-stage models and iterative parameter estimation [IPE]). Crizotinib improved OS compared with chemotherapy (Table 3).

Table 3 Overview of PROFILE 1014 clinical effectiveness results

	Crizotinib (n=172)	Chemotherapy (n=171)
Unadjusted overall survival[1]		
Median follow-up, months (range)	17.4 ([redacted])	16.7 ([redacted])
Hazard ratio (95% CI)	0.821 (0.536–1.255)	
Overall survival at 12 months: % (95% CI)	84 (77–89)	79 (71–84)
Adjusted overall survival		
RPSFT (Wilcoxon): Hazard Ratio (95% CI)[3]	0.604 (0.265–1.420)	
RPSFT (Log-rank): Hazard Ratio (95% CI)[3]	0.674 (0.283–1.483)	
2-stage (Log-normal; not adjusted for covariates): Hazard Ratio (95% CI)[4]	0.610 (0.395–0.942)	
2-stage (Log-normal; adjusted for smoking status and ECOG PS at PD by IRR, missing ECOG imputed from closest time point): Hazard Ratio (95% CI)[4]	0.624 (0.405–0.963)	
2-stage (Log-normal; adjusted for smoking status and ECOG PS at PD by IRR, missing ECOG imputed as ≥ 2): Hazard Ratio (95% CI)[4]	0.649 (0.421–1.000)	
IPE (Weibull; adjusted for ECOG PS, brain metastases, smoking) : Hazard Ratio (95% CI)[3]	0.626 (0.395–0.992)	
IPE (Log-normal; adjusted for ECOG PS, brain metastases, smoking) : Hazard Ratio (95% CI)[3]	0.633 (0.401–1.000)	
IPE (Log-logistic; adjusted for ECOG PS, brain metastases, smoking) : Hazard Ratio (95% CI)[3]	0.571 (0.349–0.935)	
IPE (Exponential; adjusted for ECOG PS, brain metastases, smoking) : Hazard Ratio (95% CI)[3]	0.674 (0.432–1.051)	
Progression-free survival (primary outcome)		
Median (95% CI), months (range)	10.9 (8.3-13.9)	7.0 (6.8-8.2)
Hazard ratio (95% CI)[2]	0.45 (0.35–0.60)	
Progression-free survival at 18 months: % (95% CI)	31 (23–39)	5 (2–10)
Tumour response rates		
Objective response rate: % (95% CI)	74 (67–81)	45 (37–53)
Change in tumour size: median best change : % (95% CI)	[redacted])	[redacted])

Abbreviations: CI, confidence interval; ECOG PS: Eastern Cooperative Group performance status; IPE: Iterative Parameter Estimation; PD: progressive disease; RPSFT: Rank Preserving Structural Failure Time

[1]unadjusted for crossover of patients between arms in the trial

[2]Calculated using a cox-proportion hazard ratio model stratified by ECOG PS, race and brain metastases

[3]Adjusted for crossover (from randomized chemotherapy to crizotinib) and (from randomized crizotinib to chemotherapy [only pemetrexed/cisplatin or pemetrexed/carboplatin])

[4]Adjusted for crossover (from randomized chemotherapy to crizotinib)

Source: adapted from tables 21 to 23 and pages 73 to 79 of the company's submission and company's response to clarification question A1.

4.4 The company presented evidence on patient reported outcomes and health related quality of life. In summary, the results showed that:

- there was no statistically significant difference in EQ-5D (using the visual analogue scale; [redacted]) at 6 cycles compared with baseline with chemotherapy
- there was a statistically significant higher EQ-5D (using the visual analogue scale; [redacted]) between cycles 3 to 16, and 18 to 21 compared with baseline with crizotinib
- in a mixed-model analysis there was a statistically significantly higher EQ-5D with crizotinib compared with chemotherapy ([redacted]
- there was a statistically significant (P<0.001) greater overall improvement in global health related quality of life (as measured by EORTC QLQ-C30) with crizotinib compared with chemotherapy
- There was also a statistically significant (P<0.001) overall higher overall reduction from baseline in symptoms of dyspnoea, coach and chest pain (as measured using EORTC QLQ-LC13) with crizotinib compared with chemotherapy.

  For further results on other patient reported outcomes (such as time to deterioration, and tumour response rates), see pages 83 to 86 of the company's submission.

The company did subgroup analysis for PFS by ECOG performance, race, brain metastases age, sex, smoking status time since diagnosis, adenocarcinoma histology, and type of disease. The company stated that crizotinib improved PFS similarly across all subgroups for crizotinib compared with chemotherapy.

4.5 The company also provided evidence from 2 non-randomised studies (PROFILE 1001 and Davis et al, 2015). Results from the restrospective cohort study (Davis et al, 2015) are available in Table 6. The company stated that PROFILE 1001 was an ongoing study and no further analyses

were expected until [redacted].

For more information about these studies, please see pages 88 to 100 of the company's submission.

Meta-analyses and indirect comparison

4.6 The company did not provide a meta-analysis because PROFILE 1014 was the only RCT which investigated crizotinib as a first-line treatment for people with ALK–positive NSCLC using the comparison defined in the NICE scope. Therefore, the company did not submit any indirect or mixed treatment analyses.

ERG comments

4.7 The ERG considered that PROFILE 1014 was well conducted. The ERG noted that the open label design put it at a high risk of bias for the primary outcome (progression free survival). It noted that the open label design combined with the treatment available after disease progression could lead to a high risk of bias for overall survival.

Progression free survival

4.8 The ERG believed that the results for PFS may not be generalisable to clinical practice because the PROFILE 1014 trial defined progression on radiographic criteria (RECIST) and not symptomatic criteria. Because progression was based on tumour size, patients switched to second-line therapy quicker than what would be expected in clinical practice.

4.9 The ERG noted that the company used a Cox proportional hazards model stratified by ECOG performance status, race and brain metastases to estimate the hazard ratio for crizotinib compared with chemotherapy for progression free survival. The ERG noted that the company in its model assumes proportional hazards between treatments. The ERG stated that the proportional hazard assumption may not be appropriate because:

- The treatments (crizotinib or chemotherapy) are administered differently: crizotinib is prescribed until disease progression compared with chemotherapy which is offered for a limited number of cycles.
- The Cox proportional hazards method is only reasonable when the majority of events have taken place; the ERG noted that the data from PROFILE 1014 is immature.
- Separate parametric models could be fitted requiring fewer assumptions.

The ERG explored this issue by fitting separate parametric models in its exploratory analyses (see section 5.36 onwards).

Overall survival

4.10 The ERG noted that for the estimates of overall survival for crizotinib compared with chemotherapy were consistent across different survival models. However, it noted that the results were highly uncertainty because:

- Only a small proportion of patients randomised in PROFILE 1014 had died by the data cut-off date (driven by number progressing, rather than numbers dying) and that the median overall survival had not been reached.
- A high proportion patients randomised to chemotherapy had crossed-over to crizotinib therapy following disease progression using radiographic criteria (RECIST) in PROFILE 1014. Approximately 70% of the patients randomised to chemotherapy subsequently received crizotinib. The ERG stated this underestimates the effect of crizotinib on mortality in the intention to treat analysis.
- The company assumed proportional hazards:
  - The ERG considered that the hazard ratio was not likely to be constant over time. In its response to clarification, the company stated that because patients switch treatments in PROFILE 1014, they may not follow a proportionally extrapolated survival curve. The

ERG believed that the company did not justify assuming proportional hazards.

  - The ERG also noted that the treatments are administered differently. The benefits from chemotherapy could diminish after the treatment regimen has ended, but the benefits of crizotinib could continue for a longer period of time. The ERG stated that this could explain why the hazard ratios change over time.

- There was a lower than expected mortality rate for people randomised to chemotherapy in PROFILE 1014. The ERG noted that this was different to other chemotherapy trials.
- The company adjusted for cross-over adjustment for patients who switched from chemotherapy to crizotinib (see section 4.11), but not for people randomised to crizotinib who went onto receive other therapies. The ERG stated that this could over-estimate the effect of crizotinib. For further details, see pages 52 to 54 of the ERG's report.

4.11 The ERG examined the company's approach to adjusting for cross-over between treatments. In summary:

- The ERG was aware that when a high proportion of people switch between treatments, an ITT analysis underestimates the treatment effect.
- It noted that the RPSFT and IPE models assume a common treatment effect, that is, 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 stated that it was unclear whether this assumption would hold because:
  - Patients randomised to chemotherapy who switch between treatments may have more advanced disease compared with patients who had been randomised to crizotinib and therefore may not have the same capacity to benefit from treatment compared with patients randomised to crizotinib.

  - Patients who met the radiographic criteria for disease progression but who did not experience symptomatic progression may still benefit from treatment when switching to crizotinib.
  - There is some evidence showing that crizotinib is an effective second-line therapy. Therefore, some patients may benefit from treatment after disease progression.
- The ERG noted that the RPSFT and IPE models have problems when the comparator is an active treatment and prolongs survival. These models require that patients are either "on" or "off" treatment at any one time. That is, if the patients in the control group receive an active treatment (such as chemotherapy) followed by supportive care after disease progression, then the "off" treatment represents more than 1 type of treatment. Therefore RPSFT and IPE models are not considered appropriate.
- The ERG noted that the 2-stage method assumes that there are no unmeasured confounders and that the investigators collect data on the disease-related baseline characteristics and prognostic covariates before the patient switches treatment. The model assumes no time-dependent confounding between the time of progression and the time of switching treatment. The ERG was aware that the company adjusted its models for smoking status and ECOG, and did not collect the data at the time of disease progression. In its response to clarification questions, the company stated that there was a long delay between disease progression and treatment switching in some patients in PROFILE 1014. Therefore, the ERG questioned whether the 2-stage model was appropriate.
- The ERG noted that the company did not consider the IPCW method as an appropriate analysis after consultation with the EMA. However, it stated that there was no indication that this method would perform worse than RPSFT and IPE models.

In summary, the ERG believed that although none of the methods used by the company were considered the most relevant, the 2-stage method was likely to be the best available because it did not assume a common treatment effect. Because patients received a wide range of treatments after disease progression, the ERG considered that all the methods of adjusting for cross-over generated biased risk estimates.

Adverse effects of treatment

4.12 The company provided pooled safety information based on 1,669 patients from PROFILE 1001, PROFILE 1005, PROFILE 1007 and PROFILE 1014. The company stated that the most frequent adverse event experienced by patients on crizotinib were vision disorders (62%), nausea (57%) and diarrhoea (54%). It also stated that 12% patients taking crizotinib permanently discontinued treatment compared with 14% of people taking chemotherapy in PROFILE 1014.

See pages 102 to 109 of the company's submission for information on adverse event profiles from PROFILE 1014 and PROFILE 1001.

ERG comments

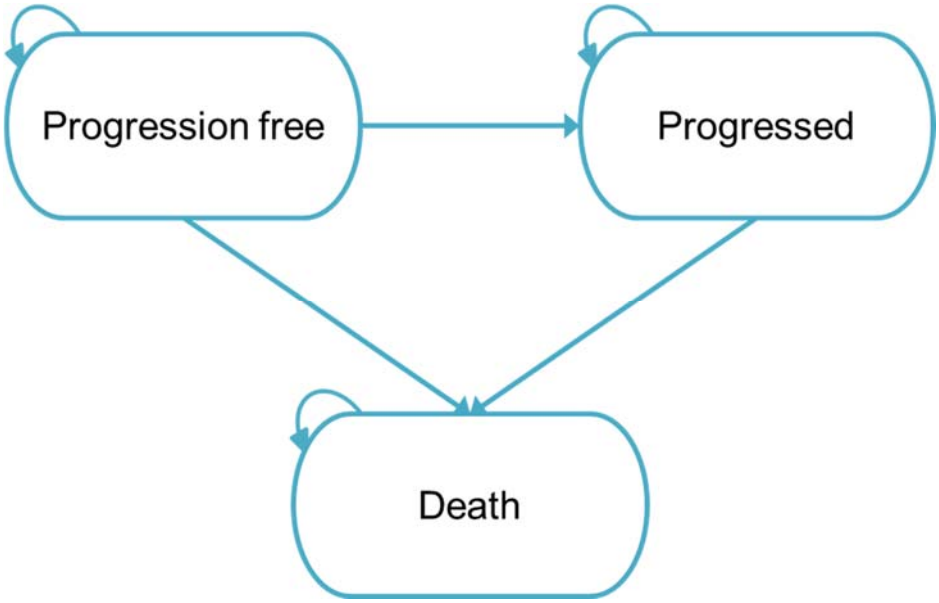
4.13 The ERG considered that crizotinib may cause other as yet unidentified adverse reactions because of the short-term nature of the evidence base.

5 Cost-effectiveness evidence

Model structure

5.1 The company presented an economic model of a cohort of adults with previously untreated, ALK-positive, advanced NSCLC. The cycle length was 30 days and a half-cycle correction was applied. The model had a 15 year time horizon because patients with ALK-positive NSCLC usually don't survive longer than 15 years. The model was conducted from an NHS and personal social services perspective and an annual discount rate of 3.5% was applied to costs and health effects.

Figure 1 Company's model structure



Source: Figure 17, page 122 of the company's submission

5.2 The model structure had 3 health states: 'progression free', 'progressed disease' and 'death' (Figure 1). Patients in the model begin on either crizotinib or chemotherapy in the 'progression free' state and are at risk of progression or death. The health states were defined as:

- Progression free: the patient's disease was stable or responding to treatment and not actively progressing.
- Progressed: the patient's disease has progressed. This was defined using the Response Evaluation Criteria in Solid Tumours (RECIST). Patients moved onto second-line treatment (docetaxel) and then third-line (best–supportive care).
- Death.

5.3 The company used the extrapolated survival function equations for PFS and OS to calculate the proportion of patients in each health state at each time point. The proportion of cohort in the death state is estimated from overall survival (1 minus the proportion of people alive).

5.4 Patients start in the progression free health state. When crizotinib or chemotherapy is stopped following disease progression, patients receive second-line therapy (docetaxel) followed by best supportive care.

Model details

Clinical parameters and variables

5.5 The company used Kaplan Meier curves from PROFILE 1014 to choose a parametric extrapolation and then to estimate the proportion of patients in each health state. The company used PROFILE 1014 to estimate the proportion of patient's experiences adverse events and treatment-dependent utility for the progression free health state.

5.6 The company stated that PROFILE 1014 overestimated median OS because it had a healthier population compared with the population in the UK. Therefore, the company adjusted both PFS and OS to reflect UK patient characteristics (the covariates were: race, ECOG status and presence of brain metastases, age, sex, smoking status and presence of adenocarcinoma) using 'real-world' data from Davis et al 2015 (Table 4).

Table 4 Baseline demographics and patient characteristics for covariate adjusted progression free survival and overall survival

Covariate	Base-case: real-world data (Davis et al. [2015])	Crizotinib (PROFILE 1014)	Pemetrexed plus cisplatin/ carboplatin (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	51.8%	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	–	26.2%	27.5%	26.8%
% non-adenocarcinoma	–	6.4%	5.8%	6.1%
ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PFS: progression-free survival; PS: performance status.				

Source: adapted from Table 42, page 130 from the company's submission

5.7 To adjust for cross-over between the chemotherapy and crizotinib to estimate in overall survival (see section 4.3), the company used a 2-stage crossover adjustment model controlling for covariates (with missing ECOG PS data imputed from the closest time point).

5.8 To estimate treatment effects (progression free survival and overall survival), the company tested and compared several parametric models (such as Exponential, generalised Gamma, Gompertz, Log-logistic, log-normal and Weibull models) using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) and visual inspection using the Kaplan-Meier curves (Figures 2 to 5). In the base-case analysis, the company used the generalised gamma curve to estimate PFS for both crizotinib and chemotherapy. The company used a Weibull curve to estimate OS for both crizotinib and chemotherapy.

5.9 The company tested other parametric models such intention to treat analyses for overall survival, separate parametric models for each of crizotinib and chemotherapy groups using the same covariates for prognostic factors. In response to questions B12–B16 for clarification, the company submitted a fully stratified model and independent parametric models for each treatment with separate covariates for prognostic factors (see section 5.34).

Figure 2 Company's estimated PFS parametric curves for crizotinib using patient characteristics from PROFILE 1014 (note: company used a generalised Gamma curve in its base case)

Source: figure 20, page 132 from the company's submission

Figure 3 Company's estimated PFS parametric curves for chemotherapy using patient characteristics from PROFILE 1014 (note: company used a generalised Gamma curve in its base case)

Source: figure 21, page 132 from the company's submission

Figure 4 Company's estimated OS parametric curves (adjusting for cross-over) for crizotinib using patient characteristics from PROFILE 1014 (note: company used a Weibull curve in its base case)

Source: figure 23, page 136 from the company's submission

Figure 5 Company's estimated OS parametric curves (adjusting for cross-over) for chemotherapy using patient characteristics from PROFILE 1014 (note: company used a Weibull curve in its base case)

Source: figure 24, page 136 from the company's submission

Costs

5.10 The costs for each health states included drug acquisition costs, the administration cost for intravenous chemotherapy, the costs associated with subsequent with medical management and best supportive care, the cost of treating adverse events and the cost of ALK-tests (in the crizotinib group only). Unit costs for drugs were taken from:

- For crizotinib, a patient access scheme, in the form of a simple discount.
- For pemetrexed, the Monthly Index of Medical Specialities (MIMS; January 2016).
- For cisplatin, carboplatin and docetaxel the electronic market information tool (eMit) for generic drugs.

5.10.1 The company based the costs of each health state costs on the previous NICE technology appraisal for crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. It took unit costs from 2014/15 from NHS Reference costs and the PSSRU. The costs for each health state (per month) were:

- patients in the 'progression free' health state and patients in the 'progressed disease' health state receiving second-line treatment £192.75
- patients in the 'progressed disease' health state receiving third-line treatment £195.13.
- in response to clarification, the company stated that the standard cost of palliative care before death was £7,318.

This cost included the cost of hospital care and terminal care services before death.

5.11 The company based the costs of treating adverse events on the NICE technology appraisal for crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. The costs of adverse events associated with chemotherapy with pemetrexed were: anaemia £374.27 and thrombocytopenia £750.09 (corrected in response to clarification). There was no cost associated with elevated serum concentrations of hepatic transaminase, leukopenia, or neutropenia because they could be managed with either reducing the dose, interrupting treatment or 'watch and wait' monitoring. The company multiplied the costs of the adverse events by the proportion of patients experiencing each event and added the one-off cost of adverse events to each treatment group. These were: £0 for the crizotinib group and £82.04 (corrected in response to clarification) for the chemotherapy group. See section 5.5.7 of the company's addendum for further information on the cost of adverse events.

5.12 The company applied the costs associated with ALK-testing only to the crizotinib group. The expected cost per patient to identify one ALK-positive patient was [redacted].

Utility values

5.13 The company estimated health state utilities from PROFILE 1014 for progression free disease with crizotinib or with chemotherapy. The company estimated utility values for the progressed disease (second-line treatment with docetaxel) and the progressed disease (third-line treatment with best supportive care) health states from PROFILE 1007 and Nafees et al (2008) respectively (see Table 5).

5.14 The company assumed that of patients treated beyond progression with crizotinib, 73% experienced a utility value lasting for 3 cycles estimated to be the midpoint between the utilities associated with the progression free disease with crizotinib and progressed disease (second-line treatment with docetaxel) health states. The company also applied a transitional utility the first-cycle following disease progression.
The company did sensitivity analysis for utilities. See section 5.32.

5.15 The company used the following mean utility values in its model: progression free disease with crizotinib [redacted] (95% CI [redacted] to [redacted]); progression free disease with pemetrexed plus cisplatin/carboplatin [redacted](95% CI [redacted] to [redacted]); treatment beyond progression with crizotinib (sustained for 4 cycles) [redacted] (95% CI [redacted] to [redacted]); progressed disease with second-line treatment with docetaxel 0.66 (95% CI 0.58 to 0.74) progressed disease with third-line treatment with best supportive care 0.47 (95% CI 0.38 to 0.57).

Table 5 Utility values used in the company's model

Health state	Utility value: mean (95% CI)
Progression free with crizotinib (Source: PROFILE 1014)	[redacted]
Progression free with pemetrexed plus cisplatin/carboplatin (Source PROFILE 1014)	[redacted]
Treatment beyond progression with crizotinib: Sustained utility for 4 cycles (Source: PROFILE 1014 & PROFILE 1007)	[redacted]
Progressed disease with second-line treatment with docetaxel (Source PROFILE 1007)	0.66 (0.58, 0.74)
Progressed disease with third-line treatment with best supportive care (Source Nafees *et al.* 2008)	0.47 (0.38, 0.57)

Source: table 25 in the ERG's report

5.16 The company did not include disutility values associated with adverse events in its base case analysis because the on-treatment health-related quality of life would already include adverse events, but did include disutility from adverse events in sensitivity analysis. See page 148 of the company's submission. See section 5.32.

ERG comments

5.17 The ERG's clinical advisor stated that PROFILE 1014 (that is, mainly people with non-squamous NSCLC) reasonably reflects the prognosis for people with squamous NSCLC.

5.18 The ERG considers the perspective and time horizon used by the company to be appropriate. The ERG noted that the company discounted costs and benefits by the same amount regardless of whether the cost or benefit occurred at the start or end of the year. The ERG explored this issue in its exploratory analyses (see section 5.36).

Intervention, comparators and lines of therapy

5.19 The ERG noted that 54% of patients will receive cisplatin and 46% will receive carboplatin in combination with pemetrexed in the chemotherapy group (the comparator) of the company's model. The ERG's clinical expert suggested that 30% of patients would receive cisplatin and 70% carboplatin in clinical practice. The ERG explored this issue in its exploratory analyses (see section 5.36).

5.20 The ERG was concerned that patients on chemotherapy stop treatment after 6 cycles of therapy in the company's model. The ERG's clinical advisor stated that people on chemotherapy receive pemetrexed maintenance chemotherapy available on the Cancer Drugs Fund if they had been previously treated with cisplatin chemotherapy. In its response to clarification questions, the company stated that the NICE scope excluded pemetrexed maintenance therapy. The ERG stated that pemetrexed maintenance chemotherapy could be a potentially important comparator.

5.21 The ERG considered that the company inappropriately omitted second-line crizotinib therapy in the treatment pathway. The ERG was concerned that the company, in adjusting for cross-over, did not account for the second-line therapies.

5.22 The ERG noted that in PROFILE 1014 after disease progression and stopping crizotinib or chemotherapy, most patients received a second-line therapy. These included several unnamed experimental drugs and ceritinib. Many patients treated with chemotherapy who did not switch to crizotinib received no second-line therapy. The ERG noted that this created an imbalance in the second-line therapies received by people randomised to crizotinib and chemotherapy after an adjustment for cross-over had been carried out. The ERG stated that this imbalance is likely to result in the overall survival benefit of crizotinib being overestimated.

Duration of treatment and discontinuation

5.23 The ERG identified several issues with crizotinib in the company's model. It noted that:

- The company assumed that patients receive a further 4 cycles of crizotinib after disease progression; this translates to a median time on crizotinib after progression of 3.1 months in PROFILE 1014. The ERG considered the company's approach as inappropriate because the mean duration on treatment after progression was [redacted] months (equivalent to [redacted] cycles of treatment) in PROFILE 1014. The ERG explored this issue in analyses (see section 5.35)
- Only some people with progressed disease received 4 cycles of chemotherapy since some died in each cycle. The ERG stated that instead people received a 2.2 mean cycles of treatment. The ERG stated that this underestimated the time on crizotinib after disease progression, and reduced the total QALYs and costs accrued on crizotinib. The ERG stated that this lowered the ICER. The ERG explored this issue (see section 5.35)
- The company estimated the median and mean values for the number of people who discontinue treatment assuming that, as happened at the end of the trial, people stopped treatment. That is, the company considered that someone whose disease had not progressed by the end of PROFILE 1014 (who were 'censored') had a duration of treatment only to the end of the trial; in 'real life' these patients would continue treatment until (or beyond) disease progression. Because [redacted] of people were still on therapy with crizotinib at the data-cut-off date, the company underestimated the median and mean time on crizotinib. The ERG stated that this underestimated the ICER. It explored this issue in its exploratory analysis (see section 5.35).

5.24 The ERG identified several issues with chemotherapy in the company's model. The ERG noted:

- A discrepancy between the mean number of cycles of chemotherapy from the company's model compared with the mean number of cycles from PROFILE 1014. The ERG explored this issue (see section 5.35).
- That the company assumed that people are initiated on 6 cycles of chemotherapy. The ERG's clinical advisors suggested that the some people could be initiated on 4 cycles of chemotherapy in clinical practice. The ERG also noted that in NICE's technology appraisal for pemetrexed for the first-line treatment of non-small-cell lung cancer, the clinical benefits of chemotherapy between 4 cycles and 6 cycles of were often marginal, implying that a 4 cycle chemotherapy regimen is more cost effective compared with a 6 cycles chemotherapy regimen. It explored this issue in its exploratory analysis (see section 5.35 onwards).

5.25 The ERG also outlined the following concerns about the company's assumptions for second-line therapy and best supportive care. It noted:

- That the company used similar assumptions for duration of second-line therapy as it did for crizotinib) and therefore, had similar flaws. For further information see section 5.23 and page 85 of the ERG's report. The ERG explored these issues in exploratory analysis (see section 5.36).
- That the mean duration of second-line therapy was the same for both people treated with both crizotinib and chemotherapy in the company's model. The ERG stated that there was no reason to suggest that mean duration of second-line therapy would be the same for patients randomised to crizotinib or chemotherapy.
- That the company assumed that all patients received second-line therapy. However, the ERG noted that [redacted]% of people treated with crizotinib and [redacted]% of people treated with chemotherapy patients received no second-line treatment in PROFILE 1014.

5.26 The ERG were concerned that the projected survival gains observed in the model appeared to be inconsistent with the survival rates in the UK. It noted that the 1-year survival rate of stage 3 NSCLC was 35% compared with the predicted survival on chemotherapy of 52% in the model (which included both people with stage 3 and 4 NSCLC).

Utilities

5.27 The ERG identified several issues relating to the company's utility values, in summary, these were:

- Progression free health state utility values: The ERG's clinical advisor stated that people who complete chemotherapy have higher utility compared with people undergoing chemotherapy because of side-effects. The ERG explored this issue (see section 5.35).
- Sustaining utility during treatment after progression: Although the ERG considered it plausible that people treated after disease progression experience utility benefit, using a midpoint utility between before and after progression was not based on clinical evidence. The ERG also thought it was unlikely that people treated with crizotinib with progressed disease would have higher utility than people treated with chemotherapy who had not progressed. The ERG explored this issue (see section 5.35).
- Transition utility following progression between lines of therapy: The ERG considered that a transition utility was inappropriate because it double-counted utility. The ERG noted that the company used estimates based on an average of people in the health state, therefore, it included people with higher utility (that is, people who had just entered to health state compared with people who had been experiencing symptoms for longer). The ERG explored this issue (see section 5.35).

Further details about the ERG's consideration on the utilities

(progressed disease and adverse event health states) are available on pages 87 to 91 of the ERG report.

Costs

5.28 The ERG had several concerns with the costs used in the company's model:

- It considered that after a patient starts a pack of crizotinib or chemotherapy, it would not be reused if the person stopped treatment. Therefore, the ERG considered the company's assumption of no drug wastage unrealistic. Incorporating drug wastage costs would increase the total cost of crizotinib or chemotherapy and on balance, increase the ICER. The ERG explored this issue in exploratory analysis (see section 5.35).
- It considered costs from NICE's technology appraisal on Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene as the most relevant source for administration costs. The ERG considered that an administration cost for each cycle of crizotinib should be applied to the model. The ERG explored this issue in exploratory analysis (see section 5.35).
- The ERG's clinical advisors suggested that the tests for ALK varied in clinical practice. They noted that in some centres test all patients with immunohistochemistry followed by a FISH test for people with a positive result. The ERG also noted that the company underestimate the cost of immunohistochemistry in the its model. The ERG explored a higher cost of testing for ALK (see section 5.35).

Company's base-case results and sensitivity analysis

5.29 In response to clarification, the company corrected minor errors. The company's incremental cost-effectiveness ratios (ICERs) for all the comparisons and sensitive analyses incorporated the patient access scheme for crizotinib, as do all the ICERs in this document.

5.30 In the company's base case the ICER was £47,620 (incremental costs [redacted]; incremental QALYs [redacted]) per quality-adjusted life year (QALY) gained for crizotinib compared with pemetrexed plus cisplatin/carboplatin.

Clinical outcomes

5.31 The company compared the clinical outcomes estimated in the model with published studies of crizotinib (Table 6) and pemetrexed plus platinum based chemotherapy (Table 7).

Table 6 Clinical outcomes from company's model compared with published studies for crizotinib

Outcome	Crizotinib		
	Model result (adjusted for real-world patients)	PROFILE 1014 phase III trial	Davis et al. (2015) real-world data
Median PFS (months)	9.9	10.9	9.6
Median OS (months)	21.7	Not reached	24
Mean OS (months)	29.0	Data not mature	NR

Source: table 68, page 172 from the company's submission

Table 7 Clinical outcomes from company's model compared with published studies for pemetrexed plus platinum based chemotherapy

Outcome	Chemotherapy: Pemetrexed with cisplatin/carboplatin			
	Model result (adjusted for real-world patients)	PROFILE 1014 phase III trial	JMDB trial phase III trial	FRAME real-world data
Median PFS (months)	5.9	7.0	5.3	5.6
Median OS (months)	13.8	Not reached	11.8	10.6
Mean OS (months)	17.9	Data not mature	NR	NR

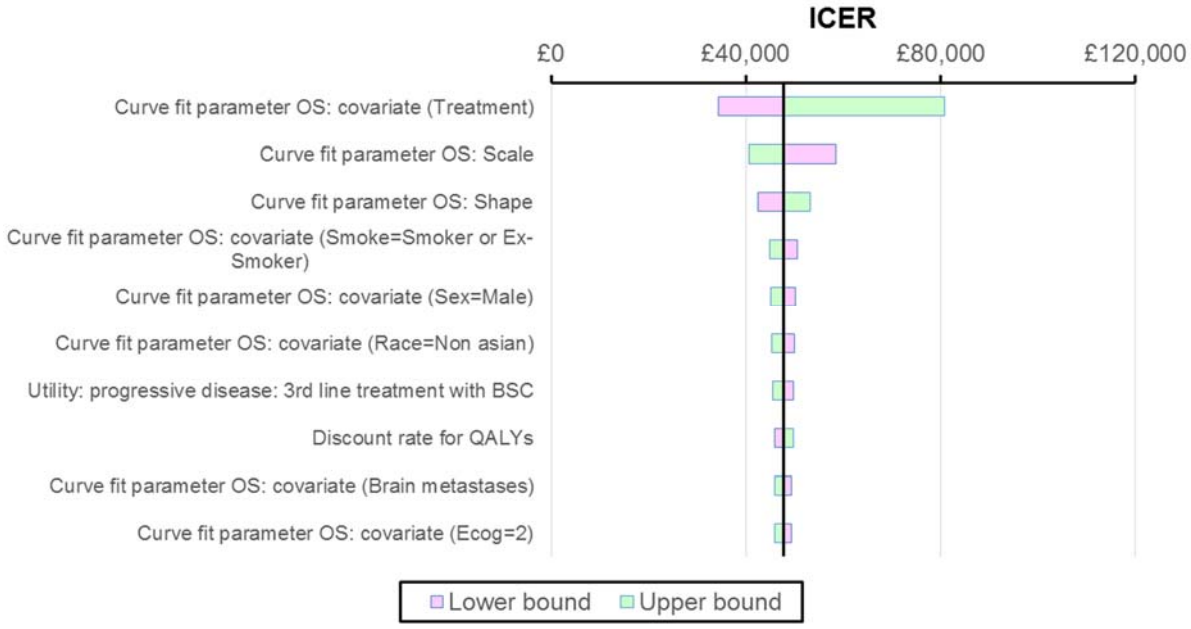
Source: table 69. Page 172 from the company's submission

Sensitivity analyses

5.32 The company undertook deterministic sensitive analyses to explore parameter uncertainty. The company stated that the ICER was most sensitive to the covariates used to calculate overall survival, specifically,

the parameters used for curve fitting (treatment, scale, shape, smoker, race, sex). The ICER was also sensitive to the utility applied to 3rd line treatment with best supportive care and the discount rate for utilities (Figure 6).

Figure 6 Company's tornado diagram of deterministic sensitivity analyses



BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year.
Source: Figure 1 in the company's PAS submission

5.33 The company undertook probabilistic sensitivity analyses which showed a similar mean ICER compared with the deterministic base case ICER. The mean probabilistic ICER was £46,405 (incremental costs [redacted] incremental QALYs [redacted]) per QALY gained for crizotinib compared with pemetrexed plus cisplatin/carboplatin. The probability of cost-effectiveness was more than 59.7% for a maximum ICER of £50,000 per QALY gained for crizotinib compared with pemetrexed plus cisplatin/carboplatin.

See section 4.10, pages 7 to 10 of the company's PAS submission for further information on the probabilistic sensitivity analysis (including a scatter plot / and cost-effectiveness acceptability curve).

5.34 The company undertook several probabilistic scenario analyses:

- Excluding wastage for pemetrexed plus cisplatin/carboplatin made little difference to the ICER (£47,223 per QALY gained).
- Excluding ALK-testing costs reduced the ICER reduced the ICER to £43,914 per QALY gained.
- Changing the method of crossover adjustment had a modest impact on the ICER:
  - using the TSB adjustment instead of TSA increased the ICER to £48,535 per QALY gained
  - using the TSC adjustment instead of TSA decreased the ICER to £45,692 per QALY gained
  - using the RPSFT-Wilcoxon adjustment instead of TSA increased the ICER to £48,497 per QALY gained
  - using the RPSFT-Log-rank adjustment instead of TSA increased the ICER to £52,541 per QALY gained.
- Using characteristics of patients from PROFILE 1014 instead of real world data reduced the ICER to £41,386 per QALY gained.
- Changing parametric distributions had a modest impact on the ICER:
  - using a gamma distribution for PFS, and a Gompertz distribution for OS decreased the ICER to £43,337 per QALY gained
  - using a Weibull distribution for PFS, and a Weibull distribution for OS modestly changed the ICER to £46,389 per QALY gained
  - using a Weibull distribution for PFS, and a Gompertz distribution for OS decreased the ICER to £43,469 per QALY gained
  - using a Gompertz distribution for PFS, and a Weibull for OS decreased modestly changed the ICER to £47,530 per QALY gained
  - using a Gompertz distribution for PFS, and a Gompertz for OS decreased modestly changed the ICER to £43,947 per QALY gained.
- Applying sustained utilities to treatment before progression instead of before and after progression, a higher proportion of treatment on

carboplatin than cisplatin, applying a one-off cost for crizotinib administration, including utility decrements due to adverse events and excluding had ICERs similar to the base case probabilistic ICER.

- Applying 4 cycles of chemotherapy instead of 6 cycles to represent clinical practice increased the ICER to £51,793 per QALY gained.
- Reducing the time horizon greatly increased the ICER. Increasing the time horizon had no substantial impact on the ICER.
- A scenario using a squamous population instead of non-squamous population substantially increased the ICER to £152,012 per QALY gained.

ERG comments

5.35 In response to clarification, the company corrected errors but the ERG then identified several more errors in the company's model; in summary, the company:

- discounted costs and benefits on an annually instead of per cycle
- included time zero as a cycle in the model
- did not include a one-off administration cost for crizotinib
- included arbitrary administration costs for both crizotinib and chemotherapy
- incorrectly calculated the QALY for the time on second-line treatment and best support care
- incorrectly calculated the number of patients at 8 cycles after progression for crizotinib
- mis-specified the duration of time people were treated with on crizotinib after disease progression
- mis-specified the duration of time on docetaxel for both crizotinib and chemotherapy patients the ERG has not been able to rectify this error, due to lack of appropriate data)

- mis-specified the duration of time on best supportive care for both crizotinib and chemotherapy (the ERG has only been able to partially rectify the mis-specification, due to lack of appropriate data).

ERG exploratory analysis

5.36 The ERG corrected the errors in the company's model (see section 5.35), and conducted several exploratory analyses:

- Reducing the number of chemotherapy cycles. This modestly increased the ICER for crizotinib compared with chemotherapy.
- Including drug wastage for people who die part way through a cycle of treatment. Including drug wastage for crizotinib or both crizotinib and pemetrexed modestly increased the ICER for crizotinib compared with chemotherapy. Including drug wastage for only pemetrexed modestly reduced the ICER for crizotinib compared with chemotherapy.
- Removing transition utilities. This modestly reduced the ICER for crizotinib compared with chemotherapy.
- Using a lower, alternative utility after disease progression with crizotinib. This modestly increased the ICER for crizotinib compared with chemotherapy.
- Using a higher, alternative utility before disease progression after receiving chemotherapy modestly increased the ICER for crizotinib compared with chemotherapy.
- Using a smaller cohort of people treated with cisplatin, and larger cohort treated with carboplatin for chemotherapy. This had a minimal impact on the ICER for crizotinib compared with chemotherapy.
- Using a higher cost of ALK-testing modestly increased the ICER for crizotinib compared with chemotherapy.
- Adding administration costs for crizotinib increased the ICER for crizotinib compared with chemotherapy.

For further details see pages 135 to 138 of the ERG report.

5.37 The ERG's preferred base case exploratory analyses included:

- Applying drug wastage for people who die part way through a cycle of treatment in both crizotinib and chemotherapy group.
- Removing transition utilities.
- Applying a utility of [redacted] for people who have completed chemotherapy treatment but have not progressed.
- Assuming that 25% of people treated with chemotherapy has cisplatin and 75% were treated with carboplatin.
- Applying alternative costs of £4,500 for ALK testing.
- Using per cycle drug administration costs for crizotinib.

5.38 The ERG's exploratory analyses showed (Table 8):.

Table 8 ERG exploratory analyses: deterministic base-case and corrected ICERs with PAS (cost per QALY)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
Company's base case	[redacted]	[redacted]	[redacted]	[redacted]	£46,306
Company's base-case (with the ERG's corrections)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
ERG's preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	£74,225

Source: adapted from table 64, page 139 of the ERG's report

The ERG used fully stratified parametric models to estimate progression free survival and overall survival (that is, by using baseline prognostic covariates separately for each treatment). The ERG tested and compared several parametric functions using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Although a number of different

functions fit the data for progression free survival, the ERG considered that the generalised Gamma, log-logistic and log-normal models provided the best fit for crizotinib, and considered for chemotherapy that the generalised Gamma and Weibull models provided the best fit. For overall survival, the ERG considered that the generalised gamma, Gompertz and Weibull models the best fit for crizotinib the ERG considered that the exponential and Weibull models offered the best fit for chemotherapy. The ERG's exploratory analyses using the ERG's preferred base-case and fully stratified survival models estimated much higher ICERs than the company's base-case results (Table 9).

Table 9 ERG exploratory analyses: deterministic ICERs using different survival models with PAS (cost per QALY)

	Fitted models		Crizotinib		Chemotherapy		
	PFS	**OS**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
Company's base case	**Gamma same curves for both treatments**	**Weibull same curves for both treatments**	[redacted]	[redacted]	[redacted]	[redacted]	£46,306
ERG's preferred base-case (proportional hazard model)	**Gamma same curves for both treatments**	**Weibull same curves for both treatments**	[redacted]	[redacted]	[redacted]	[redacted]	£74,225
ERG's preferred base-case (fully stratified model)	**Gamma same fitted curves for both treatments**	**Weibull same fitted curves for both treatments**	[redacted]	[redacted]	[redacted]	[redacted]	£89,592
ERG's preferred base-case (fully stratified model and curves selected using lowest AIC)	**Log-normal for crizotinib Gamma for chemotherapy**	**Gamma for crizotinib Exponential for chemotherapy**	[redacted]	[redacted]	[redacted]	[redacted]	£130,088

Source: adapted from table 66, page 140 from the ERG's report

Innovation

5.39 The company offered the following justifications for considering crizotinib to be innovative:

- The current standard of care is intravenous chemotherapy every 3 weeks. Crizotinib is the only orally available therapy. The company stated that people prefer oral therapies. The company stated that this would also reduce service requirements and healthcare resources.
- Crizotinib addressed an area of clinical unmet need and is more effective than current standard of care. It also stated that it is better tolerated than chemotherapy.
- That people with ALK-positive NSCLC are younger compared with the wider NSCLC population and therefore could allow for people return to employment.
- That it did not incorporate the expected benefits of crizotinib to patient's carers in its model.

6 End-of-life considerations

Table 10 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	According to the company's clinical experts the average life expectancy is estimate to be 15 months with current standard of care. In a retrospective analysis of 36 crizotinib naïve patients, the median overall survival was 20 months with people undergoing chemotherapy (Shaw et al, 2011). A number of studies (see table 10 in the company's submission) in the NSCLC population, together with expert opinion, suggest a life expectancy between 10.4 to 20.0 months with first-line pemetrexed plus platinum-based therapy. The company's modelled estimates suggests a median life expectancy of 13.8 months, and a mean life-expectancy of 17.9 months for crizotinib compared with pemetrexed plus platinum-based chemotherapy
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	The company's estimates that people live longer median 7.9 months, mean 11.1 months for crizotinib compared with pemetrexed plus platinum-based chemotherapy. The company estimates that the minimum benefit to survival associated with crizotinib was 3.9 months.

7 Equality issues

7.1 No equities issues were identified from the scoping process, or in the evidence submitted.

8 Authors

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Technical Lead

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Appendix A: Clinical efficacy section of the draft European public assessment report

The European public assessment report (EPAR) is available here.

Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of crizotinib within its marketing authorisation for previously untreated, anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer.

Background

Lung cancer falls into 2 histological categories: non-small-cell lung cancers, which account for 85–90% of all lung cancers, and small-cell lung cancers. Non-small-cell lung cancer may be grouped by tumour histology into squamous cell carcinoma, adenocarcinoma and large-cell carcinoma, with the latter 2 being collectively referred to as 'non-squamous' lung cancer. Some non-small-cell lung cancers are associated with chromosomal alterations described as anaplastic lymphoma kinase (ALK) fusion genes. ALK fusion genes occur between the tyrosine kinase portion of the ALK gene and other genes. They are believed to be involved in the growth of tumours. ALK translocation can occur in non-small cell lung cancer of any histology, although it is thought to be most common in tumours with adenocarcinoma histology and is uncommon in tumours with squamous cell carcinoma histology.[1]

In England, there were 34,889 people newly diagnosed with lung cancer in 2011. Approximately 30% of people present with locally advanced disease (stage III; the cancer may have grown into the surrounding tissues and there may be cancer cells in the lymph nodes) and 40% with metastatic disease (stage IV; the cancer has spread to another part of the body).[2] It is estimated that approximately 3% of people with stage III or IV non-small-cell lung cancer have ALK fusion genes, equating to around 735 patients in England.[3]

For most people with non-small-cell lung cancer, the aim of treatment is to extend survival, and improve disease control and quality of life. NICE clinical guideline 121 recommends platinum-based chemotherapy as a first-line treatment for people with stage III or IV non-small-cell lung cancer and good performance status. For people with non-small-cell lung cancer of non-squamous tumour histology, NICE technology appraisal guidance 181 recommends pemetrexed in combination with cisplatin as an option for the first-line treatment of locally advanced or metastatic disease.

Appendix B

The technology

Crizotinib (Xalkori, Pfizer) is a selective small-molecule inhibitor of the anaplastic lymphoma kinase receptor tyrosine kinase and its oncogenic variants (that is, ALK fusion events and selected ALK mutations). Crizotinib is administered orally.

The Committee for Medicinal Products for Human Use has recommended that a marketing authorisation should be granted for crizotinib for treating adults with previously untreated, ALK-positive, advanced non-small cell lung cancer.

Crizotinib has a marketing authorisation in the UK for the treatment of adults with previously treated, ALK-positive, advanced non-small cell lung cancer.

Intervention(s)	Crizotinib
Population(s)	People with untreated, anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer.
Comparators	For people with non-squamous tumour histology: • Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin) For people with squamous tumour histology: • A third-generation drug (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin) For people with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate: • Single-agent chemotherapy with a third-generation drug (for example, gemcitabine or vinorelbine)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.

Appendix B

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 use of crizotinib is conditional on the presence of ALK mutation. The economic modelling should include the costs associated with diagnostic testing for ALK mutation 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.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene' (2013) NICE Technology Appraisal 296 Review date May 2016 'Pemetrexed for the first-line treatment of non-small-cell lung cancer' (2009) NICE Technology Appraisal 181 Guidance on static list Appraisals in development: 'Ceritinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer' NICE technology appraisals guidance [ID729]. Publication expected January 2016 Related Guidelines: 'Lung cancer: The diagnosis and treatment of lung cancer' (2011) NICE guideline 121 Review date December 2015 Related Quality Standards:

Appendix B

	'Lung cancer for adults' (2012) NICE quality standard 17 Related NICE Pathways: Lung Cancer (2012) NICE pathway
Related National Policy	**National Service Frameworks** Cancer **Department of Health** Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy NHS England (2014) Manual for Prescribed Specialised Services 2013/14. Chapter 105: Specialist cancer services (adults) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1,2, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

References

1 Scagliotti G, Stahel RA, Rosell R et al. (2012) ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development. European Journal of Cancer 48: 961-973.

2 Cancer Research UK (2011) Lung cancer statistics. Accessed March 2015.

3 Thomas A, Büttner R, Wolf J et al. (2013) Genomics-based classification of human lung tumors. Science Translational Medicine 5(209): 209ra153.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal (STA)

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

Final matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Pfizer (crizotinib) Patient/carer groups • Black Health Agency • British Lung Foundation • Cancer Black Care • Cancer Equality • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Roy Castle Lung Cancer Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care • UK Lung Cancer Coalition Professional groups • Association of Cancer Physicians • Association of Respiratory Nurse Specialists • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Thoracic Oncology Group • British Thoracic Society • Cancer Research UK • National Lung Cancer Forum for Nurses • Primary Care Respiratory Society UK • Royal College of General Practitioners	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord Healthcare (carboplatin, cisplatin, docetaxel, gemcitabine, paclitaxel) • Allergan UK (docetaxel, gemcitabine, paclitaxel, vinorelbine) • Celgene (paclitaxel) • Dr. Reddy's Laboratories (docetaxel) • Eli Lilly (gemcitabine, paclitaxel, pemetrexed) • Hospira UK (carboplatin, cisplatin, docetaxel, gemcitabine, paclitaxel) • medac GmbH (docetaxel, gemcitabine, paclitaxel, vinorelbine) • Pierre Fabre (vinorelbine) • Sanofi (docetaxel) • Sun Pharmaceuticals (carboplatin,

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Bradford Districts CCG • NHS Brent CCG • Welsh Government	gemcitabine) <u>Relevant research groups</u> • Cochrane Lung Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <u>Evidence Review Group</u> • Centre for Reviews and Dissemination and Centre for Health Economics - York • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland ; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Crizotinib for the first-line treatment of anaplastic lymphoma kinase-positive, advanced non-small-cell lung cancer [ID865]

Company evidence submission

ID865

File name	Version	Contains confidential information	Date
ID865 Crizotinib 1L Company evidence submission [ACIC] noPAS (27Jan16)	1	Yes	27th January 2016
ID865 Crizotinib 1L Company evidence submission ACIC noPAS (27Jan16 _ Amended redacting 18Mar16)	1.1	Yes	18th March 2016
ID865 Crizotinib 1L Company evidence submission ACIC noPAS_noPAS_REDACTED 18 May 16	1.2	No	18 May 2016

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 250 pages, excluding appendices and the pages covered by this template.

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.

Contents

Tables and figures

List of tables

List figures

1 Executive summary

1.1 Statement of decision problem

The objective of this appraisal is to determine the clinical and cost-effectiveness of crizotinib within its marketing authorisation for previously untreated, anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).[1] Further details of the decision problem and how it has been addressed in this submission are presented in Table 2 on the following page.

1.2 Description of the technology being appraised

A summary of the technology being appraised is presented in Table 1. In this submission, crizotinib is presented for consideration as a first-line treatment, as per the licensed indication.

Table 1: Summary of the technology being appraised

UK approved name and brand name	Crizotinib (Xalkori®)
Marketing authorisation/CE mark status	Crizotinib received a positive opinion from the Committee for Human Medicinal Products on 22nd October 2015 for the indication detailed in this submission, with subsequent Marketing Authorisation granted on 24th November 2015.
Indications and any restriction(s) as described in the summary of product characteristics	Crizotinib is indicated for: • The first-line treatment of adults with ALK-positive advanced NSCLC. • The treatment of adults with previously treated ALK-positive advanced NSCLC. At the anticipated time of appraisal, the reimbursement status of crizotinib in previously treated patients in England is uncertain, due to the Cancer Drugs Fund (CDF) transition arrangements. Crizotinib is unfunded in previously treated patients in Wales. Crizotinib should only be initiated in patients whose ALK-positive status has been established.
Method of administration and dosage	Oral; 250 mg twice daily, taken continuously until disease progression or unacceptable toxicity.

Table 2: Summary of the decision problem

	Final scope issued by NICE [1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated, ALK-positive, advanced NSCLC.	People with untreated, ALK-positive, advanced NSCLC.	N/A – the decision problem matches the final scope. It should be noted that the majority of patients (~97.7%) with ALK-positive NSCLC are expected to be of non-squamous tumour histology (see Section 3.1). Clinical RCT evidence for first-line treatment with crizotinib is limited to the PROFILE 1014 phase III trial which included patients with non-squamous tumour histology only, as best represents the patient population. The cost-effectiveness of crizotinib in patients with squamous histology has been explored however in a scenario analysis (see Section 5.2.1).
Intervention	Crizotinib	Crizotinib	N/A – the decision problem matches the final scope.
Comparator(s)	For people with non-squamous tumour histology: • Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin) For people with squamous tumour histology: • A third-generation drug (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin) For people with non-squamous or	For people with non-squamous tumour histology: • Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin) For people with squamous tumour histology: • Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin) [scenario analysis]	The decision problem addressed matches the final scope for the population of patients with non-squamous tumour histology who are typically treated with pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin). This represents the base case comparison in this submission. ALK-positive squamous patients are very rare and comprise around only 0.08% of squamous NSCLC (derived in Section 3.1). In the absence of any RCT data for crizotinib or chemotherapy in ALK-positive squamous patients, an extrapolation of non-squamous clinical data are presented in a modelled scenario analysis, with costs adjusted accordingly. The comparator for this squamous evaluation is thus the same as for the non-squamous, pemetrexed in combination with platinum chemotherapy.

	Final scope issued by NICE [1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	squamous tumour histology for whom treatment with a platinum drug is not appropriate: • Single-agent chemotherapy with a third-generation drug	Not addressed – see rationale.	Expert clinical advice from a UK advisory board highlighted that this group accounts for less than 2% of the ALK-positive patient population and so does not represent standard of care. In the absence of any clinical data for single agent chemotherapy in ALK-positive patients, a comparison of cost-effectiveness was unfeasible and this comparator has not been considered.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	All outcomes listed have been considered (see Section 4.7).	N/A – the decision problem matches the final scope.
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 (QALY). 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 use of crizotinib is conditional on	The economic analysis is consistent with the final scope, presenting results as incremental cost-effectiveness ratios (ICERs), valuing health benefits in terms of QALYs and using an appropriate time horizon of 15 years. The perspective of the analysis is that of the NHS and PSS. The base case analysis applies the cost of ALK-testing in the crizotinib arm.	N/A – the decision problem matches the final scope.

	Final scope issued by NICE [1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	the presence of ALK mutation. The economic modelling should include the costs associated with diagnostic testing for ALK mutation in people with advanced NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Subgroups to be considered	None detailed	N/A	N/A
Special considerations including issues related to equity or equality	None detailed	N/A	N/A

Abbreviations: ALK: anaplastic lymphoma kinase; ICER: incremental cost-effectiveness ratio; N/A: not applicable; NHS; National Health Service; NSCLC: non-small cell lung cancer; PSS: Personal Social Services; QALY: quality-adjusted life year; RCT: randomised controlled trial.

1.3 Summary of the clinical effectiveness analysis

Crizotinib demonstrated a statistically significant improvement in progression free survival (PFS) (see Section 4.7.1). Additionally, it led to a rapid and durable treatment response for the first-line treatment of ALK-positive, advanced NSCLC (see Section 4.7.2).

The PROFILE 1014 phase III randomised controlled trial (RCT) was conducted in a patient population that directly matches the decision problem and provides direct head-to-head evidence across 340 patients treated with either interventional crizotinib (n = 171) or comparator pemetrexed plus platinum-based chemotherapy (n = 169), which is the current standard of care in the UK.[2] Median PFS was significantly prolonged in the crizotinib group (10.9 months versus 7.0 months; hazard ratio [HR], 0.45; 95% CI, 0.35 to 0.60; P<0.001). Prolonged PFS was observed in patients treated with crizotinib; 31% of patients remained progression-free at 18-months compared to 5% patients treated with chemotherapy.

Crizotinib was also associated with a significantly higher objective response rate (ORR) (74% vs. 45%, P<0.001) and a numerically longer median duration of response (11.3 months [95% CI 8.1–13.8] vs. 5.3 months [95% CI 4.1–5.8]) versus pemetrexed plus platinum based chemotherapy.[2] Furthermore, patients in the crizotinib arm achieved a greater median best percentage change from baseline in tumour size than with chemotherapy (*[Academic / commercial in confidence information removed]*reduction in tumour size from baseline with crizotinib whilst on treatment vs. *[Academic / commercial in confidence information removed]*with chemotherapy).[3]

First-line treatment with crizotinib is associated with extended OS for patients who are otherwise at the end of life (see Section 4.7.2).

In PROFILE 1014, survival data were immature at the time of data analysis. In addition, the analysis of OS was confounded by the high rate of crossover from the chemotherapy arm to crizotinib arm (70%). In analyses to adjust for crossover, as recommended by NICE, crizotinib exhibited a consistent estimate of relative OS benefit versus chemotherapy, with hazard ratios for death estimated from multiple validated established models all lying within a narrow range (HR, 0.571 to 0.674). In the absence of any methodological or clinical reason to select either of the extremes in preference to the other, the median value from this range (HR 0.624 [0.405, 0.963]) is chosen for the modelled base case.

In the economic evaluation base case, crizotinib produced a median OS benefit of 7.9 months versus chemotherapy; this benefit and the pertaining absolute OS figures were validated as plausible through UK clinical expert consultation. This OS benefit was plausible considering previously published RCTs and real world data (Table 67 and Table 68). Other modelled crossover-adjusted HRs for OS produce consistent estimates, suggesting a reliable OS advantage for crizotinib compared to pemetrexed plus platinum-based therapy, likely driven through PFS benefit and the substantial reduction of tumour burden whilst on treatment (see Section 5.7.2).

Please see section 4.13 for a discussion on the end of life criteria.

Treatment with first-line crizotinib was associated with significantly higher utility scores, as measured by EuroQol-5 Dimensions (EQ-5D), and significantly greater improvements from baseline in HRQoL and symptom severity relative to chemotherapy (Section 4.7.2).

In PROFILE 1014, treatment with crizotinib was associated with a significantly greater overall improvement in global health related quality of life (HRQoL) compared to chemotherapy, as measured using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC QLQ-C30) (P<0.001).[2] A significantly greater overall reduction from baseline in the symptoms of dyspnoea, cough and chest pain were reported in the crizotinib group relative to the chemotherapy group, as measured using the EORTC QLQ-Lung cancer module 13 (LC13) (P<0.001).[2]

Furthermore, time-to-deterioration in the lung cancer-related symptoms of dyspnoea, cough and chest pain (as a composite endpoint) was also significantly prolonged in the crizotinib group relative to the chemotherapy group (HR, 0.59; 95% CI, 0.45 to 0.77; P<0.001) in PROFILE 1014.[2] Improvements from baseline in health utility as measured using EQ-5D was significantly higher in the crizotinib group than the chemotherapy group in a mixed-model analysis (P<0.05) (see Section 4.7.2), demonstrating that crizotinib not only halts the HRQoL effects of the disease, but actually improves the lives of patients compared to their time before treatment.[2]

These comparative improvements in HRQoL observed in patients receiving crizotinib compared to pemetrexed plus platinum chemotherapy can be explained through a correlation between HRQoL and reduction in the tumour whilst on treatment, measured via the median best percentage change from baseline in tumour size (see Section 4.7.2).

PROFILE 1014 demonstrated that crizotinib was associated with a generally well-tolerated and manageable side effect profile. This is consistent with that observed in trials in previously treated advanced ALK-positive NSCLC patients including the phase III PROFILE 1007 trial in the second-line setting (see Section 4.12).

Crizotinib was generally well-tolerated by patients in PROFILE 1014 with no new safety concerns reported beyond the PROFILE 1007 second-line trial. Adverse events (AEs) from any cause that were associated with permanent discontinuation of study treatment occurred in 12% and 14% of patients in the crizotinib and chemotherapy groups, respectively.[2] Treatment-related AEs associated with discontinuation were 5% and 8% for the crizotinib group and chemotherapy group, respectively. It is expected that the number of AEs and discontinuations would be higher for crizotinib, as the numbers are not adjusted for treatment duration, which was a median of treatment 10.9 months with crizotinib, but only 4.1 months with chemotherapy.[2]

The well-tolerated safety profile of crizotinib provides further support of the HRQoL improvements observed with use of crizotinib during the PROFILE 1014 trial (see Section 4.12 for further discussion).

Crizotinib meets NICE's end of life criteria: it is indicated for a small patient population, with current life expectancy <24 months, and offers an extension to life of >3 months (see Section 3.4).

The patient population eligible for crizotinib is expected to be very small. An estimate of the number of non-squamous, ALK-positive, advanced NSCLC patients expected to receive first-line crizotinib in England and Wales is 459 (see Section 3.4 for full details). The ALK translocation is predominantly found in patients with non-squamous histology [4]; therefore, it would be rare for an ALK-positive patient to present with squamous cell carcinoma (see Section 3.1).

Previously published OS estimates for standard of care (pemetrexed in combination with platinum chemotherapy) range from 10.6 months to 20 months (Table 10). There is a paucity of

quality OS RCT data for chemotherapy specifically within the ALK-positive NSCLC population owing to the paralleled discovery of the ALK-mutation and the development of targeted ALK therapies, and due to crossover being permitted in the crizotinib trials. Nevertheless, the range of estimates for life expectancy on chemotherapy are all fewer than 24 months (see Table 10).

As stated above, OS data in PROFILE 1014 were immature at the time of PFS analysis and analyses were confounded by the high rate of crossover. From the range of crossover adjusted HRs, the mid-range HR was modelled in the base case and crizotinib produced an OS advantage of 7.9 months median (11.1 months mean) versus standard of care chemotherapy (see Section 5.7.2). For completeness, another four validated methods of calculating the crossover-adjusted HR for OS were also modelled; these showed a similar OS benefit, consistently greater than 3 months.[5] This benefit is explained through crizotinib's superior tumour response and superior tumour shrinkage; this effect on the tumour can place patients in a healthier position at the point they progress than at baseline when they started treatment, thus improving the chances for prolonged post-progression survival (see Sections 4.7.2 and 5.7.2).

1.4 Summary of the cost-effectiveness analysis

The patient population represents those who present in UK clinical practice, and the comparator in the base case is the standard of care currently used in UK clinical practice (see Section 5.2.1 and Section 5.2.4).

The cost-effectiveness analysis considered patients with previously untreated, ALK-positive NSCLC. This is consistent with the decision problem outlined in Table 2 and the licensed indication for crizotinib detailed in this submission. As described above, the clinical evidence for first-line crizotinib (PROFILE 1014) is restricted to patients with non-squamous tumour histology, which is consistent with the patients expected to present in clinical practice. The base case analysis considers only patients with non-squamous histology (see Section 5.2.1), but a scenario analysis is also presented for patients with squamous cell carcinoma.

The primary comparator for crizotinib in the economic evaluation is pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin) (see Section 5.2.4). Feedback from four UK clinical experts indicated that pemetrexed plus platinum-based chemotherapy is used currently in the first-line treatment of ALK-positive, advanced NSCLC patients.

The follow-on (second line) therapy assumed in the model is docetaxel; this is aligned with existing NICE recommendations and routine clinical practice in England and Wales. Although it is acknowledged crizotinib was funded in the second-line in England via the CDF, it is not considered a treatment option in the model due to the uncertainty of this future funding. Crizotinib in the second-line is not funded in Wales.

The model design was consistent with the approaches accepted in previous NICE appraisals in oncology; the design is consistent with the NICE reference case (see Section 5.2.2).

The cost-effectiveness analysis was performed using an “area under the curve” structure in both a deterministic and probabilistic (Monte Carlo simulation) framework (see Section 5.2.2). The model structure (see Figure 17) includes the three most relevant disease-related health states from a patient, clinician and National Health Service (NHS) perspective: *progression free*, *progressed disease* and *death*. It is consistent with models presented as part of previous NICE appraisals of technologies in oncology and advanced NSCLC specifically (see Section 5.2.2).

The analysis was conducted in line with Reference Case from the perspective of the NHS and the Personal Social Services (PSS) in England and Wales. A discount rate of 3.5% per annum was applied to both costs and benefits. The analysis was run using 30-day model cycles with a time horizon of 15 years (reflecting the maximum life expectancy of patients).

The PROFILE 1014 phase III trial provided direct head-to-head evidence for both the intervention and comparator; these informed both the clinical input data and the utility input data in the model. UK costs were used in line with NICE recommendations (see Section 5.3).

Clinical data incorporated into the model were based on the phase III PROFILE 1014 RCT, with standard multivariable parametric curve fitting used to extrapolate outcomes beyond the trial follow-up (see Section 5.3). For OS, estimates based on crossover-adjusted analyses were included. Following feedback from UK clinical experts on the patient population included in PROFILE 1014, covariate-adjusted PFS and OS were included in the model to reflect patient

characteristics seen in real-world data, and therefore more generalizable to a non-trial population (see Section 5.3.1.1).

Utility data were incorporated into the model to reflect patient preferences for the three health states included in the model and for occurrence of AEs (see Section 5.4). Key utility values applied in the model were obtained on treatment in the PROFILE 1014 trial. Other utilities including post-progression and AE disutilities were obtained from a systematic review of the literature (Section 5.4.3). A 'sustained' utility value was applied to those patients receiving treatment beyond progression whereby their utility dropped from pre-progression, but some benefit was maintained for the duration of continued treatment (see Section 5.4.7); in PROFILE 1014, patients were permitted to continue treatment with crizotinib if a clinical benefit was perceived by the study investigator.

Costs were applied to the model from the perspective of the NHS and PSS. The costs included were: drug acquisition costs, administration costs (where relevant), NHS resource use costs associated with routine medical care, monitoring and supportive care, and the costs of managing AEs (see Section 5.5). In addition, the cost of ALK testing was applied to the crizotinib cohort in the base case analysis (see Section 5.5.8.2), as per the NICE final scope. The cost of treatment beyond progression was included in the base case. Resource use items were obtained using clinical expert opinion, and unit costs were derived from the latest NHS reference costs (2014-15).

Crizotinib is cost-effective versus pemetrexed plus platinum-based chemotherapy (with Patient Access Scheme [PAS] applied) (see Section 5.7).

A PAS has been submitted to the Department of Health for consideration. The results of the base case analysis are presented in Table 3 for crizotinib at list price, and in a separate document for crizotinib with the PAS. Considering end-of-life criteria (see section 4.13), crizotinib is a cost-effective treatment option compared to pemetrexed plus platinum-based chemotherapy when it is provided with the PAS, both deterministically and probabilistically. At list price, the deterministic ICER is *[Academic / commercial in confidence information removed]*, and the probabilistic ICER is *[Academic / commercial in confidence information removed]*.

Table 3: Deterministic base case results – crizotinib at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER (cost/QALY)
Pemetrexed plus cisplatin/carboplatin	£21,480	1.49	*[Academic / commercial in confidence information removed]*	
Crizotinib	£79,884	2.42	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALYs: quality-adjusted life years.

Modelled estimates of OS predict a median survival advantage with crizotinib versus pemetrexed-plus platinum-based chemotherapy of greater than 3 months (see Section 5.7.2).

The cost-effectiveness evaluation of crizotinib found that patients receiving crizotinib experienced a median life expectancy increase of 7.9 months (mean of 11.1 months) compared to patients receiving pemetrexed plus platinum-based therapy; the modelled OS for both treatment arms aligns with respective published literature and clinical opinion (see Table 67 and Table 68 in Section 5.7.2). The modelled OS estimates support the consideration of crizotinib as an end-of-life medicine, (detailed in Section 4.13).

Sensitivity analyses supported the robustness of the base case results and show crizotinib is consistently cost-effective with the PAS versus pemetrexed plus cisplatin/carboplatin (see Section 5.8).

The probabilistic ICER was very similar to the deterministic estimate in the base case (see Section 5.8.1). The probabilistic ICER indicated that at a willingness-to-pay threshold of £50,000 per QALY gained, crizotinib has a high probability of cost-effectiveness versus pemetrexed plus platinum-based chemotherapy when provided with the PAS. One-way sensitivity analyses indicated that the key drivers of the model are covariate parameters attributed to the calculation of OS estimated from multivariate parametric modelling, with the covariate of treatment effect having the largest impact (see Section 5.8.2).

Probabilistic sensitivity analyses in which a variety of assumptions were varied/changed were conducted to test a number of parameters and assumptions (see Section 5.8.3). Alternative crossover adjustment methods were explored but these had a small effect on the ICER; the small change to the ICER with the other two-stage models beyond the method used in the base case with the PAS can be found in a separate document.

Crizotinib was not cost-effective in the scenario for squamous patients, however this scenario reflects a situation in which every diagnosed squamous NSCLC patient is tested for ALK; in clinical practice it is understood that only that squamous patients with ‘typical’ ALK-positive characteristics would be tested, and potentially not at all centres. As such, the cost of identifying the rare, few patients with ALK-positive, squamous NSCLC was increased considerably.

Removing the adjustment to reflect real-world patient characteristics that is included in the base case and instead matching the modelled cohort exactly to the clinical trial cohort lowers the ICER to *[Academic / commercial in confidence information removed]* (deterministic), or *[Academic / commercial in confidence information removed]* (probabilistic), when crizotinib is offered at list price; a robust analysis has been undertaken and a conservative position presented in the base case.

Crizotinib is targeted at a small patient population; the budget impact for the introduction of crizotinib in the first-line setting is estimated to be *[Academic / commercial in confidence information removed]* **at list price when including the cost of ALK-diagnostic testing.**

On the introduction of crizotinib as a first-line treatment for patients with ALK-positive, advanced NSCLC, the budget impact to the NHS in England and Wales is estimated at *[Academic / commercial in confidence information removed]* (see Section 6). This includes the drug acquisition costs, the treatment administration costs, and also the cost of ALK-testing. The

analysis assumes that 100% of patients receive an ALK-test and the uptake of first-line crizotinib will be administered in all of these patients (see Section 6.3 for more details).

Conclusive remarks

Crizotinib, for the first-line treatment of ALK-positive NSCLC, is a valuable treatment option for patients in England and Wales and represents value for money to the NHS for the following reasons:

- Life expectancy remains poor for lung cancer sufferers. Mean survival for these patients is expected to be less than two years following treatment with standard of care. Given the limited response to treatment and poor survival rates, together with the toxicities often associated with chemotherapy, ALK-positive NSCLC patients in the UK face a significant unmet clinical need in the first-line setting. Therefore, there remains an unmet need despite the availability of current chemotherapy options.

- Direct head-to-head evidence demonstrates that crizotinib is an efficacious first-line treatment for patients with ALK-positive, advanced NSCLC and results in improved tumour responses, delayed progression and extended survival compared to standard of care treatment with pemetrexed plus platinum-based chemotherapy. Significant HRQoL benefits associated with crizotinib over chemotherapy have also been shown.

- Crizotinib meets end of life criteria as current life expectancy is between 12 and 20 months (Table 10), to which crizotinib offers a mean life extension of 11.1 months, and a median of 7.9 months (Section 5.7.2).

- Crizotinib is well tolerated. The most frequent treatment-related grade 3/4 adverse events that occur are manageable.

- Results of multiple sensitivity analyses showed the ICER to be consistently below £50,000 per QALY with the PAS. Internal and external validation of the cost-effectiveness evaluation confirmed the model results as robust, conservative, and confidently determined crizotinib to be a cost-effective treatment option when provided with the PAS.

- A range of sensitivity analyses demonstrate that the results are robust and provide a credible estimate of cost-effectiveness.

- The budget impact of crizotinib to the NHS in England and Wales, including the cost of ALK-testing for all patients, is estimated at *[Academic / commercial in confidence information removed]* at list price.

2 The technology

2.1 Description of the technology

2.1.1 Give the brand name, UK approved name, the therapeutic class and a brief overview of the mechanism of action. For devices, provide details of any different versions of the same device.

Brand name: Xalkori®

UK approved name: crizotinib

Therapeutic and pharmacological class: anti-neoplastic agent; protein tyrosine kinase inhibitor (TKI)

Mechanism of action

Crizotinib is a first-in-class, orally available, small-molecule, receptor tyrosine kinase (RTK) inhibitor with selective, dose-dependent activity against anaplastic lymphoma kinase (ALK) RTK and its oncogenic variants (e.g. ALK fusion proteins and selected ALK mutant variants).[6] Crizotinib has also demonstrated inhibitory activity against c-Met/hepatocyte growth factor receptor (c-Met/HGFR) and Recepteur d'Origine Nantais (RON).[6]

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Indicate whether the technology has a UK marketing authorisation/CE marking for the indications detailed in this submission. If so, give the date on which this was received. If not, state the current UK regulatory status, with relevant dates (for example, date of application and/or expected date of approval from the Committee for Human Medicinal Products).

Crizotinib (Xalkori®) received a positive opinion from the Committee for Human Medicinal Products (CHMP) on 22nd October 2015 for the indication detailed in this submission (see Section 2.2.2), with subsequent European Union (EU) Marketing Authorisation (MA) granted on 24th November 2015.

2.2.2 Give the (anticipated) indication(s) in the UK. For devices, provide the date of (anticipated) CE marking, including the indication for use. If a submission is based on the company's proposed or anticipated marketing authorisation, the company must advise NICE immediately of any variation between the anticipated and the final marketing authorisation approved by the regulatory authorities.

Crizotinib has the following indications in the UK:

- *XALKORI is indicated for the first-line treatment of adults with ALK-positive advanced NSCLC.*[7] This licensed, first-line indication represents the indication detailed in this submission. EU marketing authorisation was granted on 24th November 2015.

- *XALKORI is indicated for the treatment of adults with previously treated ALK-positive advanced NSCLC.*[6] EU marketing authorisation was granted on 23rd October 2012 for patients previously treated for advanced NSCLC.

2.2.3 Summarise any (anticipated) restrictions or contraindications that are likely to be included in the (draft) summary of product characteristics (SmPC).

According to the SmPC, crizotinib is subject to restricted prescription as detailed in Section 4.2 of the SmPC (see **Error! Reference source not found.**). This states that crizotinib treatment should be initiated and supervised by a physician experienced in the use of anticancer medicinal products, and only in patients whose ALK-positive status has been established using well-validated and accurate tests. Dose adjustment guidelines for patients with either renal or hepatic impairment, and for the management of AEs, are also described (see **Error! Reference source not found.**).

In addition, the SmPC states that crizotinib is contraindicated in patients with hypersensitivity to crizotinib or excipients, and in patients with severe hepatic impairment.

2.2.4 Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in an appendix.

See **Error! Reference source not found.**.

2.2.5 Provide the (draft) assessment report produced by the regulatory authorities (that is, the European public assessment report for pharmaceuticals) and a (draft) technical manual for devices in an appendix.

The full EPAR, including the SmPC, is presented in **Error! Reference source not found.**.

2.2.6 Summarise the main issues discussed by the regulatory authorities (preferably by referring to the [draft] assessment report [for example, the European public assessment report]). State any special conditions attached to the marketing authorisation (for example, if it is a conditional marketing authorisation).

European Public Assessment Report (EPAR) conclusions [8]

In granting the extension of the MA for crizotinib to include the first-line indication, the CHMP noted, in the extension of indication variation assessment report, that:

- *"In the first-line setting of ALK-positive NSCLC, crizotinib showed a statistically significant 3.9 months improvement of PFS compared to chemotherapy. This benefit in a patient population, for which there is currently no targeted treatment approved outweighs the risks related to gastrointestinal AEs, elevated transaminases and neutropenia."*
- *"Considering the various [cross-over] analyses presented, the treatment effect estimates of crizotinib on OS in presence of cross-over remain overall consistent, reassuring on the robustness of the primary [RPSFTM] analysis results."*
- *"No new crizotinib safety signal has been identified from study 1014 and from supportive studies and the risk profile remains unchanged."*
- *"[*In conclusion*] the benefit risk ratio of crizotinib in the first-line treatment of adult patients with ALK-positive advanced NSCLC patients is considered positive."*

Conditions and requirements of the marketing authorization [6, 8]

The original MA for crizotinib was granted on the condition that the MA holder met the obligations detailed in Annex II, Sections C, D and E, of the EPAR – Product Information, which are summarised below:

- Section C: submission of periodic safety update reports are required in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.
- Section D: adherence to an agreed risk management plan (RMP), including pharmacovigilance activities, and the provision of educational material for healthcare professionals prior to the launch of crizotinib in each Member State, with a focus on the risk of AEs, such as QTc prolongation.
- Section E: submission of updated OS data from study PROFILE 1007 within 9 months after the required 238 OS events has been reached (due Q1 2016).

The conversion from conditional to full MA could not be accepted as part of the extension of indication as the updated OS data from PROFILE 1007 has not yet been provided.[8]

On granting conditional MA for crizotinib, originally as a second-line treatment of ALK-positive, advanced NSCLC, the CHMP accepted the positive clinical benefit to risk ratio associated with the introduction of crizotinib from the incomplete clinical evidence available at the time of approval.[9] In doing so, it was acknowledged that crizotinib would represent a valuable therapeutic approach for ALK-positive NSCLC, which as a "*seriously debilitating diseases or life-threatening diseases* [places crizotinib] *within the scope of Commission Regulation 507/2006 on the conditional marketing authorisation*."[9]

The Committee also recognised the unmet medical need for patients with ALK-positive NSCLC, stating that "*to date, there are no therapies specifically indicated for the treatment of patients with ALK-positive NSCLC*" and that "*although there are treatments available for NSCLC, there is very limited information on the efficacy of anticancer therapies in ALK-positive NSCLC*."[9]

2.2.7 If the technology has not been launched, supply the anticipated date of availability in the UK.

Crizotinib was launched in the UK in November 2012 for the treatment of adults with previously treated ALK-positive, advanced NSCLC. Crizotinib was granted EU marketing authorisation for use in the first-line setting on 24th November 2015 and is now available in the UK.

2.2.8 State whether the technology has regulatory approval outside the UK. If so, please provide details.

Crizotinib was granted 'accelerated approval' in the United States of America by the U.S. Food and Drug Administration (U.S. FDA) on 26th August 2011.[10] The 'accelerated approval' program is designed "*to provide patients with earlier access to promising new drugs, followed by further studies to confirm the drug's clinical benefit*."[10-12] Crizotinib was also granted 'fast-track' designation by the U.S. FDA and was considered under the 'priority review' program, both of which are designed to expedite the approval of drugs that have demonstrated superior effectiveness and are to treat serious conditions/fill an unmet medical need.[12-14]

Crizotinib was subsequently granted regular approval by the U.S. FDA on 20th November 2013, based on the results of the phase III randomised controlled trial, PROFILE 1007.[15] Crizotinib has since been awarded 'breakthrough therapy' designation by the U.S. FDA for the treatment of patients with ROS-1-positive NSCLC.[16] The 'breakthrough therapy' designation was introduced by the U.S. FDA in 2012 as an additional expedited development program alongside 'fast-track' designation.[12, 17]

Crizotinib is approved for use in ALK-positive NSCLC in *[Academic / commercial in confidence information removed]* countries across North America, South America, Africa, Europe, Asia and Australasia. A full list of countries is available on request.

2.2.9 State whether the technology is subject to any other health technology assessment in the UK. If so, give the timescale for completion.

Crizotinib will be subject to health technology appraisal as a first-line therapy in adults with ALK-positive, advanced NSCLC by the Scottish Medicines Consortium (SMC). A submission to the SMC was made on 4th January 2016.

NICE have previously conducted an appraisal of crizotinib in adult patients with previously treated ALK-positive, advanced NSCLC [TA296].[5] Crizotinib in previously treated patients will again be appraised by NICE under the CDF transition arrangements (a submission will be made in February 2016). In addition, following an assessment by the SMC, crizotinib has been accepted for use in NHS Scotland for the treatment of adults with previously treated ALK-positive, advanced NSCLC [Drug ID 865/13].[18]

2.3 Administration and costs of the technology

2.3.1 For pharmaceuticals, complete the table 'Costs of the technology being appraised' in the company evidence submission template, including details of the treatment regimen and method of administration. Indicate whether the acquisition cost is list price or includes a patient access scheme, and the anticipated care setting.

Details of the treatment regimen, including the method of administration and unit costs associated with crizotinib are provided in Table 4.

Table 4: Costs of the technology being appraised

	Cost	Data source
Pharmaceutical formulation	200 mg hard capsule and 250 mg hard capsule 200 mg hard capsule is white opaque and pink opaque, with "Pfizer" imprinted on the cap and "CRZ 200" on the body. 250 mg hard capsule is pink opaque, with "Pfizer" imprinted on the cap and "CRZ 250" on the body.	SmPC [6]
Acquisition cost (excluding VAT)	NHS List price: £4,689.00 for 1 pack of 60× 200 mg (or 60x 250 mg) capsules	British National Formulary. (online) [19]
Method of administration	Oral	SmPC [6]
Doses	250 mg	SmPC [6]
Dosing frequency	Twice daily (a total of 500 mg daily). Crizotinib is to be taken continuously until disease progression or unacceptable toxicity.	SmPC [6]
Average length of a course of treatment	Crizotinib is to be taken continuously until disease progression or unacceptable toxicity. In the phase III RCT, PROFILE 1014, the median duration of treatment was 10.9 months in the crizotinib group. This also corresponded to the median PFS in the crizotinib group (data cut-off: 30th November 2013). Based on an estimated treatment duration of 10.9 months (331.8 days) and a pack size of crizotinib lasting 30 days, the average course of treatment equates to an estimated 11 packs of crizotinib.	SmPC [6] Solomon *et al.* (2014a) [2]
Average cost of a course of treatment	Based on an average course of treatment of 11 packs of crizotinib (rounded up to include wastage), the average cost of a course of treatment is expected to be £51,579.00 at list price	N/A
Anticipated average interval between courses of treatments	Crizotinib is to be taken daily, continuously; there are no scheduled intervals between treatment courses.	N/A
Anticipated number of repeat courses of treatments	Crizotinib should be taken continuously until disease progression, rather than as distinct courses. Please see estimated treatment duration length above.	N/A
Dose adjustments	Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, the dose of crizotinib should be reduced to 200 mg taken twice daily or 250 mg once daily if further reduction is necessary (see **Error! Reference source not found.** for details).	SmPC [6] PROFILE 1014 CSR [3]
Anticipated care setting	Treatment should be initiated and supervised by a physician experienced in the use of anticancer medicinal products, followed by home administration.	SmPC [6]

Abbreviations: CSR: clinical study report; N/A: not applicable; PAS: patient access scheme; PFS: progression-free survival; RCT: randomised controlled trial; SmPC: Summary of Product Characteristics; VAT: value-added tax.

2.3.2 Provide details of any patient access scheme that has been referred to NICE for inclusion in the technology appraisal by ministers and formally agreed by the company with the Department of Health before the date of evidence submission to NICE for the technology

A PAS has been submitted to the Department of Health and is still being considered.

2.3.3 For devices, provide the list price and average selling price in a table similar to the table presented in the template, 'Costs of the technology being appraised'.

Not applicable.

2.4 Changes in service provision and management

2.4.1 State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is indicated in the marketing authorisation) or whether there are particular administration requirements for the technology.

ALK diagnostic testing in the UK

The identification of patients with ALK-positive tumours who would be eligible to receive licensed crizotinib requires histopathological and molecular testing of patient tumour samples. There exists current infrastructure for the service provision and management of molecular testing, including testing to confirm ALK-status, with several providers set up with this testing facility.[20-23]

A two-tiered approach whereby testing is performed initially with immunohistochemistry (IHC) and positive results are then validated by fluorescence *in situ* hybridisation (FISH) is endorsed by the European Society for Medical Oncology (ESMO) and the Royal College of Pathologists.[24, 25] The Roche Ventana IHC and Abbott Vysis FISH diagnostic tests have been approved by the U.S. Food and Drug Administration (FDA) for use in identifying ALK-positive NSCLC patients who may be eligible for treatment with crizotinib, with both tests also receiving CE marking for use in Europe; however, no specific test are detailed in the SmPC for crizotinib.[6, 26-29]

A recent advisory board with four UK clinical experts in attendance confirmed that reflex or upfront (i.e. requested at the first multi-disciplinary team meeting) ALK-testing using IHC and FISH is a common current testing strategy carried out in the non-squamous NSCLC patient population. The testing of non-squamous patients primarily is reflective of the predominance of ALK-translocations in tumours of this histology (see Section 3.1); however, patients with squamous cell carcinomas may be tested if they present with other features characteristic of ALK-positive NSCLC, such as younger age at diagnosis and non-smoker status. The cost-effectiveness of testing and treating squamous patients is considered in the economic evaluation in a scenario analysis (see Section 5.8.3).

2.4.2 Identify the main resource use to the NHS associated with the technology being appraised. Describe the location or setting of care (that is, primary and/ or secondary care, commissioned by NHS England specialised services and/or clinical commissioning groups), staff costs, administration costs, monitoring and

tests. Provide details of data sources used to inform resource estimates and values

The main resource use to the NHS associated with crizotinib is estimated to be the drug acquisition costs, which is detailed in Table 4. The location of care, administration costs and monitoring requirements for crizotinib are presented in Table 5.

Table 5: Resource use to the NHS associated with crizotinib

Resource	Estimated use
Location of care	Patients will have crizotinib prescribed by their oncologist, whom patients will visit on a monthly basis. The patients would receive the care in their own home however, as the pack of capsules is self-administered by the patient.
Administration costs	2.4.3 As patients self-administer orally, the administration is themselves in their own home. Hence, there are no resource for administration (see **Table 65: Assumptions in the modelled base case** for more details on how this applied in the model).
Monitoring and testing	The following parameters are monitored as standard for NSCLC patients, whether treated with crizotinib or chemotherapy: • Complete blood counts, including differential white blood cell counts as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. • Renal function, with tests including urea and creatinine once a month and as clinically indicated, with more frequent repeat testing if biochemical deterioration documented. • Liver function, with tests including ALT and total bilirubin once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. • Hypersensitivity reactions during for the first few doses of medication. • CXR and CT scans. • Heart rate and blood pressure during administration of treatment The following parameters will be monitored over and above standard care and are specific to treatment with crizotinib: • QT interval in patients with a history or predisposition for QTc prolongation, or who are taking medicinal products known to prolong the QT interval. Monitoring should be conducted periodically using electrocardiograms, renal function and electrolytes. Heart rate and blood pressure should be monitored regularly. • Patients with pulmonary symptoms indicative of interstitial lung disease (ILD) /pneumonitis should be monitored. Other potential causes of ILD/pneumonitis should be excluded. • Vision disorders which persist or worsen in severity. It is recommended that ophthalmological evaluation be considered in these cases. • Patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored (clinical assessment) for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention). • Periodic monitoring with imaging and urinalysis should be considered in

	patients who develop renal cysts. [6]

Abbreviations: ALT: alanine aminotransferase; CT: computerised tomography; CXR: chest x-ray; ILD: interstitial lung disease; NHS: National Health Service; NSCLC: non-small-cell lung cancer; QTc: corrected QT interval.

2.4.4 Specify if the technology requires additional infrastructure in the NHS to be put in place.

There exists current infrastructure for the service provision and management of molecular testing to confirm ALK-status, so no additional infrastructure is assumed to be required.

2.4.5 State if and to what extent the technology will affect patient monitoring compared with established clinical practice in England.

It is recommended that patients receiving crizotinib be monitored for some AEs. Many of the recommended monitoring practices (e.g. liver function tests for hepatotoxicity; blood tests for haematologic laboratory abnormalities) are performed as part of usual clinical practice in patients receiving second-line therapy for NSCLC.

For adverse event monitoring of patients receiving crizotinib over and above usual clinical practice please see Table 6. The additional monitoring requirements that are unique to crizotinib are not believed to pose a substantial burden in terms of patient monitoring compared to established practices.

2.4.6 State whether there are any concomitant therapies specified in the marketing authorisation or used in the key clinical trials (for example, for managing adverse reactions) administered with the technology.

There are no specific therapies that need to be administered alongside crizotinib, although patients may require concomitant medications to manage the symptoms of metastatic NSCLC, or to manage treatment related toxicities. Supportive care for gastrointestinal events such as nausea, diarrhoea, vomiting and constipation may require treatment with standard antiemetic and/or anti-diarrhoeal or laxative medicinal products, as listed in Table 7, and will be directed by the supervising medical practitioner based on grade of toxicity and patient medical and treatment history.[6]

Table 7: Concomitant medicines for the treatment of adverse events

Adverse event	Therapy prescribed
Diarrhoea	Loperamide
Nausea/vomiting	Domperidone or Metoclopromide
Constipation	Lactulose Senna Dioctyl sulfosuccinate

2.5 Innovation

2.5.1 If you consider the technology to be innovative with potential to make a substantial impact on health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation: state whether and how the technology is a 'step-change' in the management of the condition; provide a rationale to support innovation, identifying and presenting the data you have used.

Crizotinib is an innovative, first-in-class, targeted therapy that addresses a high unmet need. It represents a step change in management associated with benefits that are not accounted for in the ICER, including carer burden, the value to wider society, and the convenience of autonomy for patients. Consequently, the truly transformative benefits offered by this medicine to NSCLC patients are undervalued in the evaluation of cost-effectiveness. If these additional factors were incorporated into the analyses, then the cost per QALY would be well within the acceptable threshold levels.

A first-in-class targeted therapy with a new mechanism of action

ALK is a tyrosine-kinase target in NSCLC.[30, 31] Those with ALK aberrantly activated through a chromosomal rearrangement see an expression of oncogenic fusion kinase, which may cause the cell to grow uncontrollably.[32-35] Tumours with this change to the ALK gene are considered ALK-positive. No NSCLC targeted therapies are currently licensed in the UK that specifically target the inhibition of ALK – for these patients, first-line chemotherapy is the only treatment option currently available and is administered to ALK-positive and ALK-negative patients alike.

Licensed as the first specific inhibitor of ALK in NSCLC for previously untreated patients, crizotinib is able to block the activity of this abnormal ALK protein which not only slows the growth and spread of the cancer in ALK-positive NSCLC, but can actually cause the cancer to shrink. The result to patients is improved health status, symptom reduction and prolonged survival.[2]

An innovative therapy recognised at the regulatory level

The clinical benefits associated with crizotinib have been acknowledged in the EU and US regulatory approval processes with the granting of ‘conditional’ and ‘accelerated’ approvals by the EMA and U.S. FDA, respectively.[10, 36] These approval programs are designed to accelerate patient access to promising drugs, and are granted to medicines that are used to treat serious conditions and that fill an unmet clinical need.[12, 36] The approval of crizotinib as part of these programs is demonstrative of a ‘step-change’ in the management of ALK-positive NSCLC with crizotinib. Indeed, the development of crizotinib effectively paralleled the discovery of the ALK translocation.

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

The current standard of care is intravenous chemotherapy, administered every 3 weeks. By comparison, 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 have to spend lengthy periods of time each month to receive chemotherapy infusions in secondary care. A preference for orally-available therapies amongst cancer patients has been previously demonstrated in a number of studies.[37, 38] This benefit to patients is coupled with a reduction in service requirements and healthcare resource use related to assisted administration

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

Current standard of care chemotherapy achieves an objective response in 45% of patients with ALK-positive NSCLC. In a disease area where the majority of patients therefore fail to respond, crizotinib provides a solution to this unmet need, increasing the response rate to 74% (P<0.001).[2] As crizotinib is a first-in-class therapy, its unique and specific mechanism of action allows it to achieve this far greater objective response.

The further benefit is a reduction in unnecessary drug exposure to platinum-based chemotherapy in the high proportion of patients that do not respond to first-line chemotherapy; not only does crizotinib's innovative impact on response rate reduce the number of patients who unnecessarily incur adverse events with no benefit to treatment, but drug 'wastage' is reduced meaning costs are saved.

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

Another resulting advantage of crizotinib's novel mechanism of action over traditional chemotherapy is that tumour behaviour may not only seen to be controlled, but is often reduced in size to a smaller mass than at the start of treatment. Crizotinib-treated patients see a greater median best percentage reduction in target lesion size from baseline compared to patients treated with chemotherapy of *[Academic / commercial in confidence information removed]* vs. *[Academic / commercial in confidence information removed]* [2, 39] The innovative way in which crizotinib targets the tumour enables it to put patients in a healthier position at the time they progress than when they started on treatment, representing a true 'step-change' in the way first-line patients are treated.

Correlated with this tumour control are significant delays in the time to deterioration in lung-specific symptoms and significant improvements in HRQoL compared to chemotherapy (see Section 4.7.2).[2] As treatment in advanced NSCLC is not curative, palliation through the reduction of symptoms and improvements in HRQoL is considered to be a key goal of therapy, alongside extension of life.[40, 41]

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

Historic life expectancy in ALK-positive NSCLC patients is between 12 and 20 months with chemotherapy, but the innovative nature in which crizotinib can reduce the tumour size and illicit a response delays progression and delays death. OS estimates using multiple established crossover-adjusted analyses, demonstrated a clear survival advantage for crizotinib (median: 21.7 months; mean: 29.0 months) compared to pemetrexed plus platinum-based therapy (median: 13.8 months; mean: 17.9 months) (see Section 5.7.2). Crizotinib represents a life-extending medicine for patients with previously untreated ALK-positive, advanced NSCLC who are otherwise at end of life with current first-line chemotherapy.[42] Full consideration of crizotinib as an end-of-life medicine is presented in Section 4.13.

Benefits to wider society when responding to crizotinib

Patients with ALK-positive NSCLC are typically younger than patients who are ALK-negative, with a median age in the early 50s for ALK-positive patients, as opposed to mid–late 60s for ALK-negative NSCLC.[4, 43] The clinical benefits associated with crizotinib, and 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 this submission's calculation of comparative cost-effectiveness analyses from an NHS perspective. Cost-savings related to reduced productivity losses have previously been proposed for the use of targeted therapies over chemotherapy in advanced NSCLC.[44] In addition patients with NSCLC may themselves be carers and improving their treatment outcomes would also have a wider societal benefit that is not captured in the QALY calculation.

Alleviation in carer burden

An aspect the cost-effectiveness analyses does not take into account is the expected benefits that crizotinib may provide to patient's 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.[45, 46] Given the improvements in patient HRQoL observed with crizotinib in PROFILE 1014, it is plausible to assume that treatment with crizotinib would likely reduce the carer burden compared to current chemotherapy options in the short term, especially 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.[2]

3 Health condition and position of the technology in the treatment pathway

Summary of the health condition and treatment pathway

Lung cancer

- Lung cancer is the second most common cancer in the UK, with NSCLC accounting for 88.1% of lung cancer cases; the majority of patients (66%) are diagnosed at an advanced stage of disease.
- NSCLC can be stratified by genotype and histology; ALK-positive NSCLC accounts for 3.4% of NSCLC, is predominantly non-squamous (~97.7%) and is associated with patients of younger age and non-smoker status.

Effects of ALK-positive NSCLC on patients and carers

- The symptom burden of NSCLC is high; common lung-specific symptoms include cough, dyspnoea and chest pain; symptoms and treatment toxicities are associated with a considerable negative impact on HRQoL.
- No curative options are available for patients with advanced NSCLC; extension of life and palliation of symptoms are key goals of therapy.
- Current chemotherapy first-line treatment options may just delay deterioration in HRQoL; adverse events associated with chemotherapy may impact negatively on HRQoL.
- NSCLC is also associated with considerable carer burden which is related to symptom severity; delayed deterioration of symptoms with crizotinib is likely to reduce carer burden.

Treatment pathway and existing NICE guidelines

- Chemotherapy is the only current first-line treatment option for patients with ALK-positive, advanced NSCLC.
- Crizotinib is being positioned as an alternative to first-line chemotherapy and would be the first targeted therapy for this indication; three targeted therapies are currently recommended for the first-line treatment of EGFR-positive NSCLC.
- Pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin) is the appropriate comparator for the first-line treatment of ALK-positive, advanced NSCLC.
- NICE TA181 recommends the use of pemetrexed-cisplatin in patients with advanced NSCLC whose tumour is of adenocarcinoma or large-cell carcinoma histology (i.e. non-squamous); pemetrexed-carboplatin is also used routinely in UK clinical practice.
- Single-agent chemotherapy with third-generation drugs is used in a small minority of patients (1–2%); due to limited usage, this treatment option is not presented as a comparator in this submission

Expected patient numbers and current life expectancy

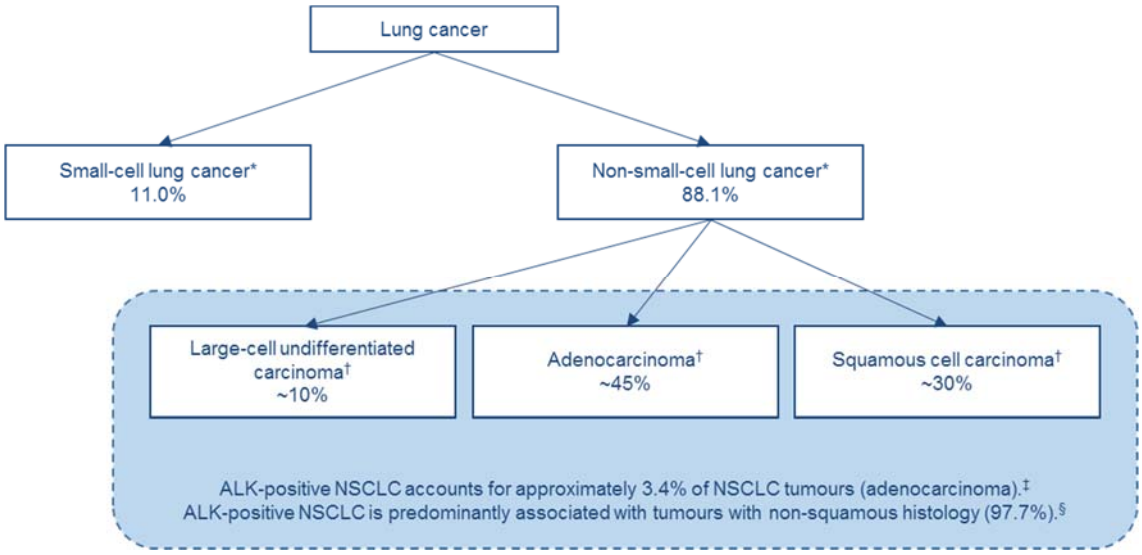
- Prognosis for lung cancer is poor; patients with advanced disease are often at end-of-life with one-year survival rates at 35% for stage III and 14% for stage IV disease; the prognosis for ALK-positive NSCLC is no more favourable.
- Established median overall survival on first-line chemotherapy with pemetrexed is around 11.8 months based on published phase III clinical trials.
- Around 459 patients per year are expected to be eligible first-line crizotinib in England and Wales.
- Crizotinib is being submitted for consideration as an end-of-life medicine

3.1 *Provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.*

Lung cancer

Lung cancer can be categorised into two major types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). NSCLC accounts for the majority (88.1% in England and Wales) of lung cancer cases and can be sub-typed further into three histological types: adenocarcinoma (~45% of NSCLC), large-cell undifferentiated carcinoma (~10% of NSCLC) and squamous cell carcinoma (~30% of NSCLC) (see Figure 1). 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.

Sources:
* The proportion of patients with SCLC and NSCLC correspond to those reported in the National Lung Cancer Audit Report (2015) for England and Wales.[47] The sum of percentages does not equal 100% due to the exclusion of carcinoid with accounts for the remaining 0.9% of all lung cancer.
† The proportion of lung tumours of each histology sub-type are derived from the Clinical Lung Cancer Genomics Project (2013).[48] These broadly agree with those presented by the American Cancer Society.[49]
‡ The proportion of NSCLC tumours (adenocarcinoma) estimated to be ALK-positive is taken from the Clinical Lung Cancer Genomics Project (2013).[48]
§ The proportion of ALK-positive NSCLC tumours that are non-squamous is derived from the PROFILE 1001 (n=149) and PROFILE 1005 (n=901) clinical trials in which patients were not pre-selected by histology.[50, 51]

Lung cancer is the second most common cancer in the UK, accounting for 13% of all new cancer cases.[52] According to the National Lung Cancer Audit Report (2015), 33,027 cases of lung cancer were reported in England and Wales in 2014.[47]

The outcomes for patients with lung cancer are largely dependent on how advanced the cancer is when it is diagnosed.[53] Lung cancer is often diagnosed at an advanced stage due to the low index of suspicion surrounding the symptoms: it is expected that smokers will suffer from cough and it is not expected that non-smokers will develop lung cancer.[54] In the UK, approximately 66% of lung cancer cases are diagnosed at an advanced stage of disease (19% and 47% for

stages III and IV, respectively).[55] Due to late diagnosis, the prognosis for patients diagnosed with lung cancer is often poor (see Section 3.4).

Patients who receive first-line standard-of-care therapy are followed up clinically and radiologically until they experience disease progression. Progressive disease has been defined in the Response Evaluation Criteria In Solid Tumours (RECIST) guidelines (version 1.1), as detailed in Table 8.[56] RECIST is a tool used for defining progression consistently within the trial setting; progression in clinical practice is often less rigorously defined.

On progression after active first-line treatment, patients can receive an active second-line therapy 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 symptom burden and overall survival.[57, 58]

Table 8: RECIST version 1.1 definitions of tumour response

Tumour response	Definition
Complete response	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 diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease	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 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.

Source: Eisenhauer *et al.* (2009) [56]

ALK-status and molecular sub-types of NSCLC

ALK was initially identified as an oncogenic driver in patients with anaplastic large-cell lymphoma.[59] It has since been identified as a key oncogenic driver in a number of other cancers, including NSCLC in 2007.[60] In lung cancer, the most common ALK fusion partner is understood to be EML4, although several variants of EML4 and two other transforming ALK fusion partners have been described.[59] Different fusion partners are not thought to impact on the efficacy of crizotinib, as the ALK protein (and binding site for crizotinib) is consistent.[59, 61] Inhibition of ALK 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.[60, 62, 63] Specifically, crizotinib— via inhibition of ALK —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.[62]

The prevalence of ALK-positive NSCLC is estimated to be around 3.4% of NSCLC; which is considerably lower than tumours harbouring EGFR or Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations, which account for between ~15% and 30% of NSCLC, respectively.[48] ALK-translocations, EGFR mutations and KRAS mutations have thus far been

demonstrated to be mutually exclusive of one another in NSCLC tumours.[61, 64] The distinction between ALK-positive and EGFR-positive tumours extends to the response of patients to targeted therapies against EGFR-tyrosine kinase inhibitors (EGFR-TKIs); for example, patients with ALK-positive NSCLC do not tend to respond any more favourably to treatment with EGFR-TKIs than patients with ALK/EGFR wild-type tumours.[4].

The clinical and pathologic features of ALK-positive tumours have been characterised; with ALK-positivity showing associations with, non-smoker status and an earlier age of diagnosis.[4, 43, 65] In addition, ALK-translocations are almost exclusively detected in non-squamous tumour types.[4] The incidence of ALK-positivity within non-squamous patients is assumed to be 3.4%, as deduced from a sample of 1255 adenocarcinoma patients.[48] The incidence of ALK-positivity within squamous patients harder to establish, but can be calculated as follows:

- In phase I (PROFILE 1001) and phase II (PROFILE 1005) crizotinib trials, the inclusion of patients with squamous and non-squamous cell carcinoma histology was allowed. Non-squamous histology accounted for 97.74% of patients, and squamous 2.26%.[50, 51]
- From this, the ratio of squamous to non-squamous histological classification within ALK-positive NSCLC patients is 1:43 (= 97.7 / 2.3).
- Considering an incidence of ALK-positivity of 3.4% in the non-squamous group, this suggests the incidence of ALK-positive NSCLC within squamous NSCLC is around 0.08% (= 3.4% / 43).

The identification of patients with ALK-positive squamous NSCLC would therefore be extremely rare in the UK. The evidence base for crizotinib sees the significant majority of ALK-positive patients enrolled in clinical trials having tumours of non-squamous histology.[2, 31, 50, 51]

3.2 Describe the effects of the disease or condition on patients, carers and society.

Effects of NSCLC on patients and quality of life

Patients with NSCLC have a high symptom burden, with the majority of patients (≥90%) reporting symptoms including fatigue, loss of appetite, cough, pain and dyspnoea.[66, 67] Furthermore, advanced NSCLC may be associated with additional or exacerbated symptoms such as weight loss, shortness of breath due to an associated pleural effusion, swelling of the neck and face (due to obstruction of the superior vena cava by the primary cancer and/or enlarged lymph nodes or associated thromboembolic disease) and difficulty swallowing from local compression of the oesophagus.[68] In addition, patients with metastatic NSCLC may develop further symptoms related to metastatic disease. For example, approximately 25–30% patients with NSCLC will develop brain metastases over the course of disease, with many of these patients going on to suffer from neurocognitive and functional deficits.[69]

The symptom burden of advanced NSCLC has a highly detrimental effect on patient HRQoL.[66] Given that no curative options for patients with advanced NSCLC exist, one of the aims of current therapy alongside extension of life is to achieve symptom relief and gain improvements in HRQoL.[40, 41] In previous studies, patients showing an objective tumour response have been demonstrated to experience the greatest levels of symptom relief.[70] Furthermore, changes in patient-reported HRQoL outcomes have been shown to be associated with survival (for better and worse), suggesting that HRQoL may be predictive of overall survival.[71, 72]

First-line, standard-of-care treatment with pemetrexed plus platinum-based chemotherapy only results in low response rates (30.6–45%), and so may only offer patients with advanced NSCLC a reprieve in the worsening of symptoms and HRQoL relative to supportive care.[2, 73, 74] Previous clinical trials suggest that pemetrexed plus platinum-based chemotherapy is associated with PFS of only 5.3 months and OS of 11.8 months in previously untreated non-squamous, advanced NSCLC.[74] In addition, chemotherapy is associated with a number of unwanted side effects and toxicities, such as haematological AEs, alopecia, fatigue and severe nausea, that may contribute to patient burden.[75] A societal-based preference study conducted in the UK specifically for NSCLC reported a preference for the avoidance of progressive disease and common side effects of chemotherapy, such as fatigue and neutropenia in the second-line setting.[57] In contrast, targeted therapies allow for a greater precision in targeting cancerous cells which can additionally translate into a more tolerable side effect profile compared to chemotherapy.[70, 76] When this is the case, there is the potential for both significant improvements in both patient symptom burden and toxicity-related HRQoL relative to chemotherapy.

Given the limited response to treatment and poor survival rates, together with the toxicities often associated with chemotherapy, ALK-positive NSCLC patients in the UK face a significant unmet clinical need in the first-line setting. In addition, mean survival for these patients is expected to be less than three years following treatment with standard of care, as described in Section 3.4.

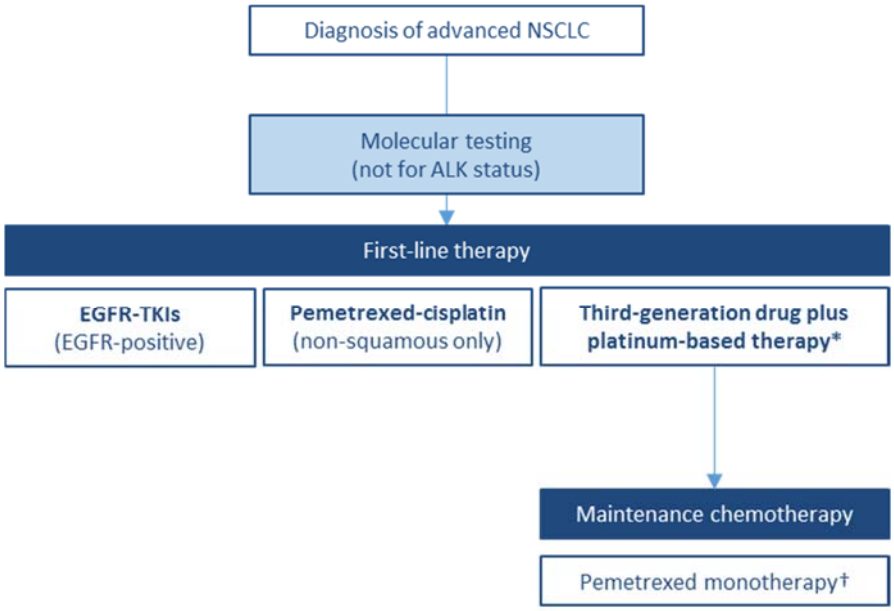
Effects on carers

It is well-established in the current literature that a cancer diagnosis profoundly impacts not only the patient but also the caregiver.[45] The caregiving role in cancer, particularly for those caring for a family member or friend, can be associated with physical, psychological, social, functional, and spiritual burdens.[45] In advanced NSCLC, the Italian HABIT study demonstrated that caregiver burden is high and that there is a positive correlation between the costs of assistance in terms of the carer's time and the severity of the patient's symptoms.[46] Over a three-month period, it was found that assistance costs increased each month for patients receiving second-line treatment for NSCLC. These cost increases correlated with score decreases on the Lung Cancer Symptoms (LCS) subscale of the FACT-L questionnaire, which measures worsened symptoms perceived by patients. Carer HRQoL and psychological well-being has also been reported to deteriorate with time.[45, 77]

3.3 *Present the clinical pathway of care that shows the context of the proposed use of the technology.*

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

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



* If patients cannot tolerate a platinum combination, single-agent chemotherapy with a third-generation drug is recommended by NICE clinical guidelines for lung cancer [CG121]
† 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 [TA309]

Sources: based on NICE clinical guidelines: lung cancer [CG121][78]; NICE pathway for the treatment of NSCLC [79]; and NICE guidance from the following technology appraisals: TA310, TA258 and TA192 for the EGFR-TKIs: afatinib, erlotinib and gefitinib, respectively;[80-82] TA181 for pemetrexed-cisplatin;[83]; TA190 for pemetrexed maintenance therapy following induction therapy with platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel [84]; and TA309 for pemetrexed maintenance therapy following induction therapy with pemetrexed-cisplatin[85]

See Section 3.5 for further details of relevant NICE guidelines and recommendations.

As shown in Figure 2, chemotherapy is the only treatment option currently available for the first-line treatment of patients with ALK-positive, advanced NSCLC. Unlike EGFR-positive NSCLC, no targeted therapies are currently available for ALK-positive patients who have not previously been treated for advanced NSCLC.

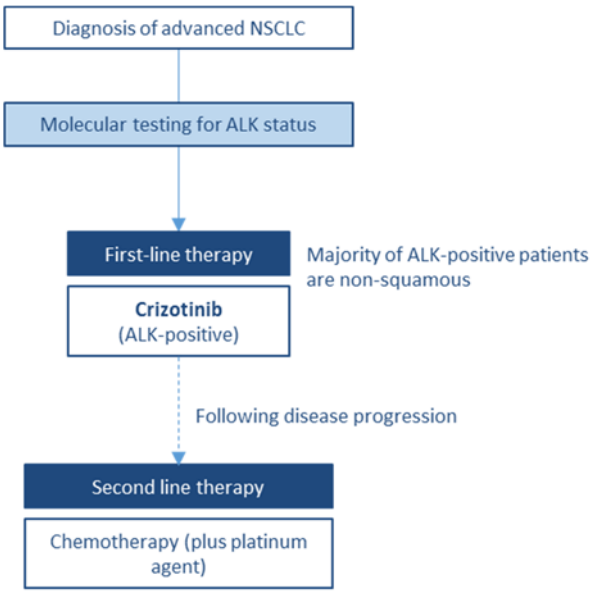
Based on consultation with a group of four UK clinical experts (treating oncologists) at a recent advisory board, the clinical pathway presented in Figure 2 is thought to be broadly consistent with what patients would expect to receive in UK clinical practice. The clinical experts provided further details on the treatment options in the first-line setting that are used in current clinical practice for the typical ALK-positive patient (i.e., patients with non-squamous, advanced NSCLC which is negative for EGFR mutations); these aspects should be considered alongside the treatment pathway presented above:

- Pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin) is used in the majority patients in UK clinical practice receiving chemotherapy. Pemetrexed plus platinum-based chemotherapy is therefore considered to be the main comparator in this submission.
    - 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.[86, 87] In one retrospective analysis, no significant difference in median PFS was observed between pemetrexed in combination with either cisplatin or carboplatin in patients with ALK-positive, advanced NSCLC.[88]
- Single-agent chemotherapy with third-generation drugs is used in patients with non-squamous NSCLC for whom platinum-based therapy is not appropriate, as recommended by CG121,[78] but consulted clinical experts indicated this proportion of patients to be less than 2%.

Positioning of crizotinib relative to the current treatment pathway

Crizotinib is being positioned as an alternative to chemotherapy for the first-line treatment of ALK-positive, advanced NSCLC, as per the licensed indication (see Figure 3). This is consistent with the final scope issued by NICE for this appraisal (see Table 2).

Figure 3: Proposed treatment pathway for the first-line treatment of ALK-positive, non-squamous, NSCLC



Crizotinib would therefore replace first-line chemotherapy in ALK-positive patients, in line with past recommendations for EGFR-TKIs in EGFR-positive NSCLC.[80-82] The rationale for introducing crizotinib as a first-line therapy is to provide patients who are most likely to respond to targeted ALK inhibition the greatest clinical benefit early on in the treatment pathway; access to crizotinib in the first-line setting would ensure that patients identified as being ALK-positive can benefit from a targeted agent at an earlier stage of their disease. Furthermore, this would delay the use of potentially ineffective and poorly tolerated chemotherapy, thus improving outcomes for patients earlier in the treatment pathway.

Comparators in this submission

As described in Section 3.1, ALK-positive NSCLC is predominantly (97.7%) associated with tumours of non-squamous histology, and the presentation of an ALK-positive patient with squamous cell carcinoma in the UK is thought to be extremely rare. For completeness however, a scenario analysis is presented in Section 5.8.3 for crizotinib versus pemetrexed plus cisplatin/carboplatin in patients with squamous cell carcinoma histology (see Section 5.2.4).

Pemetrexed plus platinum-based therapy

Based on feedback from four UK clinical experts, patients with ALK-positive NSCLC who are unaware of their ALK status would usually be treated with pemetrexed plus platinum-based chemotherapy. As noted in Section 3.5, pemetrexed in combination with cisplatin, specifically, is recommended by NICE in TA181 for the treatment of non-squamous, advanced NSCLC.[83]

Pemetrexed plus platinum-based therapy is thus considered to represent the current standard of care for patients with ALK-positive patients in the UK, and is presented as the primary comparator in this submission. 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 (see Table 2).[1]

Single-agent chemotherapy with a third-generation drug

Although listed in the final scope issued by NICE for this appraisal, single-agent chemotherapy with a third-generation drug is not presented as a comparator. Following consultation with UK clinical experts it was noted that single-agent chemotherapy is rarely used in the patient population of interest (less than 2% of patients), and so does not represent a relevant comparator for crizotinib in this submission.

3.4 *Provide information about the life expectancy of people with the disease or condition in England and the source of the data. Please provide information on the number of people with the particular therapeutic indication for which the technology is being appraised.*

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%.[89] This is considerably worse than other common cancers such as breast (87%) and prostate cancer (85%).[90] A poorer prognosis for patients with lung cancer is believed to be associated with high proportion of patients presenting at an advanced stage (66%) and the concurrent difficulty in treating patients with advanced or metastatic disease.[55] The outlook for patients with advanced-stage lung cancer in England and Wales is markedly worse than those patients with early-stage disease for whom surgery is a curative treatment option (see Table 9).

Table 9: One-year and five-year survival rates for lung cancer patients by stage (Cancer Research UK)

Stage at diagnosis	One-year survival rate	Five-year survival rate
I	71%	35%
II	48%	21%
III	35%	6%
IV	14%	Unavailable*
Stage not known	17%	6%
All stages	32%	10%

* Five-year survival rates for patients diagnosed with stage IV lung cancer could not be calculated due to so few patients surviving more than 2 years.

Source: Cancer Research UK – lung cancer survival statistics [91]

Expected life expectancy of patients treated with first-line chemotherapy

Estimates of overall survival for advanced NSCLC patients treated with first-line chemotherapy, based on relevant trial and study data, and feedback from four UK clinical experts at an advisory board, are presented in Table 10; these ranging from 10.6 months to 20 months. UK clinical expert estimation of OS in ALK-positive, advanced NSCLC patients is around 15 months.

A retrospective analysis of ALK-positive, crizotinib-naïve patients by Shaw et al. (2011) reports median OS for crizotinib-naïve patients who had received 1 to 4 lines of therapy.[30] However, this small sample size comes with it a wide range of estimates (13-26 months), and a variety of treatment regimens (44% of these patients receiving a regimen containing erlotinib, 33% not receiving any pemetrexed). The estimate of OS may therefore be limited in its reflection of what should be expected in UK clinical practice, so should not be considered in isolation.

Differences across in the estimates in Table 10 may be reflective of difference in patient populations; ALK-positive patients are typically younger and more likely to be non-smokers (and thus more "healthy") than typical NSCLC patients at presentation.[4, 43] However, a number of recent studies directly comparing ALK-positive and ALK-negative patients (including Shaw *et al.* [2011]) have reported survival data for ALK-positive patients that is not significantly different to patients with either EGFR-negative NSCLC or wild-type NSCLC.[4, 30, 92, 93]

Given the below estimates of OS, patients with ALK-positive, advanced NSCLC receiving first-line chemotherapy should be considered as being in an end-of-life setting, with a life-expectancy of less than 24 months, as is required to qualify for NICE's end-of-life criteria.[42]

Table 10: Estimates of overall survival in patients receiving current standard of care

Source	Description	Median OS, months
JMDB trial* **Scagliotti *et al.* (2008) [74]**	Phase III RCT of pemetrexed-cisplatin versus gemcitabine-cisplatin in patients with advanced NSCLC Median OS was reported for non-squamous patients: Pemetrexed-cisplatin (n=513)	11.8 (95% CI, 10.4 to 13.2)
Shaw *et al.* (2011) [30]	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 (n=36). Median OS was reported for crizotinib-naïve patients who had received multiple, previous lines of therapy (range 1 to 4), most of whom had received pemetrexed and/or platinum-based therapy. ALK-positive, crizotinib-naïve (n=36)	20 (95% CI, 13 to 26)
FRAME study **Moro-Sibilot *et al.* (2015) [94]**	Prospective observational study of non-squamous NSCLC patients treated with first-line platinum-based chemotherapy across Europe Pemetrexed-platinum (n=553)	10.6 (95% CI, 9.4 to 12.0)
UK clinical experts	Expected life expectancy of patients with ALK-positive, advanced NSCLC treated with first-line chemotherapy	~15

* This trial was used as evidence in the manufacturer's submission for TA181 [83]

Abbreviations: ALK: anaplastic lymphoma kinase; NSCLC: non-small cell lung cancer; OS: overall survival; RCT: randomised controlled trial.

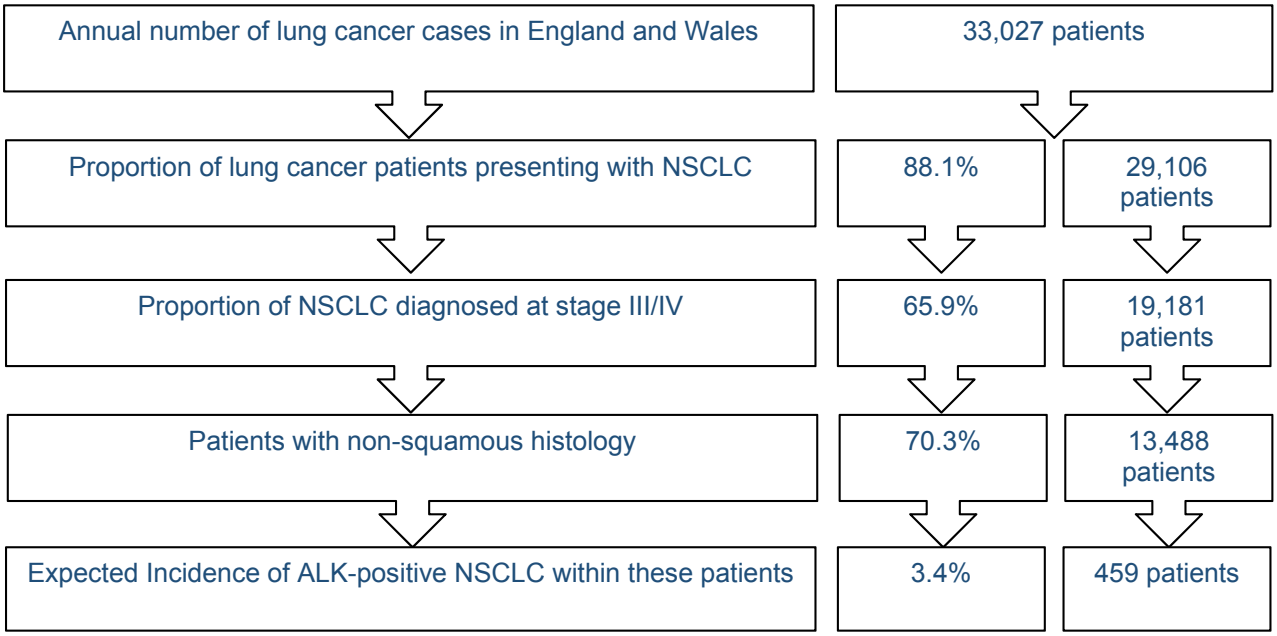
Estimated number of patients with ALK-positive, advanced NSCLC

The estimated number of patients in England and Wales who would be eligible to receive crizotinib as a first-line therapy for ALK-positive, advanced NSCLC is presented in Figure 4.

It is expected that 459 patients with non-squamous, ALK-positive, advanced, NSCLC would be diagnosed. As detailed in Section 3.1, it is rare that a patient of squamous histology would be

eligible for crizotinib as the incidence of ALK-positivity within the non-squamous NSCLC population is estimated at only 0.08% (derived in Section 3.1). The expected number of squamous patients identified each year would thus be very few, considering further that squamous patients are unlikely to be routinely tested for ALK (see discussion in Section 5.8.3).

Figure 4: Expected number of patients in England and Wales with ALK-positive, non-squamous, advanced NSCLC



Abbreviations: ALK: anaplastic lymphoma kinase; NSCLC: non-small cell lung cancer.
Sources: Rows 1 and 2 [47]; row 3 [55]; rows 4 and 5 [48]

The number of patients in England with ALK-positive, advanced NSCLC who accessed crizotinib via the Cancer Drugs Fund for second-line (or subsequent) therapy was 111 for the period April to March 2014/15.[95] This figure is much lower than the number reported in Figure 4 for all ALK-positive patients who may be expected to receive first-line crizotinib. This difference may be explained by the following:

- The National Lung Cancer Audit in 2015 indicated that only 58% of stage IIIb/IV patients with good performance status receive first line chemotherapy which reduces the number of patients suitable for second line treatment compared with those that might be suitable for first-line treatment.[47]
- From those patients that do begin first-line chemotherapy, clinical expert feedback indicates that only around 50% of these patients may be alive or fit enough for second-line treatment.
- Diagnostic and pathway challenges may means not all ALK-positive patients are being identified in practice.

Clinical expert feedback indicates that the availability of crizotinib in the first-line setting would increase the number of patients eligible, in line with Figure 4.

Full consideration of NICE's end-of-life criteria are presented in Section 4.13.

3.5 *Provide details of any relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used. Specify whether any subgroups were explicitly addressed.*

Please note that the following consider treatments in the general condition of NSCLC, and not ALK-positive NSCLC, specifically.

NICE lung cancer clinical guidance [CG 121]

Chemotherapy for NSCLC

According to current NICE clinical guidelines [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).[78] 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.[78] Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug.[78] These recommendations were issued in 2005, prior to the positive guidance of pemetrexed for the first-line treatment of non-squamous, advanced NSCLC[83], and do not make any distinction between histology-types.[78]

Relevant NICE technology appraisals for medicines used in previously untreated, advanced NSCLC

First-line pemetrexed-cisplatin [TA181]

Following a technology appraisal in 2009 [TA181], pemetrexed in combination with cisplatin is currently recommended as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC, but only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (i.e. non-squamous).[83]

The pemetrexed-cisplatin combination recommended by NICE is consistent with the licensed indication.[96] Based on feedback from four UK clinical experts, pemetrexed in combination with carboplatin is also used widely in the UK (see Section 3.3).

Maintenance therapy with pemetrexed monotherapy [TA190 and TA309]

Pemetrexed is only recommended by NICE as an option for maintenance therapy with locally advanced or metastatic NSCLC other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel (TA190).[84] Pemetrexed maintenance therapy is not recommended for patients who have received pemetrexed in combination with cisplatin as first-line chemotherapy (TA309).[85]

Pemetrexed-maintenance therapy is not considered to be a relevant comparator for this submission, in accordance with the final scope issued by NICE for this appraisal.[1]

EGFR-TKIs for first-line treatment of advanced, EGFR-positive NSCLC [TA192, TA310 and TA258]

NICE has recommended the use of three EGFR-TKIs for the treatment of EGFR-positive, advanced NSCLC (gefitinib [TA192], erlotinib [TA258] and afatinib [TA310]), and has also issued guidance for the use of diagnostic tests to identify patients with EGFR mutations.[80-82, 97]

Given that EGFR mutations and ALK-translocations are largely believed to be mutually exclusive of one another, EGFR-TKIs will not be considered as a comparator for crizotinib in the treatment of ALK-positive NSCLC.[61, 64] This is consistent with the absence of EGFR-TKIs as an appropriate comparator in the final scope issued by NICE for this appraisal.[1]

3.6 Provide details of other clinical guidelines (for example, UK guidance from the royal societies or European guidance) and national policies.

Clinical guidelines from the European Society for Medical Oncology (ESMO) for the diagnosis, treatment and follow-up of patients with metastatic NSCLC were published in 2014 and are broadly consistent with the NICE guidance and clinical guidelines described in Section 3.5.[98]

ESMO guidelines recommend that first-line treatment with platinum-doublet chemotherapy should be considered in patients with performance status 0–2 and that pemetrexed-based chemotherapy is the preferred choice for the treatment of non-squamous, advanced NSCLC.[98] Furthermore, ESMO guidelines also recommend that systematic testing for ALK-status should be performed in patients with non-squamous, advanced NSCLC, and that patients harbouring an ALK fusion should be offered treatment with crizotinib during the course of their disease.[98]

3.7 Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice

As alluded to in Sections 3.3, there is some degree of heterogeneity in the treatment of advanced NSCLC in clinical practice, with the choice of treatment dependent on tumour histology and/or genotype, patient fitness and clinician preferences. From consulting an advisory board made up of four UK clinical experts all currently retreating ALK-positive NSCLC patients, the consensus was between a choice of carboplatin or cisplatin in combination with pemetrexed – NICE guidelines recommend the use of pemetrexed-cisplatin, in accordance with the licensed indication.[83, 96] Discussions revealed that in UK clinical practice, although usage was similar between carboplatin and cisplatin, the proportion of patients are expected to receive carboplatin may be slightly higher than cisplatin. The cost of generic cisplatin is calculated at around 13 pence per mg, and carboplatin around 6 pence per mg (Appendix 21). A sensitivity analysis was conducted to investigate the impact on the ICER of a larger proportion of patients using the cheaper carboplatin in combination with pemetrexed (set to 75% using carboplatin), which differed from more equal usage in the base case of the economic evaluation. It was found that this did not affect the ICER (Table 74).

It was agreed at this advisory board that there lacked consensus over significant differences in efficacy between cisplatin and carboplatin. In line with the final scope issued by NICE, the pooled

treatment regimen of pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin) is thus included as a comparator in this submission.[1]

An official estimate for ALK-testing rates is not available, but rates for testing other mutations in NSCLC do exist.[99] In order to ensure access to equitable patients for NICE recommended treatments (should crizotinib be recommended), all eligible patients should receive ALK-tests. The modelled base case includes the cost of ALK-testing in the crizotinib arm.

3.8 Equity considerations

It is not considered that this appraisal will exclude any people protected by equality legislation, or lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

4 Clinical Effectiveness

Summary of Clinical Evidence

Direct head-to-head evidence from PROFILE 1014 demonstrates the clinical benefit of crizotinib compared to pemetrexed plus platinum-based chemotherapy for the first-line treatment of ALK-positive, advanced NSCLC

- The PROFILE 1014 phase III RCT provides evidence in a patient population that directly matches the decision problem; that is patients with previously untreated ALK-positive NSCLC. This trial provides direct head-to-head evidence across a total of 343 patients randomly assigned to either crizotinib (n = 172) or the relevant comparator of pemetrexed plus platinum-based chemotherapy (n = 171).
- This study met its primary endpoint: median PFS was significantly prolonged in the crizotinib group (10.9 months versus 7.0 months; HR, 0.45; 95% CI, 0.35 to 0.60; P<0.001).
- The long tail observed in the crizotinib arm of the Kaplan-Meier plot for PFS additionally highlights the potential for crizotinib to delay progression or death for a considerable time for some patients. In addition to median PFS benefit with crizotinib, the rate of PFS (i.e. the proportion of patients who had not yet progressed) at 18-months was vastly greater with crizotinib with nearly a third of patients progression-free at 18 months and beyond (crizotinib, 31%, compared to chemotherapy, 5%).
- Crizotinib was associated with significantly greater ORR than chemotherapy (74% vs. 45%) and greater best overall response with median best percentage reduction in tumour size from baseline of *[Academic / commercial in confidence information removed]* with crizotinib, compared to*[Academic / commercial in confidence information removed]* with pemetrexed plus platinum therapy, thus highlighting the benefits of targeted therapy.
- Median OS was not reached in either arm at the data cut-off date (30th November 2013); unadjusted HR for death with crizotinib was 0.821 (95% CI, 0.536 to 1.255); however, analyses of OS was confounded by high rates of crossover to crizotinib from the chemotherapy group (70%).
- Crossover-adjusted analyses showed a highly consistent range of HRs for death across nine parametric models, with the median value from this range (which is the selected base case) being 0.624 (0.405, 0.963, p=0.0158) using three appropriate methods of analyses: rank preserving structural failure time (RPSFT), two-stage Weibull and iterative parameter estimation (IPE) methods.
- Patients in the crizotinib group reported improved global HRQoL and symptom severity scores from baseline (as measured using EORTC QLQ-C30 and EORTC QLQ-LC13) compared to the chemotherapy. Crizotinib significantly delayed time-to-deterioration in the symptoms of cough, dyspnoea and pain in chest (HR, 0.59; 95% CI, 0.45 to 0.77; P=0.001), as measured using EORTC QLQ-LC13.

Clinical effectiveness of crizotinib observed in PROFILE 1014 is supported by real-world evidence and non-randomised trial data

- The clinical effectiveness of crizotinib in the first-line setting is supported by evidence from PROFILE 1001 and a retrospective medical chart review (Davis *et al.* 2015).
- Davis *et al.* (2015) reported survival and response rates for patients receiving first-line crizotinib in a real-world setting that were similar to PROFILE 1014 (median PFS: 9.6

4.1 Identification and selection of relevant studies

4.1.1 Advise whether a search strategy was developed to identify relevant studies for the technology. If a search strategy was developed and a literature search carried out, provide details under the subheadings listed in this section. Key aspects of study selection can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

Two systematic reviews were carried out to identify clinical data from the literature in a population with advanced/metastatic ALK-positive NSCLC. The reviews aimed to identify:

1. RCT evidence on the efficacy and safety of crizotinib in the treatment of advanced/metastatic ALK-positive NSCLC

2. Non-RCT evidence on the efficacy and safety of crizotinib in the treatment of advanced/metastatic ALK-positive NSCLC

4.1.2 Describe the search strategies used to retrieve relevant clinical data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided so that the results may be reproduced. This includes a full list of all information sources and the full electronic search strategies for all databases, including any limits applied. The search strategies should be provided in an appendix.

The systematic review process adhered to the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting checklist to ensure transparency and a reproducible method of conducting and reporting data from systematic reviews.[100, 101]

The following electronic databases were searched on the 31st July (OVID) and 3rd August (Cochrane):

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (OVID)
- The Cochrane Library, incorporating;
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Health Technology Assessment Database (HTA)

A lower date limit of 2007 was applied to all searches on the basis that the first publication reporting the existence of the ALK translocation in NSCLC was published in this year; this is in-line with a previous systematic review conducted as a part of NICE TA296.[5] To retrieve further studies not identified through the electronic database search, reference lists of included articles

were scanned, and searches for grey literature as well as completed and on-going trials, were also carried out.

Full search strategies for the RCT and non-RCT reviews are provided in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively.

4.1.3 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process in a table. Justification should be provided to ensure that the rationale for study selection is transparent. A suggested table format is provided below.

The screening process (titles ± abstracts and full paper stages) for both RCT and non-RCT evidence involved two reviewers working independently. Any disagreements were resolved through the involvement of a third reviewer or through team discussion until a consensus was reached. The identified studies were initially assessed based on titles ± abstracts. Thereafter, full papers of the eligible studies were obtained and assessed further for inclusion/exclusion. The reasons for exclusion are documented in Appendix 2.

The eligibility criteria used for the RCT review is presented below in Table 11.

Table 11. Eligibility criteria used for randomised controlled trial review

Domain	Inclusion criteria	Exclusion criteria
Population	• Adult (≥18 years, both males and females) patients with ALK-positive NSCLC • Not treated previously with a pharmacological intervention	• Studies that do not include the patient population of interest, or that do not present relevant outcomes for the population of interest separately to outcomes for other patients
Intervention	• Crizotinib	• Interventions other than crizotinib
Comparator	• Chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin)	N/A
Outcomes	• Outcomes included, but were not limited to, the following: • Survival (analysed in terms of relative risks, odds ratios or hazard ratios) • Overall survival (OS) • Progression free survival (PFS) • Response rate (complete, partial, stable disease) • Time to progression (TTP) • Secondary outcomes: • Study medication related adverse events (safety and tolerability; all grades) • Health related quality of life	N/A

Domain	Inclusion criteria	Exclusion criteria
	(HRQoL) • Clinical benefit rate • Time to treatment discontinuation	
Study design	• Phase II, III and IV randomised controlled trials • Relevant systematic literature reviews • Pooled analyses • Meta-analyses	• Phase I clinical trials
Publication type	• Published • Unpublished • Grey literature • On-going trials	N/A
Other considerations	• Only publications in the English language will be included • Articles must have been published in 2007 or later • Human subjects only	• Non-English language publications • Articles published prior to 2007 • Articles not in human subjects

The eligibility criteria used for the non-RCT review is presented below in Table 12.

Table 12. Eligibility criteria used for non-randomised controlled trial review

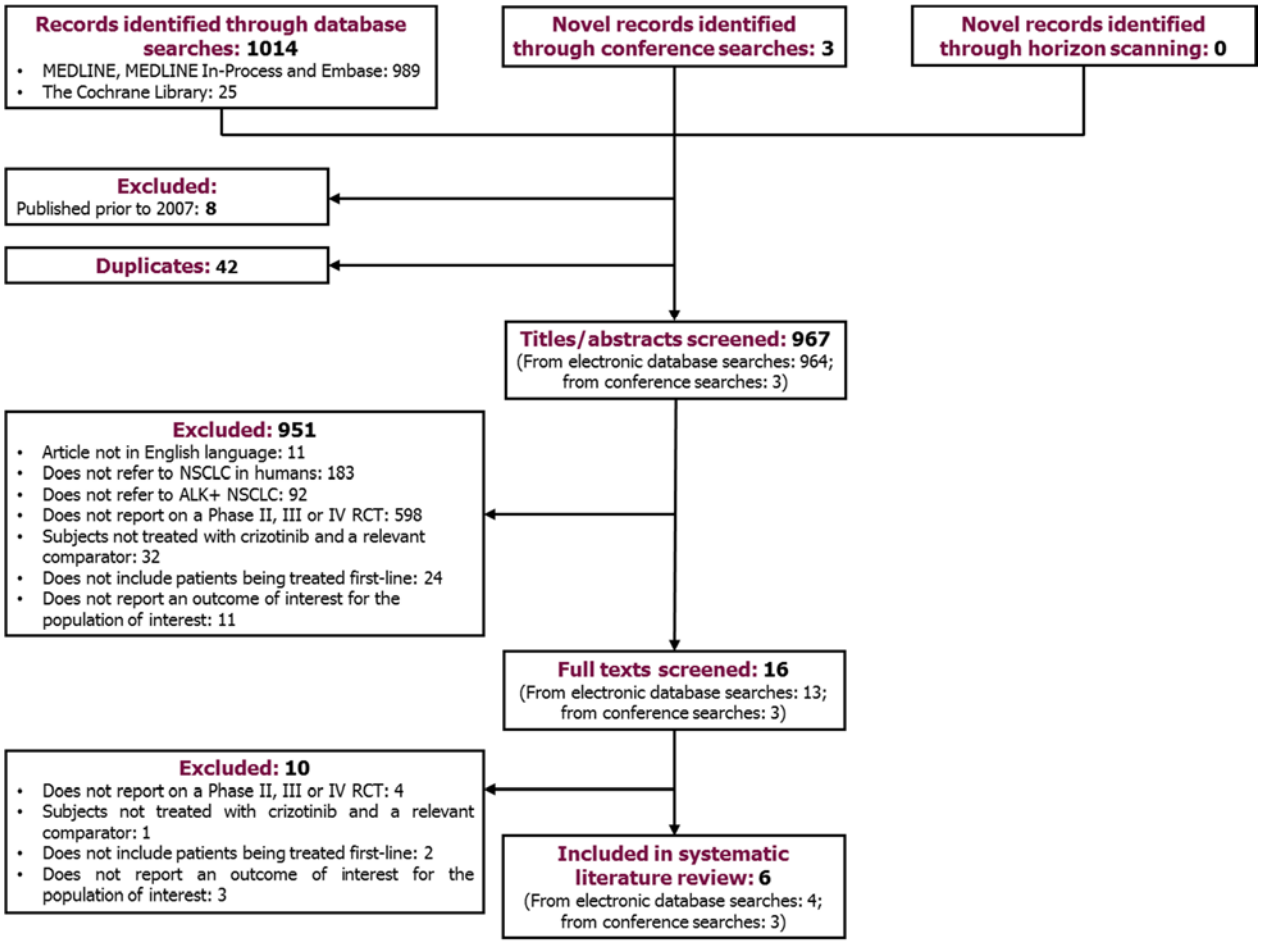
Domain	Inclusion criteria	Exclusion criteria
Population	• Adult (≥18 years, both males and females) patients with ALK-positive NSCLC • Not treated previously with a pharmacological intervention	• Studies that do not include the patient population of interest, or that do not present relevant outcomes for the population of interest separately to outcomes for other patients
Intervention	• Crizotinib	• Interventions other than crizotinib
Comparator	• Chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) • No comparator (single-arm studies)	N/A
Outcomes	• Outcomes included, but were not limited to, the following: • Survival (analysed in terms of relative risks, odds ratios or hazard ratios) • Overall survival (OS) • Progression free survival (PFS) • Response rate (complete, partial, stable disease) • Time to progression (TTP)	N/A

	• Secondary outcomes: • Study medication related adverse events (safety and tolerability; all grades) • Health related quality of life (HRQoL) • Clinical benefit rate • Time to treatment discontinuation	
Study design	• Non-RCTs • Observational studies • Retrospective analyses • Systematic reviews • Pooled analyses • Meta-analyses	• Case studies, case series, commentaries, editorials, letters and non-systematic reviews will be excluded.
Publication type	• Published • Unpublished • Grey literature • On-going trials	N/A
Other considerations	• Only publications in the English language will be included • Articles must have been published in 2007 or later • Human subjects only	• Non-English language publications • Articles published prior to 2007 • Articles not in human subjects

4.1.4 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses, such as the PRISMA flow diagram. The total number of studies in the statement should equal the total number of studies listed in section 4.2.

A PRISMA flow diagram of identified studies in the RCT systematic literature review is presented in Figure 5.

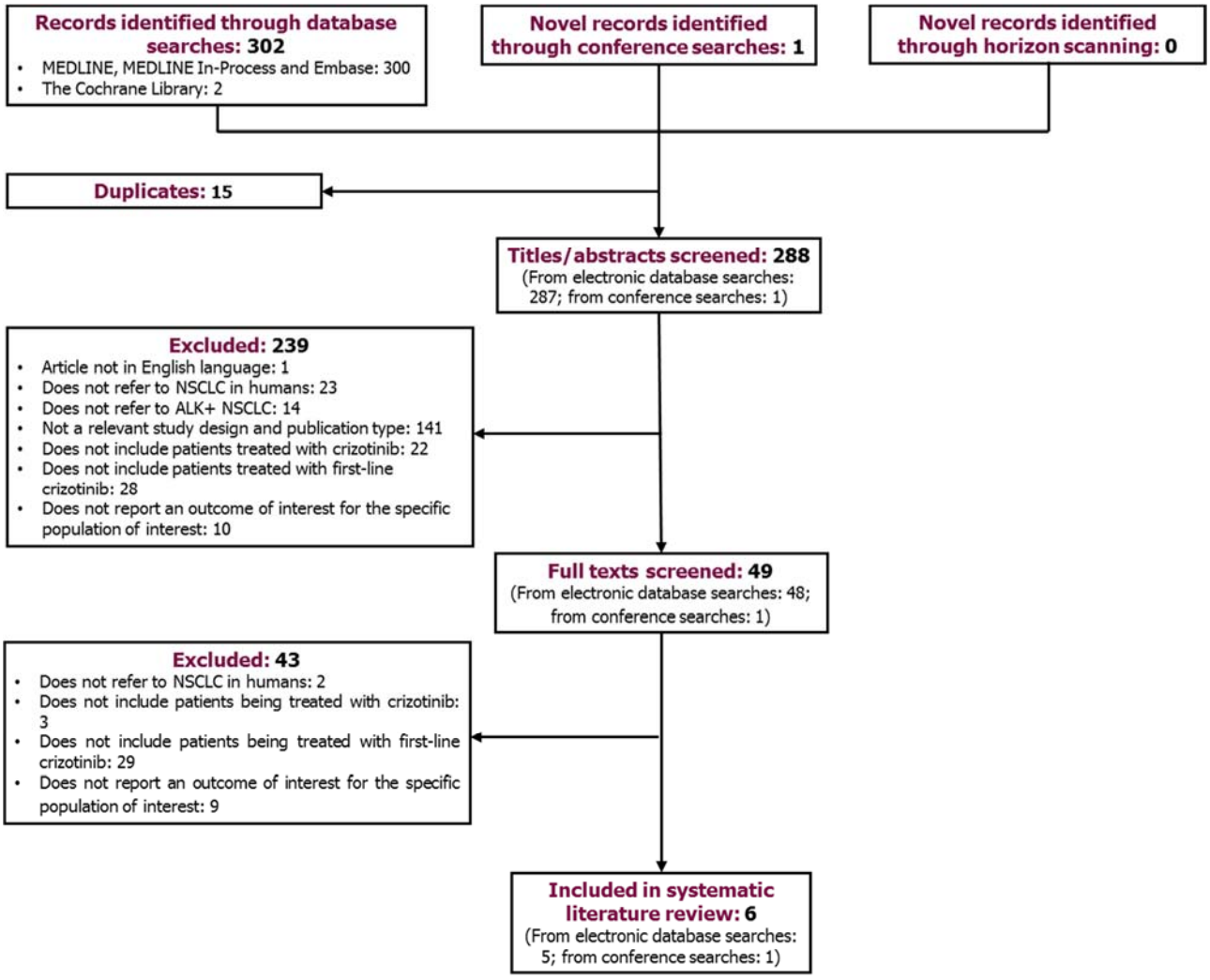
Figure 5: PRISMA flow diagram of included and excluded RCT studies



Database searches were conducted on the 31st July 2015 for MEDLINE, MEDLINE In-Process and Embase. The Cochrane Library was searched on the 3rd August 2015.

A PRISMA flow diagram of identified studies in the non-RCT systematic literature review is presented in Figure 6.

Figure 6: PRISMA flow diagram of included and excluded non-RCT studies



Database searches were conducted on the 31st July 2015 for MEDLINE, MEDLINE In-Process and Embase. The Cochrane Library was searched on the 3rd August 2015.

Studies relevant to this submission identified by the RCT and non-RCT reviews are discussed in Section 4.2 and Section 4.11.1, respectively.

4.1.5 When data from a single study have been drawn from more than 1 source (for example, a poster and a published report) or when trials are linked (for example, an open-label extension to a randomised controlled trial [RCT]), this should be clearly stated.

One full publication and five abstract publications were identified in the review and are summarised in Table 13 alongside the sources from which information presented in this submission has been derived. All publications identified in the review related to the pivotal phase III study PROFILE 1014; as such, the published peer-reviewed journal article (Solomon *et al.* [2014a]), that presents the most recent analysis has been used as the primary source in this submission.[2]

PROFILE 1014 was used as the main source of clinical evidence for the regulatory approval of first-line crizotinib in Europe and is described in the EPAR produced by the EMA.[8]

Table 13: Summary of sources of clinical evidence for relevant RCTs of crizotinib

Study name	Primary source	Secondary source(s)
NCT01154140 (PROFILE 1014)	Solomon *et al.* (2014a) [2]*	• PROFILE 1014 Study Protocol and Statistical Analysis Plan [102] • PROFILE 1014 Clinical Study Report (16th June 2015) [3] • Blackhall *et al.* (2014) [103] • Mok *et al.* (2014) [104] • Nakagawa *et al.* (2015) [105] • Solomon *et al.* (2014b) [106] • Solomon *et al.* (2015) [107]

* Including supplementary material and erratum.[108, 109]

Unless specified otherwise, information presented in this submission for PROFILE 1014 has been derived from Solomon *et al.* (2014a).[2]

4.1.6 Provide a complete reference list for excluded studies in an appendix.

The list of excluded studies from both systematic reviews (RCTs and non-RCTs) is presented in **Error! Reference source not found.**, alongside the rationale for excluding each study.

4.2 List of relevant randomised controlled trials

4.2.1 In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, state this.

The clinical SLR identified one phase III RCT (PROFILE 1014; NCT01154140) that investigated the use of crizotinib as a first-line treatment for adults with ALK-positive, advanced NSCLC.

A summary of PROFILE 1014 is provided in Table 14. In brief, adult patients with ALK-positive, non-squamous, advanced NSCLC who had not previously received treatment for advanced disease were randomised (1:1) to receive either crizotinib (250 mg twice-daily until disease progression) or chemotherapy (every 3 weeks for a maximum 6 cycles). The chemotherapy control group consisted of patients receiving pemetrexed plus either cisplatin or carboplatin, the choice of which was at the discretion of the investigator.

Table 14: List of relevant randomised controlled trials

Trial number (acronym)	NCT01154140 (PROFILE 1014)
Population	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	Crizotinib group: Crizotinib, 250 mg twice-daily, oral
Comparator	Chemotherapy group: 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.
Primary study reference	Solomon *et al.* (2014a) [2]

Abbreviations: ALK: anaplastic lymphoma kinase; AUC: area under the concentration-time curve; BSA: body surface area; i.v., intravenous; NSCLC: non-small-cell lung cancer.

4.2.2 When the RCTs listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when RCTs have been identified, but there is no access to the level of data required, this should be stated.

No RCTs investigating crizotinib identified by the SLR have been excluded from further discussion. Data from PROFILE 1014 is presented in full in the following sections.

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Items 3 to 6b of the CONSORT checklist should be provided for all RCTs listed.

PROFILE 1014 (NCT01154140) is an ongoing, 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. PROFILE 1014 is the first phase III trial investigating the use of crizotinib as a first-line therapy in ALK-positive, advanced NSCLC. A summary of PROFILE 1014 methodology and trial design is presented in Table 15. Items 3 to 6b of the CONSORT checklist are provided within this table.

Table 15: Summary of PROFILE 1014 methodology

Trial number (acronym)	NCT01154140 (PROFILE 1014)
Location	International: 244 locations across USA, Canada, Australia, Asia, Europe, South America and South Africa.[110] Eight study sites were located in the UK.[110]
Trial design	Multicentre, open-label, phase III randomised controlled trial **Stopping guidelines:** treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects, death or withdrawal of consent. **Crossover:** patients in the chemotherapy group who had disease progression defined using the Response Evaluation Criteria In Solid Tumours (RECIST) version 1,1, as verified by IRR, could crossover to crizotinib treatment if the safety screening criteria, as detailed in the study protocol, were met.[102] Patients in the crizotinib group who had disease progression were offered other available treatment, including platinum-based chemotherapy. **Treatment beyond progression:** continuation of crizotinib beyond disease progression was allowed for patients who were assigned to the crizotinib group at randomisation if the patient was perceived by the investigator to be experiencing clinical benefit.
Method of randomisation	Patients were randomised in a ratio of 1:1 to the crizotinib and chemotherapy treatment groups, respectively, based on a random permuted block design using a centralised Interactive Voice Response System (IVRS)/website.[102] Randomisation was stratified by ECOG performance status (0 or 1 vs. 2), race (Asian vs. non-Asian) and brain metastases (presence vs. absence).
Eligibility criteria for participants	**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 version 1.1 • ECOG performance status 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 • Written informed consent provided A full list of inclusion and exclusion criterion is presented below in Table 16.
Settings and locations where the data were collected	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).[102] Self-administered questionnaires to obtain patient-reported outcomes were completed on-site prior to testing, treatment, or discussion with the physician

	or site personnel. Patients also completed the EORTC QLQ-C30 and QLQ-LC13 on Day 7 of Cycle 1 at home, and were under instruction not to complete the assessments with help from friends or family.[102]
Trial drugs and method of administration	**Crizotinib group (n=172):** Crizotinib 250 mg twice-daily (at the same times each day), oral Continuation of crizotinib beyond disease progression was allowed for patients who were assigned to the crizotinib group at randomisation if the patient was perceived by the investigator to be experiencing clinical benefit. **Chemotherapy group (n=171):** Pemetrexed, 500 mg/m^2 BSA; plus either cisplatin, 75 mg/m^2 BSA, or carboplatin, target AUC of 5–6 mg/mL/min; administered intravenously every 3 weeks for a maximum of 6 cycles. The choice of cisplatin vs. carboplatin was made by the investigator. Of those patients who received at least one dose of study treatment, 91 patients received pemetrexed-cisplatin and 78 patients received pemetrexed-carboplatin; 2 patients did not receive study treatment. • Pemetrexed was administered on the first day of each 21-day cycle by i.v. infusion over 10 minutes or according to institutional administration timing. • Cisplatin or carboplatin was administered by i.v. infusion according to institutional practices, approximately 30 mins after the end of the pemetrexed infusion on the first day of each 21-day cycle. *In the PROFILE 1014 trial, one cycle was defined as being 21 days in length.*
Permitted and disallowed concomitant medication	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}.[102] **Permitted concomitant medication[102]** • 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 progressive disease (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[102]** • 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, and/or anti-arrhythmics were to be avoided in patients receiving crizotinib

	Concomitant radiotherapy and surgery [102] • 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	**Progression-free survival (PFS)** – defined as the time from randomisation to RECIST (version 1.1)-defined progression (as assessed by IRR) or death. 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.
Secondary and other outcomes	Secondary outcomes based on tumour assessments, included: • Objective response rate (ORR) and best overall response (BOR) • Time to tumour response (TTR) • Duration of response (DR) • Disease control rate (DCR) at Week 12 • Time to progression (TTP)* • Intracranial time to progression (IC-TTP)* • Extracranial time to progression (EC-TTP)* Additional secondary outcomes included: • Overall survival (OS) – including one-year and 18-months survival probabilities • Safety – including type, incidence, severity, seriousness and relationship to study medications of adverse events and any laboratory abnormalities • Patient-reported outcomes (PROs): o EORTC QLQ-C30 o EORTC QLQ-LC13 o Time to deterioration (TTD) in either cough, dyspnoea and pain in chest symptoms, as assessed using EORTC QLQ-LC13 o EQ-5D Patients completed self-administered questionnaires on Day 1 of each 3-week cycle until the end of treatment/study withdrawal. The EORTC QLQ-C30 and –LC13 were also administered on Day 7 and 15 of Cycle 1. Full details of the outcomes reported in PROFILE 1014 are presented separately in Table 17.
Pre-planned subgroups	• PFS by stratification factors/baseline characteristics • IC-TTP and EC-TTP by treatment group and baseline brain metastases
Duration of study and follow-up	Between January 2011 and July 2013, a total of 343 patients had been randomly assigned to treatment groups. The pre-specified primary endpoint (229 events of progression or death) was reached in November 2013. At the time of the data cut-off date (30th November 2013) for the primary analysis, the median follow-up for overall

	survival was 17.4 months in the crizotinib group and 16.7 months for those assigned to chemotherapy. All data presented from PROFILE 1014 in this submission correspond to the data cut-off date of 30th November 2013.

* Results for these secondary outcomes are presented in **Error! Reference source not found.**.

Abbreviations: ALK: anaplastic lymphoma kinase; AUC: area under the concentration-time curve; BOR: best overall response; BSA: body surface area; DR: duration of response; EC: extracranial; ECOG: Eastern Co-operative Oncology Group; 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: EuroQoL-5 Dimensions; IVRS: Interactive Voice Response System; FISH: fluorescence *in situ* hybridisation; IC: intracranial; IRR: independent radiologic review; *i.v.*, intravenous; NSAIDs: non-steroidal anti-inflammatory drugs; NSCLC: non-small-cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progressive-free survival; PRO: patient reported outcome; RECIST: Response Evaluation Criteria In Solid Tumours; TTD: time to deterioration; TTP: time to progression; TTR: time to response; UK: United Kingdom; USA: United States of America.
Source: Solomon *et al.* (2014a) [2] – unless otherwise stated

Eligibility criteria for PROFILE 1014

Patients were considered for enrolment if they had histologically or cytologically confirmed locally advanced or metastatic non-squamous NSCLC that was positive for an ALK translocation and had received no previous systemic treatment for advanced disease. ALK-status of patient tumours was determined prior to randomisation using the Vysis Break Apart FISH Probe Kit (Abbott Molecular).

The full eligibility criteria for PROFILE 1014 are presented in Table 16.

Table 16: Eligibility criteria for PROFILE 1014

Inclusion criteria	Exclusion criteria
1. Histologically or cytologically proven diagnosis of locally advanced, not suitable for local treatment, recurrent, or metastatic non-squamous NSCLC. 2. Positive for translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as determined by an ALK break-apart FISH test and defined by an increase in the distance between 5' and 3' ALK probes or the loss of the 5' probe. 3. No prior systemic treatment for locally advanced or metastatic disease (exception below): o Prior adjuvant chemotherapy for Stage I-III or combined modality chemotherapy radiation for locally advanced disease allowed if completed >12 months prior to documented PD. 4. Patients with brain metastases were only eligible if treated and neurologically stable with no ongoing requirement for corticosteroids, e.g. dexamethasone, for at least 2 weeks and were not taking medications contraindicated in Exclusion Criteria 12-14. 5. Any major surgeries must have been completed at least 4 weeks prior to initiation of study treatment. Any prior radiation (except palliative) or minor surgeries/procedures must have been completed at least 2 weeks prior to the initiation of study treatment. 6. Palliative radiation (≤10 fractions) must have been completed 48 hours prior to crizotinib therapy commencing. Any acute toxicity must have	1. Current treatment on another therapeutic clinical study. 2. Prior therapy directly targeting ALK. 3. Carcinomatous meningitis or leptomeningeal disease. 4. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function. 5. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, or cerebrovascular accident including transient ischemic attack. Appropriate treatment with anticoagulants was permitted. 6. Ongoing congestive heart failure. 7. Ongoing cardiac dysrhythmias of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.0) Grade ≥2, uncontrolled atrial fibrillation of any grade, or machine-read ECG with corrected QT interval (QTc) >470 msec. The concomitant use of medicinal products known to prolong QTc was not advised and these were to be avoided. 8. Peripheral neuropathy with Grade ≥1 (CTCAE Version 4.0). 9. History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis,

recovered to Grade 1 or less (except alopecia). 7. Tumours must have had measurable disease as per RECIST (Version 1.1). 8. Female or male, 18 years of age or older (for patients enrolled in Japan: consent from a legally acceptable representative was required for all patients who were under 20 years old; for patients enrolled in India, the upper age limit was 65 years old). 9. ECOG performance status of 0–2. 10. Adequate organ function as defined by the following criteria: Hepatic function: o Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities were due to underlying malignancy. Patients enrolled in France with ALT ≥3 and ≤5 x ULN must not have had evidence of advanced fibrosis as detected by FibroTest >0.48. o Total serum bilirubin ≤1.5 x ULN. Bone marrow function: o Absolute neutrophil count (ANC) ≥1500/μL. o Platelets ≥100,000/μL. o Haemoglobin ≥9.0 g/dL. Renal function: o Creatinine clearance (based on modified Cockcroft-Gault formula) ≥60 mL/min. 11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) had been informed of all pertinent aspects of the study prior to enrolment. 12. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures including completion of PRO measures.	but not history of prior radiation pneumonitis. 10. Previous treatment with crizotinib. 11. Pregnancy or breastfeeding. 12. Use of drugs or foods that are known potent cytochrome P450 (CYP)3A4 inhibitors within 7 days prior to the first dose of crizotinib, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconzole, and grapefruit or grapefruit juice. 13. Use of amprenavir, delavirdine, diltiazem, erythromycin, miconazole, and verapamil was also excluded prior to a protocol amendment (Protocol Amendment 5). The topical use of these medications (if applicable), such as 2% ketoconazole cream, could be allowed. 14. Use of drugs that are known potent CYP3A4 inducers within 12 days prior to the first dose of crizotinib, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort. Use of rifapentine, tipranavir, and ritonavir was also excluded prior to Protocol Amendment 5. 15. Concomitant use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine (after Protocol Amendment 5), ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from United States market). Use of aripiprazole, halofantrine, and triazolam was also excluded prior to Protocol Amendment 5. 16. Prior malignancy (other than current NSCLC): patients were not eligible if they had evidence of active malignancy (other than non-melanoma skin cancer or in situ cervical cancer, or localized and presumed cured prostate cancer) within the last 3 years. 17. Known human immunodeficiency virus infection. 18. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhoea or ulcer) or psychiatric conditions, or end-stage renal disease on haemodialysis, or laboratory abnormalities that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study treatment

13. Male and female patients of childbearing potential must have agreed to use a highly-effective method of contraception throughout the study and for 90 days after the last dose of assigned treatment. Male patients randomized to the chemotherapy arm had to use a highly-effective method of contraception for a total of 180 days after last dose of chemotherapy. A patient was considered of childbearing potential if, in the opinion of the investigator, he/she was biologically capable of having children and was sexually active.	administration, and which would, therefore, make the patient inappropriate for entry into this study.

Abbreviations: ALK: anaplastic lymphoma kinase; ALT: alanine transaminase; ANC: absolute neutrophil count; AST: aspartate transaminase; CTCAE: Common Terminology Criteria for Adverse Events; CYP: cytochrome P450; ECOG: Eastern Co-operative Oncology Group; EML4: echinoderm microtubule associated protein-like 4; FISH: fluorescence in situ hybridisation; NCI: National Cancer Institute; NSCLC: non-small-cell lung cancer; PD: progressive disease; PRO: patient-reported outcome; QTc: QT interval; RECIST: Response Evaluation Criteria in Solid Tumours; ULN: upper limit of normal.
Source: Pfizer Clinical Study Report (16th June 2015) [3]

Description of outcomes reported in PROFILE 1014

The definitions and methods of assessment of the primary and secondary outcomes reported in PROFILE 1014 are provided in Table 17.

- PFS was the primary outcome of PROFILE 1014. Prolonged PFS is considered to be of considerable benefit to patients, with disease progression having been shown to be associated with worsening HRQoL.[111] PFS is an accepted primary endpoint for RCTs according to EMA guideline on the evaluation of anticancer medicinal products in humans.[112]
- OS was a secondary outcome of PROFILE 1014. 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 3.4, patients with ALK-positive, advanced NSCLC are expected to have a life expectancy of less than 24-months with current standard of care.

Table 17: Description of outcomes reported in PROFILE 1014

Outcome	Description
Primary outcome	
Progression-free survival (PFS)	The time from randomisation to RECIST (version 1.1)-defined progression, as assessed by IRR, or death, whichever occurred first. The analysis of PFS, including censoring of data, is described fully in Table 19.
Secondary efficacy outcomes	
Objective response rate (ORR)	The percentage of patients with complete response (CR) or partial response (PR) according to RECIST (version 1.1), as determined via IRR, relative to the ITT population.[102]
Best overall response (BOR)	The best response (CR, PR, stable disease [SD], progressive disease [PD]) achieved by each patient whilst on study treatment.[102] The best response of SD can be assigned if SD criteria were met at least once after randomization at a minimum interval of 6 weeks
Time to response (TTR)	The time from randomisation to the first documentation of objective tumour response (PR or CR), as determined by IRR.
Duration of response (DR)	The time from the first documentation of objective tumour response (PR or CR), as determined by IRR, to the first documentation of RECIST-defined progression or death, with the use of the Kaplan-Meier method.
Disease control rate (DCR)	The proportion of patients with CR, PR or SD according to RECIST (version 1.1), as determined by IRR, relative to the ITT population.[102] The best response of SD was assigned if SD criteria were met at least once after randomization at a minimum interval of 6 weeks
Time to progression (TTP)	The time from randomisation to first documentation of objective tumour progression, as determined by IRR.[102] Intracranial progression included either new brain metastases or progression of existing brain metastases Extracranial progression included new lesions or progression of

	existing extracranial lesions.
Overall survival (OS)	The time from randomisation to the date of death due to any cause. For patients who were lost to follow-up/withdrew consent, the OS was censored on the last date that patients were known to be alive.[102] The probability of survival at 1-year and 18-months after the date of randomisation were based on Kaplan-Meier estimates.[102] Duration of follow-up: After discontinuation of study treatment and/or confirmed progressive disease, post-study survival status was collected every 2 months until death or until 18 months after the randomization of the last patient.[102]
Patient reported outcomes (PROs)*	
EORTC QLQ-C30	The EORTC QLQ-C30 questionnaire consists of 30 questions that assess 5 functional domains (physical, role, cognitive, emotional and social); global health status/QoL; and the burden of symptoms, including fatigue, nausea and vomiting, and pain.[113, 114] For global HRQoL and functioning domains, a higher score represents better HRQoL; positive changes from baseline are therefore indicative of an improvement in these domains. For symptoms, a higher score represents greater severity in symptoms; negative changes from baseline are therefore indicative of a reduction in symptoms
EORTC QLQ LC-13	The EORTC QLQ-LC13 is a lung cancer-specific module that assesses symptoms (dyspnoea, cough, haemoptysis, and site-specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of patients with lung cancer receiving chemotherapy.[115]
Time to deterioration (TTD) in symptoms	TTD in either cough, dyspnoea and pain in chest symptoms, (as assessed using EORTC QLQ-LC13) was analysed as a composite endpoint and defined as the time from randomisation to the earliest date that the patient's scores showed a 10-point or greater increase after baseline, in any of the three symptoms.[102] Patients were censored at the last assessment where they completed the respective EORTC QLQ-LC13 items relating to the three symptoms if they had not experienced 'deterioration' as defined above. Patients who crossed over or ended randomised study treatment were also censored at the time of the last assessment prior to crossover
EQ-5D	The EQ-5D questionnaire consists of the EQ-5D descriptive system and a visual analogue scale (the EQ-VAS). The EQ-5D descriptive system measures a patient's health state on 5 dimensions which include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondent's self-rated health is assessed on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) by the EQ-VAS.[116] A health utility index was calculated from questionnaire responses using the standard algorithm provided in the instrument manual.[117] The EQ-5D index is the preferred measure of health utility by NICE for use in economic evaluations, as indicated in the reference case.[118]

Safety	
Safety	Included the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory parameters.[102] AEs were classified and graded according to the Common Terminology Criteria for AEs (CTCAE) Version 4.0 Only events that occurred during the period from the first dose of study treatment until 28 days after the last dose of study treatment, and that occurred before crossover to crizotinib from the chemotherapy group, 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, or until all serious or study treatment-related toxicities had resolved or were determined to be "chronic" or "stable", whichever was later.[102]

* A change from baseline of ≥10-points for PROs was considered to be clinically meaningful.[3, 119]

Abbreviations: AEs: adverse events; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DR: duration of response; 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: EuroQoL-5 Dimensions; IRR: independent radiologic review; ORR: objective response rate; NICE: National Institute for Health and Care Excellence; OS: overall survival; PD: progressive disease; PFS: progressive-free survival; PR: partial response; PRO: patient reported outcome; RECIST: Response Evaluation Criteria In Solid Tumours; TTD: time to deterioration; SD: stable disease; TTP: time to progression; TTR: time to response; VAS: visual analogue scale.
Source: Solomon *et al.* (2014a) [2] – unless otherwise stated

4.3.2 Provide a comparative summary of the methodology of the RCTs in a table. A suggested table format is presented below.

Not applicable as only one RCT (PROFILE 1014) was identified. A summary of PROFILE 1014 methodology is presented in Table 15.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 During completion of this section consider items 7a (sample size), 7b (interim analyses and stopping guidelines), 12a (statistical methods used to compare groups for primary and secondary outcomes) and 12b (methods for additional analyses, such as subgroup analyses and adjusted analyses) of the CONSORT.

A total of 343 patients were enrolled in the study and were randomised (1:1) to the crizotinib and chemotherapy treatment groups. The trial populations used in the analysis of outcomes are presented in Table 18.

Table 18: Trial populations used PROFILE 1014 for the analysis of outcomes

Analysis	Trial population
Primary analysis **(and secondary efficacy analyses)**	Intention-to-treat (ITT) population – included all patients who were randomised to study treatment at the initial randomisation. The ITT population was used for the primary analysis PFS and was also the primary population for evaluating secondary efficacy outcomes.[102] • Crizotinib group (n=172) • Chemotherapy group (n=171)
Safety analyses	As-treated (AT) population – included all patients who received at least one dose of study treatment assigned to them at the initial randomisation.[102] Safety analyses were conducted in the AT population. • Crizotinib group (n=171) • Chemotherapy group (n=169)
Analysis of PROs	PRO evaluable population* The PRO evaluable population included all patients from the ITT population who had also completed a baseline PRO assessment and at least one post-baseline PRO assessment prior to crossover or end of randomised study treatment.

* Completion rates by treatment group for each PRO instrument is presented alongside results in Section 4.7.2.

Abbreviations: AT: as treated; ITT: intention-to-treat; PRO: patient reported outcome.
Source: Solomon *et al.* (2014a) [2] – unless otherwise stated

Sample size

Please refer to Table 19 for details of the sample size calculation.

Interim analyses and patient stopping guidelines

As part of PROFILE 1014, an interim analysis for futility and sample size re-estimation was planned after 103 (45%) of target PFS events had been documented by IRR. Based on a review of the interim analysis, conducted after 110 PFS events had occurred, the independent third-party Data Monitoring Committee recommended that the study continue as is, without adjusting the sample size.[3]

In PROFILE 1014, treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects, death or withdrawal of consent.

Statistical methods for between group comparisons

Two-sided log-rank tests stratified according to baseline stratification factors were used for between-group comparisons of PFS and OS; stratified Cox regression models were applied to estimate hazard ratios. A two-sided stratified Cochran-Mantel-Haenszel test was used to compare the ORR between treatment groups.[2] All analyses in the chemotherapy group, with the exception of OS, included only data collected before crossover to crizotinib. OS was also analysed using methods to adjust for crossover, as described in a dedicated section below.

A step-down procedure was applied to the efficacy endpoints in the following order: PFS, ORR and OS. No other adjustments were planned for multiple testing.[108]

For PROs, repeated-measures mixed-effects modeling was performed to compare the two treatment groups with respect to the overall change from baseline scores on the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D scales, using two-sided tests that were not adjusted for multiple testing. The comparison within-treatment group differences (i.e. the change from baseline scores) utilised a two-sided paired t-test. The Kaplan–Meier method was used to estimate the time to deterioration in a composite endpoint of chest pain, dyspnea, or cough and was compared between the two treatment groups using a two-sided unstratified log-rank test.[108]

Methods for additional analyses: subgroup analyses

All subgroup analyses were pre-specified in the Statistical Analysis Plan (see Table 15). For PFS, amongst the subgroup analyses performed there was a probability of false-positive findings of 64%; and for ORR, a probability of false-positive findings of 40%. The Kaplan–Meier method was used to estimate time-to-event endpoints for subgroup analyses. Unstratified log-rank tests were used to compare PFS between the treatment groups and Cox regression models were applied to estimate hazard ratios.[108]

Methods for additional analyses: crossover-adjusted analyses for overall survival

In PROFILE 1014, OS was a secondary outcome and hence the trial was not powered to detect differences in OS.

At the time of data cut-off (30th November 2013), the median OS was not reached in either treatment group in the PROFILE 1014 trial; only 90/343 patients (26%) who were randomised to study treatment had died.[2] Furthermore, estimates of OS were believed to be confounded by the high proportion of patients (120/171 patients [70%]) randomly assigned to the chemotherapy group who subsequently crossed over to receive treatment with crizotinib (see Section 4.5.1).[2]

In anticipation that OS estimates would be confounded as a result of crossover, the Rank Preserving Structural Failure Time (RPSFT) methodology was pre-specified in the clinical trial protocol to study the impact of crossover on the OS results.[2] Further statistical methods to assess the impact of crossover on OS were also explored post-hoc in line with recommendations in Technical Support Document 16 from the NICE Decision Support Unit (DSU), and as requested by the EMA.[120, 121]

A prospective feasibility assessment of the most suitable methods in addition to the RPSFT (which was already conducted as part of the pre-specified trial protocol) was conducted. Given the available PROFILE 1014 patient level data, the two-stage model was concluded to be the most robust technique to employ. The IPE was also considered suitable. *[Academic / commercial in confidence information removed]* it was appropriate not to conduct analyses using the IPCW method; the design of the trial and available data resulted in it being unlikely that the key assumptions of the method would be satisfied (see **Error! Reference source not found.** for further details) and the results would not be robust. The two-stage and IPE methods were performed and submitted as the EMA agreed these were the most appropriate methods in addition to the RPSFT given the data. Considering this, the economic model explores both the RPSFT and the two-stage results and their implications for the cost-effectiveness of crizotinib (Section 5.8.3).

Results of these crossover-adjusted analyses are presented alongside unadjusted OS data in Section 4.7.2. A detailed description of each of the methods and key assumptions in relation to

the PROFILE 1014 trial are provided in **Error! Reference source not found.**. In summary nine crossover adjustments were performed with a view to exploring the consistency of the range across models:

1. RPSFT method using log-rank test
2. RPSFT method using Wilcoxon test
3. Two-stage method 'A' (TSA), covariate adjusted where missing Eastern Co-operative Oncology Group performance status (ECOG PS) data was imputed as the values from the closest time point
4. Two-stage method 'B' (TSB), covariate adjusted where missing ECOG PS data was imputed as >=2 ("worse case")
5. Two-stage method 'C' (TSC), unadjusted for covariates
6. IPE using Weibull parametric model
7. IPE using log-normal parametric model
8. IPE using log-logistic parametric model
9. IPE using exponential parametric model

4.4.2 For each trial listed, provide details of the trial population included in the primary analysis of the primary outcome and methods used to take account of missing data (for example, a description of the intention-to-treat analysis carried out, including censoring methods, or whether a per-protocol analysis was carried out).

An intention-to-treat (ITT) population was used in the primary analysis of PFS, as described in Table 18. As a time-to-event endpoint, PFS was assessed using the Kaplan-Meier method. Full details of the methods used with regards to the censoring of data are presented in Table 19.

4.4.3 For each trial, provide details of the statistical tests used in the primary analysis. Also provide details of the primary hypothesis or hypotheses under consideration, the power of the trial and a description of sample size calculation, including rationale and assumptions in a table. If the outcomes were adjusted for covariates, provide the rationale. A suggested table format is presented below.

The primary endpoint in PROFILE 1014 was PFS. A summary of the statistical tests used in the primary analysis of PROFILE 1014 is presented in Table 19 alongside sample size calculations and methods for handling missing data.

The pre-specified number of events (disease progression or death) for the PFS primary endpoint was reached in November 2013; the data cut-off date was 30th November 2013. All analyses and data summaries included all data pertaining to visits or assessments performed up to and including this data cut-off date.

Table 19: Statistical tests for the primary analysis of PROFILE 1014

Trial number (acronym)	NCT01154140 (PROFILE 1014)
Hypothesis objective	The primary endpoint was PFS. Null hypothesis (H_0): λ=0 There was no difference between crizotinib and chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in prolonging PFS. Alternative hypothesis (H_A): λ<1 Crizotinib was superior to chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in prolonging PFS. Where λ is the hazard ratio for PFS or death, whichever comes first, with crizotinib versus chemotherapy.
Statistical analysis	PFS was analysed in the ITT population using the Kaplan-Meier method. Two-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.
Sample size, power calculation	It was estimated that with 229 events of progression or death, the study would have 85% power to detect a clinically meaningful improvement in PFS of 50% with crizotinib versus chemotherapy (from 6 months with chemotherapy to 9 months with crizotinib), using a 1-sided log-rank test at a significance level of 0.025. This sample size calculation was based on an assumed median PFS of 6 months with chemotherapy and was derived from observed results for paclitaxel-carboplatin, pemetrexed-cisplatin and gemcitabine-cisplatin of 4.5–6.1 months PFS in non-squamous unselected NSCLC and 6.6 months PFS with paclitaxel-carboplatin in EGFR mutation-positive NSCLC.[3, 33, 102, 123, 124] Assuming non-uniform accrual over approximately 25 months and follow-up of at least 8 months after the last patient was randomised, a total sample size of 294 patients was required. To account for events being censored, e.g. due to potential discordance between the investigators and IRR, approximately 40 extra patients were to be enrolled for a total sample size of 334 patients.[102]*
Data management, patient withdrawals	Patients could withdraw from the study at any time at their own request, or they could be withdrawn at any time at the discretion of the investigator or Sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.[102] For the analysis of PFS, data was censored on the date of the last evaluable tumour assessment documenting absence of progressive disease for patients who: Are alive, on study and progression free at the time of data cut-off, Have documentation of disease progression or death on study after ≥2 consecutive missed tumour assessments (i.e. >14 weeks after the last on-study assessment), Are given anti-tumour therapy other than the study treatment prior to documented disease progression or death on study (in this case, the last evaluable assessment prior to start of the anti-tumour treatment was used). Patients lacking an evaluation of tumour response after randomisation or for whom the first on-study assessment occurred after Week 14 were censored on the date of randomisation unless death occurred prior to Week 14.[102]

* The actual number of patients randomized (n=343) was higher than the planned total of 334 patients because all patients who signed an informed consent form at screening were allowed to be randomized to study treatment if they met the study entry criteria.

Abbreviations: EGFR: epidermal growth factor receptor; HR: hazard ratio; IRR: independent radiologic review; ITT: intention-to-treat; NSCLC: non-small-cell lung cancer; PFS: progression-free survival.
Source: Solomon *et al.* (2014a) [2] – unless otherwise stated

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Provide details of the numbers of participants who were eligible to enter the trials. Include the number of participants randomised and allocated to each treatment. Provide details of and the rationale for participants who crossed over treatment groups, were lost to follow-up or withdrew from the RCT. Provide a CONSORT diagram showing the flow of participants through each stage of each of the trials.

PROFILE 1014 patient flow and crossover

A total of 343 patients were randomised in the study— thus comprising the ITT population; 172 patients were randomised to the crizotinib group and 171 patients were randomised to the chemotherapy group. Three patients (one in the crizotinib group and two in the chemotherapy group) were randomised but did not receive treatment, and were thus excluded from the AT population, which included only those patients who received at least one dose of study treatment.[2]

Of those patients randomly assigned to chemotherapy, *[Academic / commercial in confidence information removed]* completed the maximum 6 cycles of chemotherapy.[3] Following randomisation to chemotherapy, 120/171 patients (70%) subsequently received crizotinib; the vast majority of patients (109/120, 91%) crossed over to crizotinib due to disease progression, the remaining 11/120 patients (9%) received crizotinib as follow-up treatment to chemotherapy.[3]

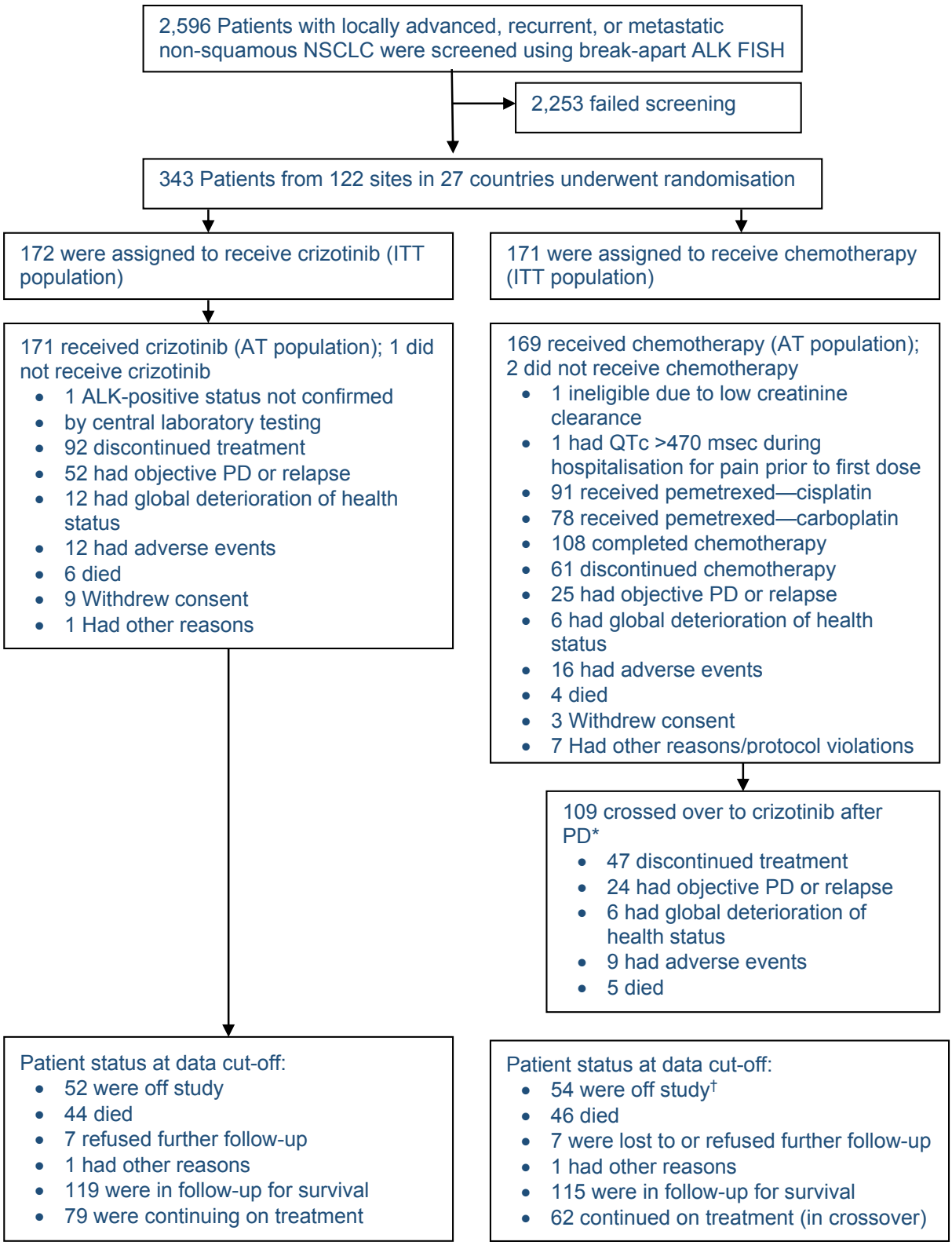
Amongst patients randomly assigned to crizotinib, 65/89 patients (73%) with progressive disease continued to receive crizotinib beyond disease progression for a median of 3.1 months (range, 0.7 to 22.6).[109] As noted in Section 4.3.1, the decision to continue crizotinib treatment beyond progression was at the discretion of the investigator and reflected a perception by the investigator that the patient was still experiencing clinical benefit. A total of 21/172 patients (12%) assigned to crizotinib subsequently received platinum-based therapy.[2]

At the data cut-off date (30th November 2013), *[Academic / commercial in confidence information removed]* were still ongoing in the study.[3] In total, 79/172 patients (46%) who had been randomly assigned to crizotinib and 62/171 patients (36%) in the chemotherapy group at randomisation who had crossed over to crizotinib were still receiving crizotinib at the data cut-off date.[2]

The median duration of follow-up for overall survival at the data cut-off date was 17.4 months for patients assigned to crizotinib and 16.7 months for those assigned to chemotherapy.[2] The death rate from any cause was relatively low at the data cut-off date; only 90/343 patients (26%) who underwent randomisation had died.[2]

Full details of patient flow, including reasons for discontinuation, are provided in Figure 7.

Figure 7: CONSORT diagram showing patient flow in PROFILE 1014



The 'intention-to-treat' (ITT) population included all patients who were randomised to a treatment
The 'as-treated' (AT) population included all patients who received at least one dose of study treatment
* For one patient in the crossover group, progressive disease (PD) was confirmed by the investigator but not by independent radiologic review.
† Off-study patients included some who had crossed over to crizotinib.
Source: Adapted from Solomon *et al.* (2014a) – Supplementary material: Figure S1 [108]

4.5.2 In a table describe the characteristics of the participants at baseline for each of the trials. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between trial groups. A suggested table format is presented below.

The baseline characteristics of patients randomly assigned to treatment in PROFILE 1014 are presented in Table 20. No significant differences between groups were observed in any of characteristics listed in the table.

Table 20: Baseline characteristics of patients in the ITT population in PROFILE 1014

Characteristic	Crizotinib (n=172)	Chemotherapy (n=171)
Age – years		
Median (range)	52 (22–76)	54 (19–78)
Male sex – no. (%)	68 (40)	63 (37)
Race – no. (%)*		
White	91 (53)	85 (50)
Asian	77 (45)	80 (47)
Other	4 (2)	6 (4)
Smoking status – no. (%)		
Never smoked	106 (62)	112 (65)
Former smoker	56 (33)	54 (32)
Current smoker	10 (6)	5 (3)
Histologic characteristic of tumour – no. (%)		
Adenocarcinoma	161 (94)	161 (94)
Nonadenocarcinoma	11 (6)	10 (6)
ECOG performance status – no. (%)†		
0 or 1	161 (94)	163 (95)
2	10 (6)	8 (5)
Extent of disease – no. (%)		
Locally advanced	4 (2)	3 (2)
Metastatic	168 (98)	168 (98)
Time since first diagnosis – months		
Median (range)	1.2 (0–114.0)	1.2 (0–93.6)
Brain metastases present – no. (%)	45 (26)	47 (27)

* Race was self-reported
† The Eastern Cooperative Oncology Group (ECOG) performance status was assessed at the time of screening: the score was not reported for one patient in the crizotinib group. Scores range from 0–5, with higher scores indicating increasing disability; an ECOG performance status of indicates that a patient is fully active, 1 that the patient is ambulatory but restricted in strenuous activity and 2 that the patients is ambulatory and capable of self-care but is unable to work.

Source: Adapted from Solomon *et al.* (2014a) – Table 1 [2]

4.6 Quality assessment of the relevant randomised controlled trials

4.6.1 The validity of the results of an individual RCT will depend on the robustness of its overall design and execution, and its relevance to the decision problem. The quality of each RCT identified in section 4.2 should be appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The quality assessment will be validated by the Evidence Review Group.

An appraisal of PROFILE 1014 was performed using the quality assessment tool based on the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care, as recommended by NICE.[100]The results of the quality assessment for PROFILE 1014 is presented in **Error! Reference source not found.** in **Error! Reference source not found.**.

In summary, PROFILE 1014 can be considered to be a high-quality and well-conducted RCT. However, bias may have been introduced in the trial due to its open-label design as blinding of patients and study investigators to study treatment was not feasible due the differences in routes of administration of the study drugs. To mitigate bias, the assessments of tumour response and disease progression were made by independent radiologic review and were blinded to treatment group.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Summary of PROFILE 1014 clinical effectiveness results

- The primary endpoint, PFS, was significantly prolonged in the crizotinib group compared to the chemotherapy group (median PFS 10.9 months vs. 7.0 months; HR, 0.45; 95% CI, 0.35 to 0.60; P<0.001).
    - The long tail observed in the crizotinib arm of the Kaplan-Meier plot for PFS additionally highlights the potential for crizotinib to delay progression or death for a considerable time for some patients.
    - The rate of PFS at 18-months was greater in the crizotinib group (31%; 95% CI, 23 to 39) compared to the chemotherapy group (5%; 95% CI, 2 to 10).
- Crizotinib was associated with greater ORR than chemotherapy (74% vs. 45%) and a greater median best percentage change in tumour size from baseline compared to chemotherapy *[Academic / commercial in confidence information removed]*.
- Median OS was not reached in either arm at the data cut-off date (30th November 2013); unadjusted HR for death with crizotinib was 0.821 (95% CI, 0.536 to 1.255); however, analyses of OS was confounded by high rates of crossover to crizotinib from the chemotherapy group (70%).
- Analyses that adjusted for crossover showed a highly consistent range of HR for death with crizotinib, from 0.571 to 0.674, across nine parametric models using three methods of analyses. The median value from this range was used as the base case, and this was an HR of 0.624 (0.405, 0.963, p=0.0158).

An overview of the key clinical effectiveness results reported in PROFILE 1014 is presented in Table 21. Primary and secondary efficacy outcomes by treatment group are discussed further in the subsequent sections.

Table 21: Overview of clinical effectiveness results in PROFILE 1014

Outcome		Crizotinib (n=172)	Chemotherapy (n=171)
Progression-free survival (PFS)*			
Median PFS, months (95% CI)		10.9 (8.3 to 13.9)	7.0 (6.8 to 8.2)
HR for progression or death with crizotinib (95% CI; P-value)		0.45 (0.35 to 0.60; P<0.001)	
Tumour response†			
ORR, % (95% CI)‡,§		74 (67 to 81)	45 (37 to 53)
Median best percentage change in target lesions from baseline, %§		*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Overall survival (OS)*			
Median OS, months		Not reached	Not reached
HR for death with crizotinib, (95% CI; P-value)	***Unadjusted***	0.821 (0.536 to 1.255; P=0.1804, 1-sided)	
	Crossover-adjusted, range using nine models ¶	0.571 to 0.674, across nine parametric models using three methods of analyses**.	

ITT population; data cut-off date: 30th November 2013
* 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
** the methods used to adjust for crossover were the Rank Preserving Structural Failure Time methodology, Iterative Parameter Estimation, and the Two-Stage approach.
† Tumour response was assessed using RECIST (version 1.1) and were confirmed by IRR
‡ P<0.001 for between-group comparison. The 95% CI were calculated with the use of the exact method based on the F distribution.
§ ORR and median best percentage change in target lesions from baseline represents a patient's best response
¶ Crossover-adjusted results from each model are presented in full in Table 23.

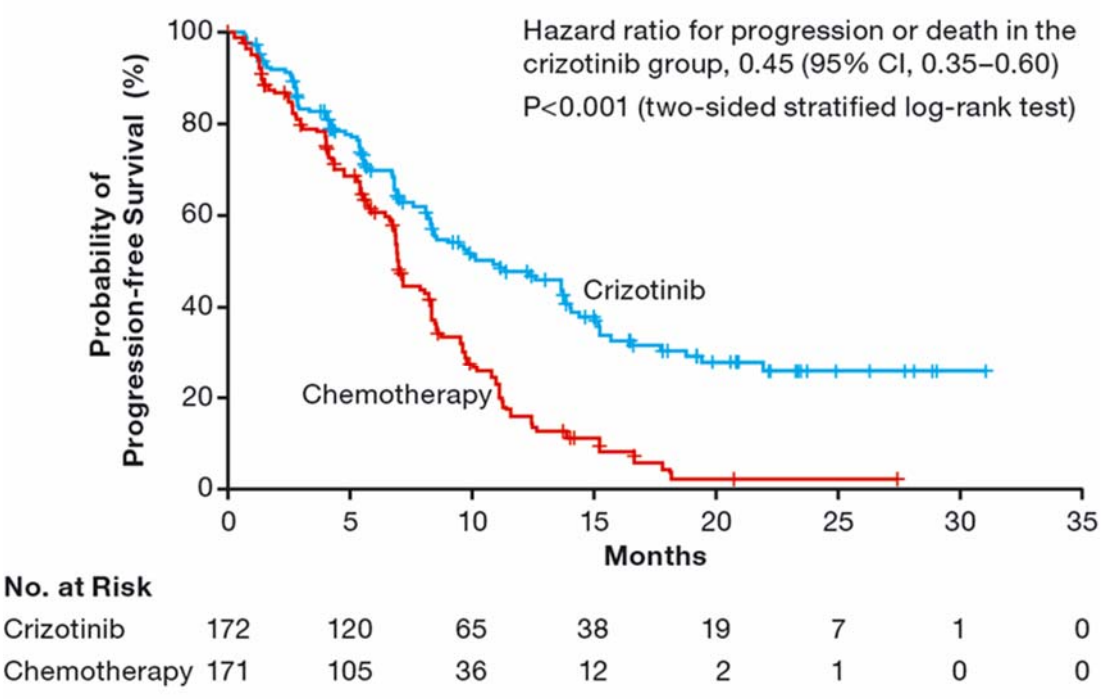
Abbreviations: CI: confidence intervals; HR: hazard ratio; IRR: independent radiologic review; ITT: intention-to-treat; PFS: progression-free survival; ORR: objective response rate; OS: overall survival; RECIST: Response Evaluation Criteria In Solid Tumours.
Sources: Solomon *et al.* (2014a) [2] and Pfizer Data on File for median best percentage change in target lesions from baseline [39]

4.7.1 Primary efficacy results in PROFILE 1014

Progression-free survival (PFS) was significantly prolonged with crizotinib versus chemotherapy

PROFILE 1014 met its primary endpoint demonstrating a significant improvement in prolonging PFS with crizotinib versus chemotherapy (see Table 21). The Kaplan-Meier curve for the analysis of PFS is presented in Figure 8.

Figure 8: Kaplan-Meier plot for progression-free survival in the ITT population in PROFILE 1014



Source: Solomon *et al.* (2014a) – Figure 2A [2]

Patients in the crizotinib group had an increase in median PFS of 3.9 months compared to patients in the chemotherapy group and a significantly reduced risk of progression or death (HR, 0.45; 95% CI, 0.35 to 0.60; P<0.001) compared to patients in the chemotherapy group.[2] The median PFS observed in the chemotherapy arm is greater than that previously observed in the non-squamous NSCLC population (7.0 months versus 5.3 months [74]) which may be reflective of the specific patient characteristics of ALK-positive NSCLC (e.g. younger, higher proportion of non- smokers).

Notably, the Kaplan-Meier plot for crizotinib was associated with a long tail and a clear separation from the plot of pemetrexed plus platinum therapy, highlighting that a proportion of patients can achieve a markedly prolonged period of PFS, which is likely to lead to OS benefits for these patients. This observation is supported by the greater rate of PFS at 18 months in the crizotinib group (31%; 95% CI, 23 to 39) versus chemotherapy (5%; 95% CI, 2 to 10).[2]

Given the severe deterioration in HRQoL associated with progressive disease, improvements in PFS associated with crizotinib represent a major clinical benefit for patients with advanced NSCLC.[111] Furthermore, such improvements in PFS are likely to be associated with prolonged OS.[125-127]

As detailed in Section 4.8, relative improvements in PFS with crizotinib versus chemotherapy were observed in PROFILE 1014 across subgroups based on stratification factors and baseline characteristics.

4.7.2 Secondary efficacy results in PROFILE 1014

Objective response rate (ORR) was significantly greater with crizotinib versus chemotherapy

The ORR in the ITT population was significantly higher in the crizotinib group than the chemotherapy group (P<0.001), with the majority of patients (74%; 95% CI, 67 to 81) achieving either a partial or complete response with crizotinib (see Table 22). Furthermore, the response to crizotinib was generally more rapid and more durable than with chemotherapy (see Table 22). Together these results suggest that significantly more patients are likely to respond to crizotinib than with chemotherapy and that treatment with crizotinib allows for faster and greater control of tumour growth.

Table 22: Response to treatment in the ITT population in PROFILE 1014

Response*	Crizotinib (n=172)	Chemotherapy (n=171)
Type of response – no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate (ORR) – % (95% CI)‡	74 (67–81)	45 (37–53)
Disease control rate at Week 12 – % (95% CI)§	79 (72 to 84)	68 (61 to 75)
Time to response (TTR) – months		
Median (range)	1.4 (0.6–9.5)	2.8 (1.2–8.5)
Duration of response (DR) – months		
Median (95% CI)	11.3 (8.1–13.8)	5.3 (4.1–5.8)

* Tumour responses were assessed using RECIST (version 1.1), and were confirmed by IRR
† Responses could not be evaluated in 4 patients in each group due to early death.
‡ P<0.001 for the comparison between groups (Two-sided Pearson chi-squared test). The 95% CI was calculated with the use of the exact method based on the F-distribution.
§ P=0.0381 for the comparison between groups (Two-sided Pearson chi-squared test). The 95% CI was calculated with the use of the exact method based on the F-distribution.

Sources: Adapted from Solomon *et al.* (2014a) – Table 2[2]; data for DCR was taken from the Pfizer Clinical Study Report (16th June 2015) [3]

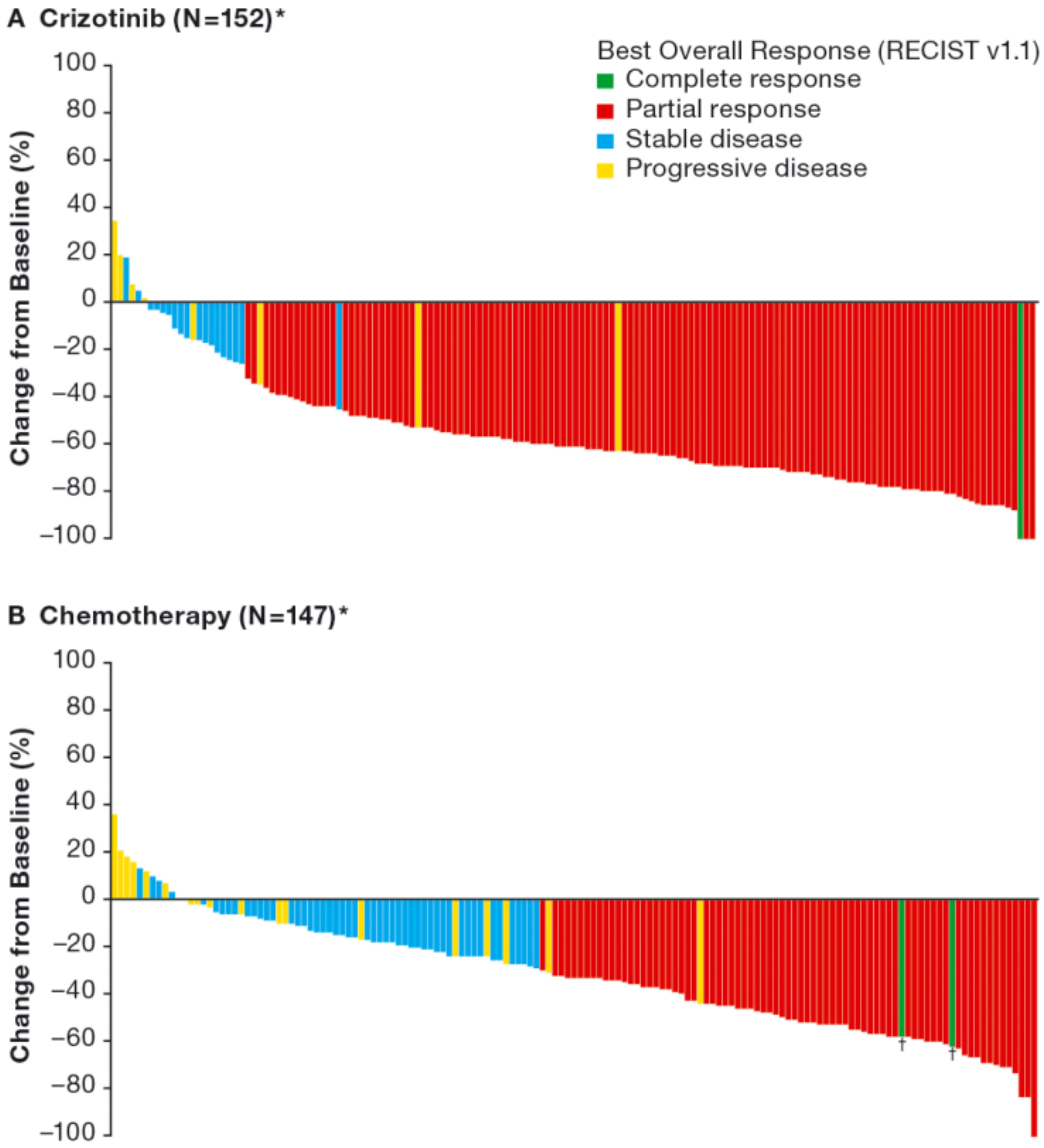
The waterfall plots in Figure 9 present best overall response (BOR) by treatment group for individual patients, with each bar representing a single patient and their best percentage change

from baseline in target lesion size whilst on study treatment. The plots illustrate the superior ORR observed with crizotinib, with the majority of patients in the crizotinib group achieving either a partial (red) or complete (green) response, as defined according to RECIST version 1.1 by reductions and disappearance of target lesions, respectively (see Table 8 for full RECIST definitions). The patient-level BOR illustrated in Figure 9 must have occurred, by definition, prior to disease progression, and are therefore not influenced by the continuation of crizotinib treatment beyond progression. Similarly, ORR, defined as the proportion of patients achieving a best response of CR plus those achieving PR, is not affected.

Figure 9 also demonstrates that patients in the crizotinib group generally had a greater percentage reduction from baseline in tumour size (i.e. improved tumour shrinkage) than those in the chemotherapy group. Post-hoc analyses revealed a greater median best percentage change in target lesions in the crizotinib group (*[Academic / commercial in confidence information removed]*) compared to the chemotherapy group (*[Academic / commercial in confidence information removed]*).[39] Such improvements in tumour response with crizotinib versus chemotherapy are demonstrative of a more targeted anti-tumour activity with crizotinib and represents a step-change benefit in this indication.

The improvements in symptom severity and HRQoL reported by patients whilst on treatment with crizotinib in PROFILE 1014 (see Figure 13 and Figure 14) are likely to be reflective of the greater reduction in tumour size demonstrated here. As RECIST-defined progression is measured using the smallest sum of target lesion diameters on study as the reference (see Table 8), patients who progress following an initial tumour response may still show overall reductions in tumour size from baseline; patients treated with crizotinib may thus have improved health relative to baseline at the time of RECIST-defined progression.

Figure 9: Summary of best responses 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.

Source: Solomon *et al.* (2014a) – Supplementary material: Figure S2 [108]

Unadjusted overall survival (OS) analyses were confounded by crossover; no significant difference was detected between treatment groups

Median OS was not reached in either group at the time of data cut-off (30th November 2013), with deaths having occurred in only 90/343 of all patients (26%) who underwent randomisation. Median follow-up for OS at the data cut-off was 17.4 months for patients randomly assigned to crizotinib and 16.7 months for those assigned to chemotherapy.

As noted in Section 4.5, the high-rate of crossover from the chemotherapy group to crizotinib in PROFILE 1014 is likely to have confounded treatment effects on OS. Of the 171 patients randomly assigned to chemotherapy, 120 patients (70%) subsequently received crizotinib, with the majority of these patients (109) crossing over to crizotinib as a result of disease progression.[2, 3]

Based on Kaplan-Meier estimates, the 1-year and 18-month probabilities of survival were 84% (95% CI, 77 to 89) and 69% (95% CI, 60 to 76), respectively, with crizotinib, and 79% (95% CI, 71 to 84) and 67% (95% CI, 58 to 75), respectively, with chemotherapy.[2, 3]

Crizotinib was associated with a reduced HR for death in the comparison to chemotherapy, though this was not significant when unadjusted for crossover (unadjusted HR for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P=0.36). In the subgroup of patients who did not crossover (*[Academic / commercial in confidence information removed]*), the HR for death with crizotinib versus chemotherapy was significant at *[Academic / commercial in confidence information removed]*), thus supporting the likelihood that treatment effects in the entire population were confounded by crossover.[3]

Crossover-adjusted overall survival is reported in the following section.

Crossover-adjusted overall survival analyses were consistent across models and demonstrated a reduced hazard for death with crizotinib

Following an assessment of the patient level trial data alongside the strengths and limitations of the various recommended statistical methods, the three most suitable methods were chosen for exploration [120, 121] following an assessment of the feasibility of the methods, and agreement from the EMA. Within these three methods, a total of nine models to adjust for crossover were run (as set out in Section 4.4).

After adjusting for crossover with the RPSFT method as pre-specified in the clinical trial protocol, the HRs for overall survival were 0.604 [95% CI: 0.265, 1.420] and 0.674 [95% CI: 0.283, 1.483] based on the two estimation procedures for the acceleration factor (Ψ); Wilcoxon and log-rank tests, respectively. The Kaplan-Meier curves of OS for crizotinib, chemotherapy unadjusted for crossover and chemotherapy adjusted for crossover using the RPSFTM (Log-Rank and Wilcoxon) method are presented in Figure 10. It should be noted that the convergence of the unadjusted and adjusted curves in the longer term is a consequence of very few survival events, not of diminishing treatment effect.

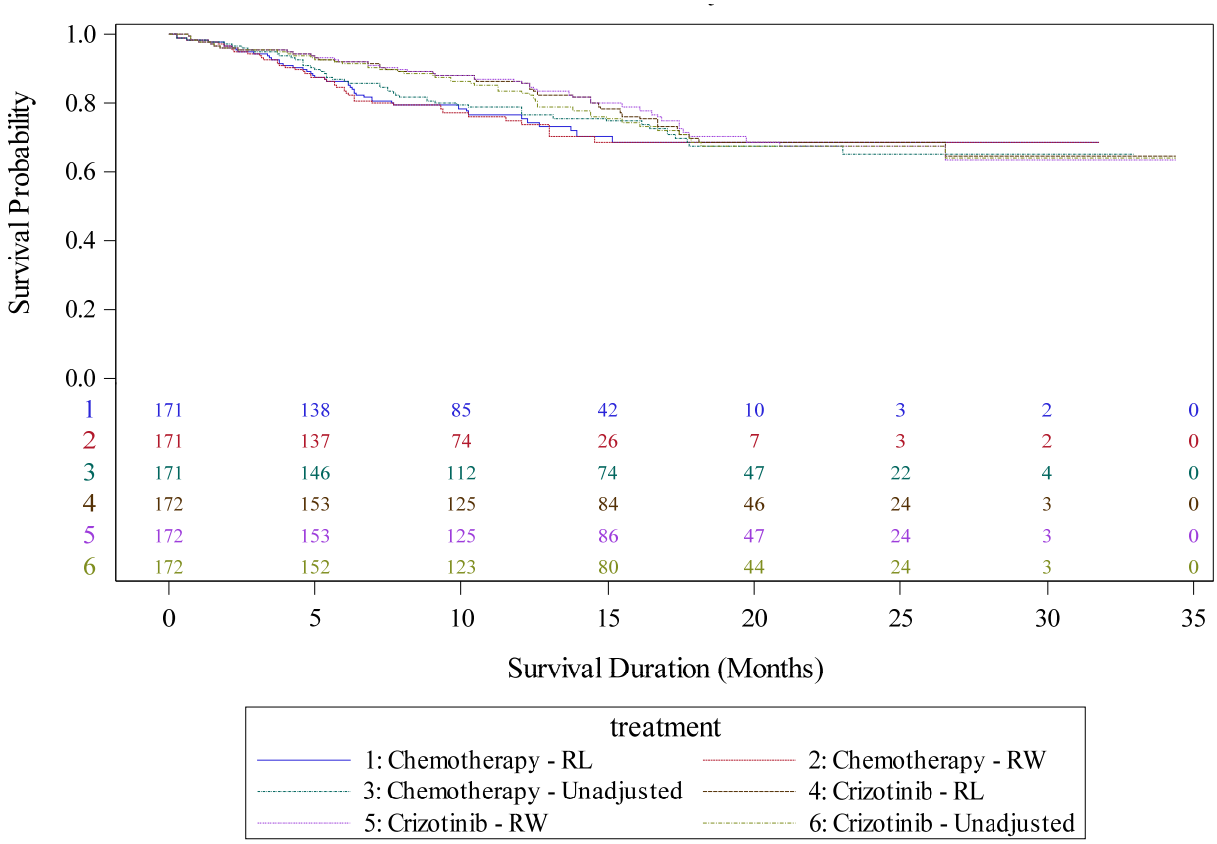
The Kaplan-Meier curves of the two-stage adjusted OS for chemotherapy, chemotherapy unadjusted for crossover and crizotinib unadjusted for crossover are presented in Figure 11. The Log-normal distribution was chosen as the best fit to the post-progression survival (PPS) for both adjusted and unadjusted models and ECOG at PD IRR and baseline smoking status were selected as covariates using a forward stepwise selection algorithm (see **Error! Reference source not found.** for further details of the methodology).

Following the calculation of adjusted survival times and after the application of stratified Cox and log-rank tests, there was a significant difference in OS in favour of crizotinib for the Log-normal model with or without covariates and methods of missing data imputation, with HRs ranging from 0.610 to 0.649 and 1-sided p-values ranging from 0.0123 to 0.0242. As the treatment effect point estimates (HRs) derived using the two-stage method are consistent irrespective of the covariates included in the model and different methods of missing data imputation, the caveats noted **Error!**

Reference source not found. in may have limited impact on the observed results. The two-stage adjusted HRs and associated 95% CIs are summarised in Table 23.

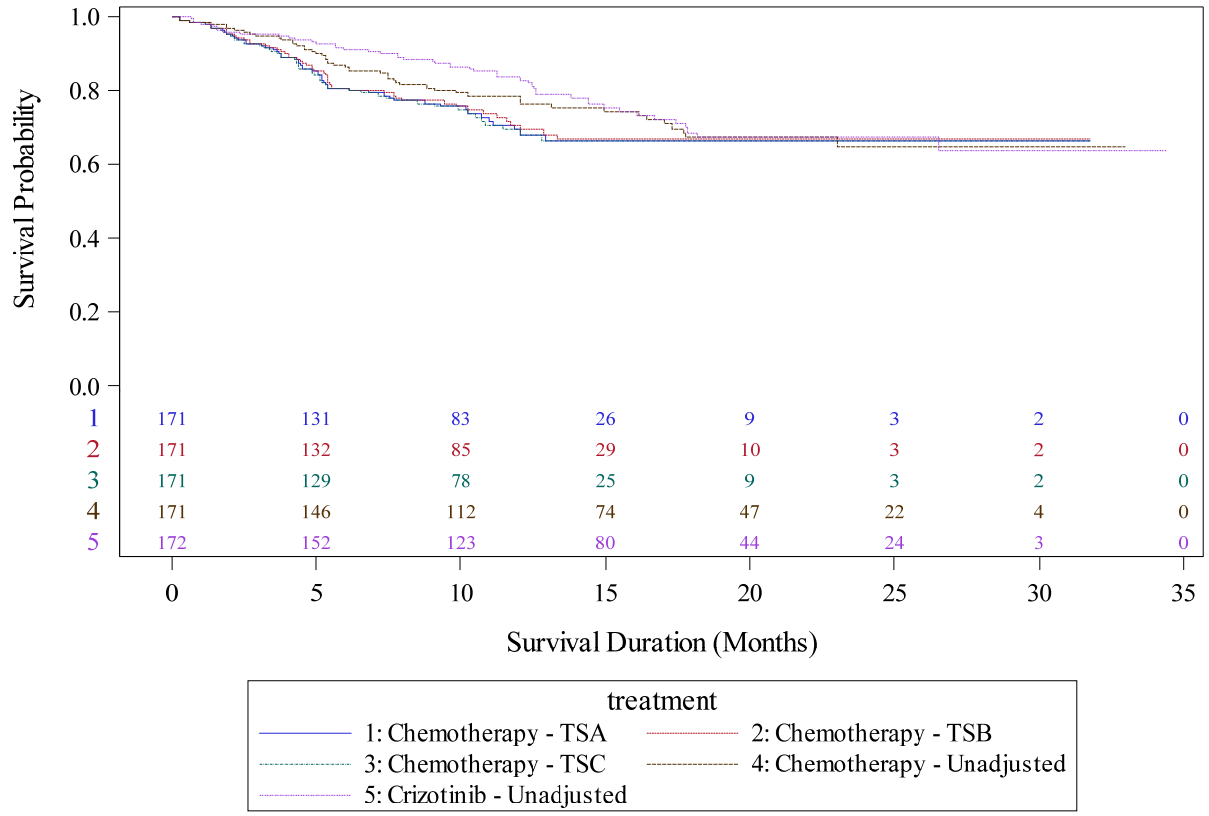
With the IPE method, the adjusted HRs were consistent across all parametric models investigated with and ranged from 0.571 to 0.674 with 1-sided p-values ranging from 0.0130 to 0.0408. The associated point estimates for each model indicated improvement in OS with crizotinib that was statistically significant for all models except for the model based on the Exponential distribution.

Figure 10: Kaplan-Meier overall survival curves: crizotinib, unadjusted chemotherapy and chemotherapy adjusted using RPSFT method (product-limit survival estimates with number of subjects at risk)



Abbreviations: RL: RPSFT crossover adjustment using log-rank test; RW: RPSFT crossover adjustment using Wilcoxon test.

Figure 11: Kaplan-Meier overall survival curves: crizotinib, unadjusted chemotherapy and chemotherapy adjusted for crossover by two-stage method (product-limit survival estimates with number of subjects at risk)



Abbreviations: TSA, two-stage crossover adjustment, covariate adjusted imputing missing ECOG as ≥2; TSB, two-stage crossover adjustment, covariate adjusted imputing missing ECOG as closest value; TSC, two-stage crossover adjustment, unadjusted for covariates.

In summary, results from all analyses of OS adjusted for crossover are highly consistent and suggest that the primary OS analysis, unadjusted for crossover, underestimated the treatment benefit of crizotinib on OS. The consistency of the hazard ratios across the nine models, despite the method-specific assumptions, greatly reduces the uncertainty around the counter-factual survival estimates of patients on pemetrexed-combination therapy.

Furthermore, the observed improvement across three from four IPE parametric models was statistically significant (1-sided p-values ranging from 0.0130 to 0.0251), whilst two from three of the two-stage models were statistically significant (rising to all three of the two-stage models when assessing at the p<0.0247 level, which was pre-specified in the PROFILE 1014 for the primary OS analysis).

Note, only the RPSFT and two-stage methods were selected for investigation in the economic modelling/parametric survival modelling given the methodological similarities between RPSFT and IPE (i.e. both methods maintain randomisation between treatment arms and assume a common treatment effect) and the pre-specified nature of RPSFT. The predicted median OS for crizotinib and pemetrexed-cisplatin/carboplatin derived from this modelling are presented in Section 5.7.2 and discussed there and in Section 5.10.1 in the context of published literature and the expected survival based on clinical expert opinion.

Table 23: Summary of overall survival analyses for PROFILE 1014 based on data at the time of final PFS analysis

Method of Analysis	Parametric Model	Adjusted for Crossover	Analysis Details	Hazard Ratio (95% CI)[1]	1-sided p-value[2]
Primary	N/A	No	N/A	0.821 (0.536, 1.255)	0.1804
RPSFTM	N/A	Yes†	Using Wilcoxon test (method **RW**)	0.604 (0.265, 1.420)	NR
			Using Log-rank test (method **RL**)	0.674 (0.283, 1.483)	NR
2-stage	Log-normal	Yes‡	Adjusted for baseline Smoking Status and ECOG PS at PD by IRR, ECOG = closest (method **TSA**)	0.624 (0.405, 0.963)	0.0158
			Adjusted for baseline Smoking Status and ECOG PS at PD by IRR, ECOG = worst (method **TSB**)	0.649 (0.421, 1.000)	0.0242
			Not adjusted for covariates (method **TSC**)	0.610 (0.395, 0.942)	0.0123
IPE	Weibull	Yes†	Adjusted for baseline ECOG PS, baseline Brain Metastases and baseline Smoking Status	0.626 (0.395, 0.992)	0.0230
	Log-normal			0.633 (0.401, 1.000)	0.0251
	Log-Logistic			0.571 (0.349, 0.935)	0.0130
	Exponential			0.674 (0.432, 1.051)	0.0408

† Adjusted for crossover (from randomized chemotherapy to crizotinib) and (from randomized crizotinib to chemotherapy [only pemetrexed/cisplatin or pemetrexed/carboplatin])
‡ Adjusted for crossover (from randomized chemotherapy to crizotinib)
[1] Based on the Cox model stratified for ECOG PS (0-1, 2), race group (Asian, Non-Asian) and presence of brain metastases (present, absent)
[2] Based on 1-sided log-rank test, stratified for race group, baseline ECOG PS and baseline brain metastases

Abbreviations: ECOG PS: Eastern Cooperative Group performance status; HR: hazard ratio; IPE: Iterative Parameter Estimation; N/A: not applicable; NR: not reported; PD: progressive disease; RL: RPSFT crossover adjustment using log-rank test; RPSFTM: Rank Preserving Structural Failure Time Model; RW: RPSFT crossover adjustment using Wilcoxon test; TSA: two-stage crossover adjustment, covariate adjusted imputing missing ECOG as ≥2; TSB, two-stage crossover adjustment, covariate adjusted imputing missing ECOG as closest value; TSC, two-stage crossover adjustment, unadjusted for covariates.

Patient-reported outcomes and health-related quality of life in PROFILE 1014

Summary of PROFILE 1014 patient-reported outcomes

- Treatment with crizotinib was associated with a significantly greater overall improvement in global HRQoL compared to chemotherapy, as measured using the EORTC QLQ-C30 (P<0.001).
- A significantly greater overall reduction from baseline in the symptoms of dyspnoea, cough and chest pain were reported in the crizotinib group relative to the chemotherapy group, as measured using the EORTC QLQ-LC13 (P<0.001).
- Time-to-deterioration in the lung cancer-related symptoms of dyspnoea, cough and chest pain (as a composite endpoint) was significantly prolonged in the crizotinib group relative to the chemotherapy group (HR, 0.59; 95% CI, 0.45 to 0.77; P<0.001).
- Improvements in symptoms are likely to be related to the superior tumour response rates and increased reductions in tumour size observed with crizotinib versus chemotherapy.
- Improvements from baseline in health utility as measured using EQ-5D was significantly higher in the crizotinib group than the chemotherapy group in a mixed-model analysis (P<0.05).

EORTC QLQ-C30 and QLQ-LC13

Completion rates of the EORTC QLQ-C30 questionnaire and QLQ-LC13 module from evaluable patients ranged from *[Academic / commercial in confidence information removed]* for crizotinib (over the first 30 of a total of 50 cycles) and *[Academic / commercial in confidence information removed]* for chemotherapy (over the maximum 6 cycles).[3] The majority of patients in the crizotinib group (*[Academic / commercial in confidence information removed]*) and chemotherapy group (*[Academic / commercial in confidence information removed]*) from the ITT population completed the EORTC QLQ-C30 and QLQ-LC13 at baseline.[3] As the sample size in the later cycles in the crizotinib group was greatly diminished (*[Academic / commercial in confidence information removed]*), the interpretation of statistical significance for within-treatment group changes from baseline was limited to the first 30 cycles for crizotinib and to 6 cycles (maximum allowed) for chemotherapy.[3]

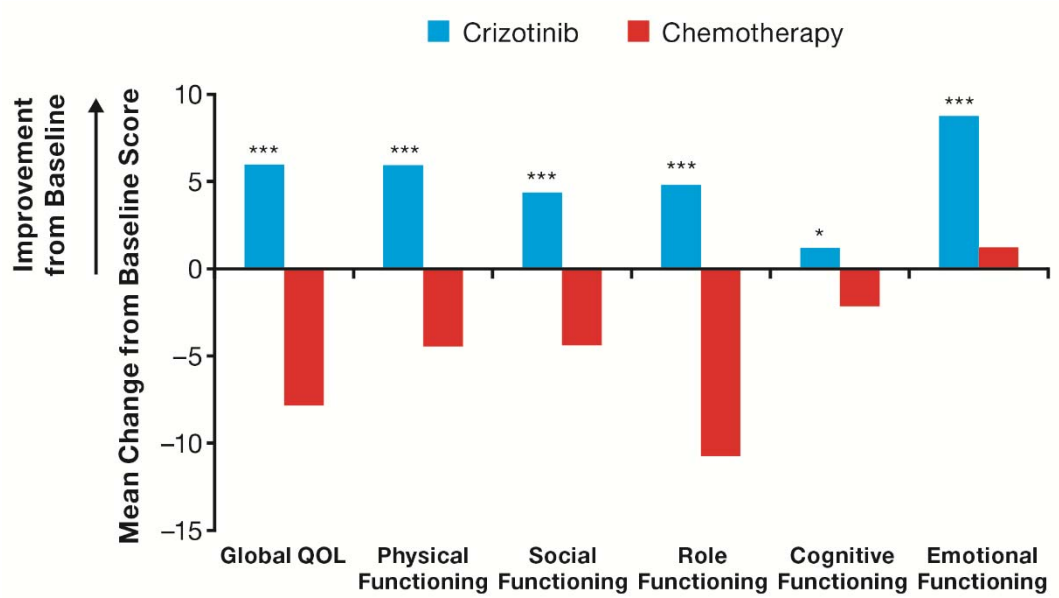
In PROFILE 1014, there was a significantly greater improvement from baseline in global HRQoL (P<0.001), and physical, social, emotional, and role functioning domains (P<0.001), reported by patients in the crizotinib group compared to those randomised to chemotherapy (see Figure 12).[2]

In addition to statistically significant improvements in global quality of life, crizotinib provided a benefit in quality of life related to individual symptoms, as assessed by the EORTC QLQ-C30 questionnaire and the EORTC QLQ-LC13 questionnaire. In the crizotinib group, a significantly greater overall reduction from baseline in the symptoms of pain, dyspnoea and insomnia – as assessed with the use of the EORTC QLQ-C30 (see Figure 13); and the symptoms of dyspnoea, cough, chest pain, arm or shoulder pain, and pain in other parts of the body – as assessed with the use of the EORTC QLQ-LC13 (see Figure 14), were reported by patients in PROFILE 1014, compared to the chemotherapy group (P<0.001 for all comparisons).[2]

The reduction in symptom severity is likely to be reflective of the significant improvements observed with crizotinib versus chemotherapy in tumour response rates and reductions in target

lesions from baseline (see Figure 9). Treatment with crizotinib is therefore associated with improvements in patient health relative to baseline at the time of disease progression.

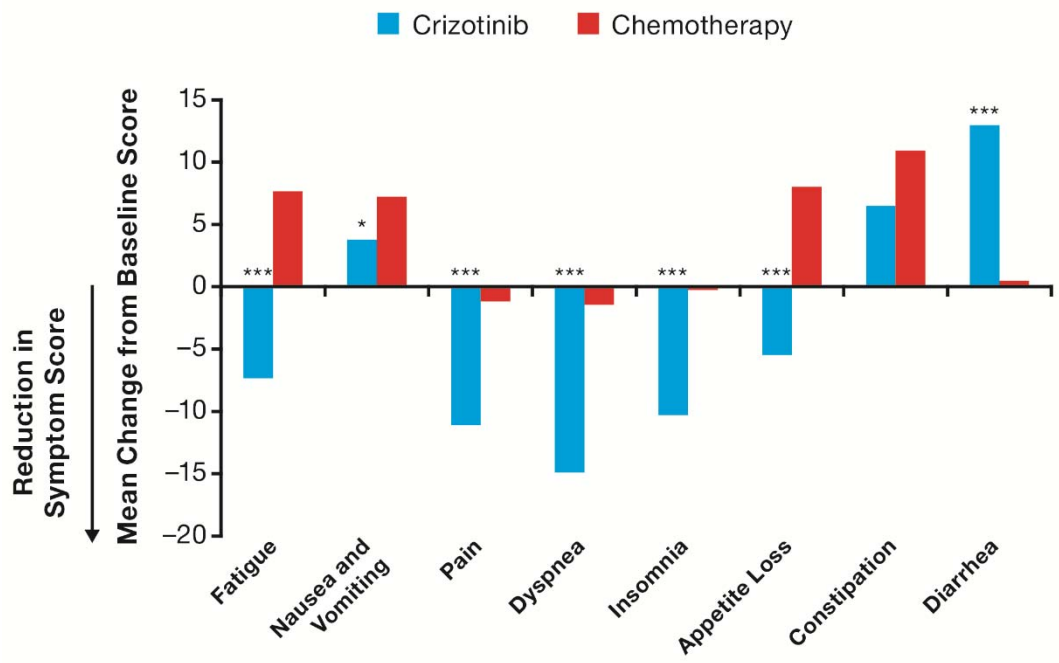
Figure 12: Change in global quality of life and functioning domains from baseline (EORTC QLQ-C30) reported in PROFILE 1014



* P<0.001 and † P<0.05 for between treatment groups comparisons.
A change of 10 points or greater was considered to be clinically meaningful.

Source: Solomon *et al.* (2014a) – Figure 2A [2]

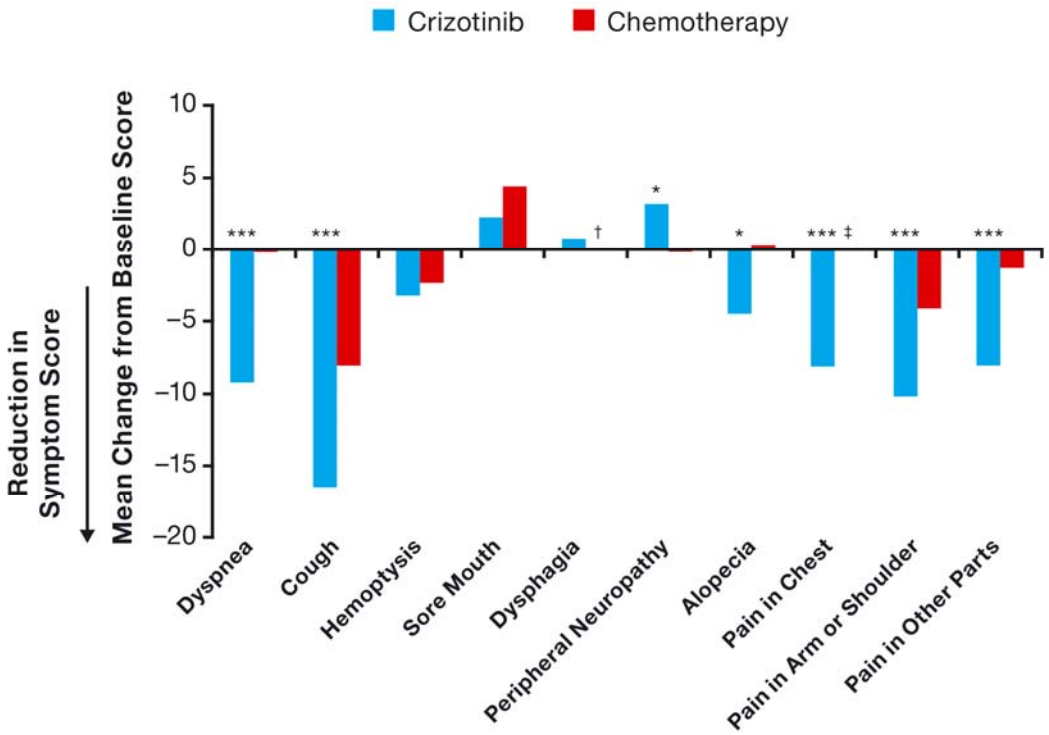
Figure 13: Change in symptom severity from baseline (EORTC QLQ-C30) reported in PROFILE 1014



* P<0.001 and † P<0.05 for between treatment groups comparisons.
A change of 10 points or greater was considered to be clinically meaningful.

Source: Solomon *et al.* (2014a) – Figure 2B [2]

Figure 14: Change in symptom severity from baseline (EORTC QLQ-LC13) reported in PROFILE 1014



* P<0.001 and † P<0.05 for between treatment groups comparisons.
A change of 10 points or greater was considered to be clinically meaningful.

Source: Solomon *et al.* (2014a) – Figure 2C [2]

Time to deterioration (TTD) – cough, dyspnoea or pain in chest

TTD was evaluated as a composite endpoint for the symptoms cough, dyspnoea and pain in chest – as assessed using the EORTC QLQ-LC13 module. TTD was defined as the time from randomisation to the earliest date that the patient's scale scores showed a 10-point or greater increase after baseline (indicating a worsening of symptoms), in any of the three symptoms.

The composite TTD was significantly prolonged in the crizotinib group compared to chemotherapy (before crossover) (HR for worsening symptoms with crizotinib, 0.59; 95% 0.45 to 0.77; Hochberg adjusted log-rank 2-sided test P<0.001), with patients in the group estimated to have a greater probability of being event-free at 6 months (37% vs. 109] Median TTD was 2.1 months (95% CI, 0.8 to 4.2) and 0.5 months (95% CI, 0.4 to 0.7) in crizotinib and chemotherapy groups, respectively.[3] Kaplan-Meier estimates for TTD are presented in

Figure 15.

As with changes from baseline in symptom severity, the significant delay in TTD in the lung-related symptoms of cough, dyspnoea and chest pain experienced by patients in the crizotinib group versus chemotherapy is likely to be the result of greater reductions in tumour size (see Figure 9) and more durable tumour responses (see Table 22) with crizotinib.

Figure 15: Time to deterioration in the symptoms of cough, dyspnoea or pain in chest (EORTC QLQ-LC13) in PROFILE 1014

[Academic / commercial in confidence information removed]

Abbreviations: EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire – Lung Cancer 13 module
Source: Pfizer Clinical Study Report (16th June 2015) [3]

EQ-5D

Completion rates of all questions of the EQ-5D questionnaire from evaluable patients ranged from ***[Academic / commercial in confidence information removed]*** for crizotinib (over the first 30 of a total of 50 cycles) and ***[Academic / commercial in confidence information removed]*** for chemotherapy (over the maximum 6 cycles).[3] All but eight patients in the crizotinib group (***[Academic / commercial in confidence information removed]***) and seven patients in the chemotherapy group (***[Academic / commercial in confidence information removed]***) from the ITT population completed all questions of the EQ-5D questionnaire at baseline.[3]

Whereas no statistically significant changes from baseline where observed in the chemotherapy group over 6 cycles, patients in the crizotinib group showed a significant improvement from baseline (***[Academic / commercial in confidence information removed]***) in EQ-5D visual analogue scale (VAS) general health status scores in cycles 3 to 16 and 18 to 21.[3] In a mixed-model analysis, crizotinib was associated with a statistically significant greater improvement in EQ-5D VAS scores compared to chemotherapy (***[Academic / commercial in confidence information removed]***).[2]

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 (*[Academic / commercial in confidence information removed]*); improvements from baseline in EQ-5D index scores were also statistically significantly greater in the crizotinib group relative to chemotherapy (*[Academic / commercial in confidence information removed]*).[3]

Statistically significant improvements from baseline (*[Academic / commercial in confidence information removed]*) 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).[3]

4.8 Subgroup analysis

4.8.1 Provide details of any subgroup analyses carried out. Specify the rationale and whether they were pre-planned or post-hoc.

Pre-specified subgroup analyses were conducted in PROFILE 1014 for the following:

- PFS by treatment group and stratification factors— ECOG performance status (0 or 1 vs. 2), race (Asian vs. non-Asian), and brain metastases (absence vs. presence) — and selected baseline characteristics, including age (<65 years old vs. ≥65 years old), sex (male vs. female), smoking status (smoker or former smoker vs. never smoker), time since diagnosis (>1 year vs. ≤ 1 year), adenocarcinoma histology (yes vs. no) and type of disease (metastatic vs. locally advanced).[2]
- IC-TTP and EC-TTP by treatment group and baseline brain metastases (presence vs. absence) in patients randomised to study treatment in PROFILE 1014.[102]

The subgroup analyses for PFS by stratification factors were conducted in order to evaluate whether the effects of crizotinib treatment on PFS were consistent across all patient sub-populations within the ALK-positive, advanced NSCLC population. In past RCTs investigating the use of EGFR-TKIs in NSCLC, race and smoking status have been identified as determinants of treatment efficacy.[128]

Subgroup analyses were also performed in order to assess whether crizotinib was efficacious relative to chemotherapy in delaying either the progression of existing brain lesions or the development of new brain metastases. Brain metastases are a frequent occurrence in patients with NSCLC and given the need for drugs to permeate the blood-brain barrier these lesions are particularly difficult to treat using systemic therapies.[69] Time to intracranial progression is therefore an interesting outcome in the context of the tumour profile of this disease.

4.8.2 Clearly specify the characteristics of the participants in the subgroups and explain the appropriateness of the analysis to the decision problem.

The defining characteristics of participants in the subgroups analysed (e.g. brain metastases present vs absent) are listed above in Section 4.8.1. All subgroups were pre-specified and randomisation was stratified according to ECOG performance status (0 or 1 vs. 2), Asian or non-Asian race, and presence or absence of brain metastases.

These analyses are considered relevant to the decision problem as they demonstrate the broad clinical effectiveness of crizotinib across various subgroups of patients with ALK-positive, advanced, NSCLC.

4.8.3 Provide details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction.

For pre-specified subgroup analyses of PFS and TTP, the Kaplan-Meier method was used to estimate time-to-progression. Unstratified log-rank tests were used to compare PFS and TTP between subgroups and Cox regression models were applied to estimate HRs.[108]

4.8.4 Provide a summary of the results for the subgroups, with full details provided in an appendix.

A summary of results of these pre-specified subgroup analyses is provided below with full details presented in in **Error! Reference source not found.**.

Progression-free survival by treatment group and stratification factors/baseline characteristics

The relative improvements in PFS with crizotinib versus chemotherapy were similar across subgroups, including race (Asian vs. non-Asian) and baseline brain metastases (presence vs. absence) (see **Error! Reference source not found.** in **Error! Reference source not found.**).[2] These pre-specified subgroup analyses found crizotinib to have a consistent efficacy benefit relative to chemotherapy and support the notion that the presence of ALK translocations is the major determinant of patient response to crizotinib.

Intracranial and extracranial time-to-progression (IC-TTP and EC-TTP) by treatment group and baseline brain metastases

In PROFILE 1014, treatment with crizotinib was associated with a numerical improvement in IC-TTP versus chemotherapy in both patients with and without brain metastases at randomisation, but this was not considered to be statistically significant in either subgroup (see **Error! Reference source not found.** in **Error! Reference source not found.**).[3]

With regards to extracranial lesions, patients in the crizotinib group had a significantly prolonged ECT-TTP relative to those randomly assigned to chemotherapy, irrespective of the presence or absence of brain metastases at randomisation (see **Error! Reference source not found.** in **Error! Reference source not found.**).[3]

4.9 Meta-analysis

As PROFILE 1014 was the only RCT identified that investigated the use of crizotinib as a first-line treatment for adults with ALK-positive, advanced NSCLC, a meta-analysis was not applicable.

4.10 Indirect and mixed treatment comparisons

Pemetrexed in combination with cisplatin or carboplatin is the standard of care comparator for this submission. Head-to-head data are available for this comparison, thus no indirect or mixed treatment comparison is presented here.

4.11 Non-randomised and non-controlled evidence

4.11.1 In a table present the list of non-randomised and non-controlled evidence (for example, experimental and observational data) considered relevant to the decision problem and justify including each study.

As described in Section 4.1, a systematic review to identify clinical evidence from relevant non-RCTs for crizotinib as a first-line therapy for ALK-positive, advanced NSCLC was conducted. A summary of the relevant non-RCTs identified is presented in Table 24.

Of the six articles identified in the non-RCT systematic review, four reported on the single-arm, open-label, Phase I study PROFILE 1001 (Camidge *et al.* [2012] [51], Camidge *et al.* [2011] [129], Kwak *et al.* [2010] [130], and Soria *et al.* [2012] [131]) Of the remaining two studies one was an abstract that reported on a small (n=5) retrospective observational study conducted in Spain (Corral *et al.* [2013] [132]); and another was a retrospective cohort study of patients receiving crizotinib in the first-and second-line setting in US clinical practice (Davis *et al.* [2015] [133]). In this cohort study the majority of patients (81.6%) received crizotinib as a first-line treatment option.

In the retrospective Spanish study by Corral *et al.* (2013), only two patients out of the five ALK-positive patients treated with crizotinib were treatment naïve prior to receiving crizotinib, and only the partial response rate was reported (n=2, 100%).[132] Due to the small sample size and limited outcomes reported, this study was not considered relevant to the submission and is therefore excluded from further discussion.

Of the studies reporting on PROFILE 1001, Camidge *et al.* (2012) and Kwak *et al.* (2010) were full-text journal publications, while Soria *et al.* (2012) and Camidge *et al.* (2011) were congress abstracts.[51, 129-131] As Camidge *et al.* (2012) was a full-text journal publication and presented results from the PROFILE 1001 trial with the most recent data cut-off date identified (1st June 2011), it was deemed the most appropriate primary data source for PROFILE 1001 for the purposes of this submission.[51]

Table 24: List of relevant non-randomised and non-controlled evidence

Study number (acronym)	Objective	Population	Intervention	Comparator	Primary source	Secondary source(s)	Justification for inclusion
NCT00585195 (PROFILE 1001)	*Part 1 – dose escalation* To determine toxic effects and the maximum tolerated dose of crizotinib in man. *Part 2 – expanded patient cohort* To assess the tolerability and efficacy of crizotinib in patients with ALK-positive NSCLC.	Adult patients with confirmed ALK-positive, stage III or IV NSCLC. The study included patients who received crizotinib as first- and later-lines of therapy.	Crizotinib, 250 mg twice-daily in 28-day cycles, oral (in Part 2 – expanded patient cohort)	None; single-arm trial	Camidge *et al.* (2012) [51]*	Camidge *et al.* (2011) [129] Kwak *et al.* (2010) [130] Soria *et al.* (2012) [131] Pfizer: PROFILE 1001 Study Protocol [134]	Includes patients with ALK-positive, advanced NSCLC, and reports PFS and ORR for patients receiving crizotinib as a first-line therapy.
Davis *et al.* (2015)	Retrospective cohort study (medical chart review) to assess treatment patterns and clinical outcomes of patients with ALK-positive, advanced NSCLC treated with crizotinib in clinical practice.	Adult patients with confirmed ALK-positive NSCLC. The study included patients who received crizotinib at first- and later-lines of therapy.	Crizotinib, the majority of patients (81.6%) receiving first-line crizotinib were initiated on 250 mg twice-daily	None	Davis *et al.* (2015) [133]	None	Includes patients with ALK-positive, advanced NSCLC treated with crizotinib in a real-world setting, and reports PFS, ORR and 1- and 2-year survival rates for patients receiving crizotinib as a first-line therapy.

* The publication by Camidge *et al.* (2012) reports relevant data from the most recent cut-off (1st June 2011) and is therefore considered as the primary source of data for PROFILE 1001

4.11.2 If trials listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of data required, this should be stated.

Given the inclusion of ALK-positive patients treated with first-line crizotinib in PROFILE 1001 and Davis *et al.* (2015), both of these non-RCTs are considered to be relevant to this submission. Data from both of these studies is included in this submission and is presented in the following sections as supportive evidence for the clinical effectiveness of crizotinib in previously untreated, ALK-positive, advanced NSCLC patients.

4.11.3 Provide a comparative summary of the methodology of the studies in a table.

A comparative summary of the methodology of PROFILE 1001 and Davis *et al.* (2015) is presented in Table 25. The definition of study outcomes and the full eligibility criteria used in each study are presented in Table 26 and Table 27, respectively.

Table 25: Summary of PROFILE 1001 and Davis *et al.* (2015) study methodologies

Trial number (acronym)	**NCT00585195 (PROFILE 1001)**	**Davis *et al.* (2015)**
Trial design	Multicentre, international, phase I single-arm clinical trial **Part 1** – dose escalation study in patients with solid tumours. **Part 2** – expanded patient cohort to assess tolerability and efficacy in ALK positive NSCLC.	Retrospective cohort study in which the medical charts of patients receiving crizotinib in a first-line and second-line setting in clinical practice were reviewed.
Location	8 study centres: six in the USA and one each in Australia and South Korea [135]	Participating oncologists were from USA (n=107) and Canada (n=40)
Duration of study	The first patient was enrolled on 27th August 2008 and received their first dose of crizotinib on 28th August 2008. The latest data cut-off date was the 1st June 2011, at which point 149 patients had been enrolled.	Medical chart abstraction was performed in 2014 – patients were included who initiated crizotinib between: 1st August 2011 – 31st March 2013 (USA) 1st April 2012 – 31st March 2013 (Canada)
Trial drugs and administration	Crizotinib, 250 mg twice-daily in 28-day cycles, oral(n=149 at the data cut-off date of 1st June 2011) A total of 24/149 (16%) patients received crizotinib as a first-line therapy for advanced disease.* Median duration of treatment with crizotinib was 43.1 weeks (range 0.1 to 138.6) at data cut-off date 1st June 2011 **No comparator**	Crizotinib, oral • 200 mg twice-daily (n=22)/ once daily (n=3) • 250 mg twice-daily (n=111) A total of 137/212 (65%) received crizotinib as a first-line therapy for advanced disease.* Duration of treatment was not reported. **No comparator**

Permitted and disallowed concomitant medicines	**Permitted concomitant medicines [134]** • Supportive care including antiemetics and prophylaxis for treatment-induced diarrhoea • Haematopoietic growth factors (only after Cycle 1) • Anti-inflammatory or narcotic analgesics • Packed red blood cell and platelet transfusions • Hormone replacement therapy, as clinically indicated Palliative radiotherapy and elective surgery were also permitted, if necessary **Disallowed concomitant medicines [134]** • Anti-cancer therapy other than crizotinib • Potent CYP3A inhibitors and inducers	Not specified
Outcomes (including scoring methods and timings of assessments)	*Part 2 – expanded patient cohort* **Primary endpoint:** • ORR† – as measured using RECIST version 1.0.[136] **Secondary endpoints:** • Duration of response • Time to tumour response Tumour response was assessed every 8 weeks, with confirmation of CR or PR a minimum of 4 weeks after initial response. Tumour response was measured in the response-evaluable population.‡ • PFS† • OS – probability of survival at 6 and 12 months • Safety and tolerability Safety was assessed at least every 2 weeks for the first 8 weeks of treatment and at least every 4 weeks thereafter until cycle 10, when visits every 8 weeks were permissible. Adverse events were graded according to CTCAE version 3.0.§ • Plasma pharmacokinetic profile	Data were collected for: • ORR • PFS • OS • Treatment patterns including dose changes and reasons for treatment discontinuation As the study was a retrospective analysis of medical charts, assessments were not done on a uniform schedule in accordance with a protocol.

	of crizotinib	
Duration of follow-up	Median duration of treatment was 16.3 months (95% CI, 13.8 to 18.4)	Median duration of observation from initiation of first-line crizotinib to until record abstraction was 16.5 months

* The remaining 125 patients in PROFILE 1001 had received prior therapy for advanced or metastatic NSCLC (1 previous therapy: 24 [16%]; 2 previous therapies: 31 [21%]; 3 previous therapies: 19 [13%]; ≥4 previous therapies: 28 [19%]). Of the remaining 75 patients in Davis *et al.* 2015, 73 patients received second-line or later crizotinib and for 2 patients the line of crizotinib initiation was unknown
† Outcomes that were reported separately by Camidge *et al.* (2012) for patients receiving crizotinib as a first-line therapy in PROFILE 1001.
‡ In PROFILE 1001, the response evaluable population was defined as patients who received at least one dose of crizotinib and had an adequate baseline disease assessment, plus had either at least one post-baseline disease assessment at least 6 weeks after the first dose or had withdrawn from the study. Patients who had withdrawn, progressed, or died without receiving a second scan at least 6 weeks after the first dose were classified as non-responders.
§ In PROFILE 1001, safety analyses were conducted in all patients who received crizotinib

Abbreviations: CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; CYP3A: cytochrome P3A; ORR: objective response rate; OS: overall survival; PFS: progressive-free survival; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumours; USA: United States of America.
Sources: Information was derived from Camidge *et al.* (2012) and Pfizer: PROFILE 1001 Study Protocol for PROFILE 1001 [51, 134] and Davis *et al.* (2015) [133]

Definition of study outcomes in PROFILE 1001 and Davis *et al.* (2015)

The definition of key efficacy outcomes used in PROFILE 1001 and Davis *et al.* (2015) are presented in Table 26, and were similar between studies. As Davis *et al.* (2015) was a medical chart review of patients receiving treatment in clinical practice, the initiation of therapies other than crizotinib had to be taken into account when defining time-to-event outcomes.

Table 26: Definition of study outcomes in PROFILE 1001 and Davis *et al.* (2015)

Outcome	NCT00585195 (PROFILE 1001)	Davis *et al.* (2015)
ORR	The proportion of patients achieving a best response of either CR or PR, based on investigator assessment, as per RECIST version 1.0.[136]	The proportion of patients achieving a best response of either CR or PR.
PFS	The time from first administration of crizotinib until the date of objective disease progression or death from any cause.	The time from crizotinib initiation to whichever came first out of: • Clinical progression or death occurring during crizotinib treatment, up to and including 2 weeks after switch to/initiation of a new therapy, if a new therapy was initiated. • Death occurring between 2 and 14 weeks after crizotinib completion, if there was no initiation of new therapy during this period.
OS	Time from crizotinib initiation to death.	Time from crizotinib initiation to death.

Abbreviations: CR: complete response; ORR: objective response rate; OS: overall survival; PFS: progressive-free survival; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumours.
Sources: Information was derived from Camidge *et al.* (2012) and Kwak *et al.* (2010) for PROFILE 1001 [51, 130] and Davis *et al.* (2015) [133]

Eligibility criteria for PROFILE 1001 and Davis *et al.* (2015)

The eligibility criteria for Part 2 of PROFILE 1001 (see Table 27) were largely similar to that of PROFILE 1014 (see Table 16), with the exception that patients in PROFILE 1001 were not excluded based on histology and no limit was placed on the number of previous therapies for advanced disease. In terms of patient characteristics, the only notable difference between the eligibility criteria for Davis *et al.* (2015) and the PROFILE trials was that the retrospective analysis by Davis *et al.* (2015) only included patients with metastatic ALK-positive NSCLC (see Table 27), whereas the PROFILE 1014 trials also included patients with locally-advanced disease.

Table 27: Eligibility criteria for PROFILE 1001 and Davis *et al.* (2015)

	NCT00585195 (PROFILE 1001)	Davis *et al.* (2015)
Inclusion criteria	• Aged ≥18 years old • Measurable ALK-positive NSCLC (as assessed by break-apart FISH assay) • Stage III or IV disease • Adequate renal function and ECOG performance status of 0 or 1 (or 2 on agreement by investigator and sponsor)	• Age ≥18 years at diagnosis of ALK-positive NSCLC • Diagnosed with metastatic NSCLC and confirmed ALK gene rearrangement • Initiated crizotinib treatment as first- or later-line therapy between August 1, 2011 and March 31, 2013 (for US patients) or April 1, 2012 and March 31, 2013 (for Canadian patients) • Complete medical record from crizotinib initiation until ≥3 months after last crizotinib dose (if patient died less than 3 months after last dose, the patient record was still eligible)
Exclusion criteria	• Unresolved acute treatment-related toxic effects to grade 2 or more (with the exception of alopecia) • Received systemic anticancer treatment, radiation treatment or major surgery within 2 weeks of starting study treatment • Received previous ALK-directed therapy • Received previous high-dose chemotherapy needing haematopoietic-stem-cell rescue • Previous brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 2 weeks; myocardial infarction, severe or unstable angina, coronary or peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischaemic attack within 12 months or pulmonary embolus within 6 months before starting study treatment; ongoing cardiac dysrhythmias of CTCAE	• Treated with crizotinib as part of a clinical trial • ROS1-positive

	version 3.0 grade 2 or higher, uncontrolled atrial fibrillation of any grade, or QT interval, corrected over 470 ms; uncontrolled hypertension. • Use of medications that are known CYP3A4 inducers within 12 days before the first-dose of crizotinib	

Abbreviations: ALK: anaplastic lymphoma kinase; CTCAE: Common Terminology Criteria for Adverse Events; CYP3A4: cytochrome P34A; ECOG: Eastern Co-operative Oncology Group; FISH: fluorescence *in situ* hybridisation; NSCLC: non-small cell lung cancer; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase.
Sources: Information was derived from Camidge *et al.* (2012) for PROFILE 1001 [51] and Davis *et al.* (2015) [133]

Statistical analysis of the non-randomised and non-controlled evidence

PROFILE 1001

Time-to-event endpoints were analysed using the Kaplan-Meier method to generate median event times with two-sided 95% CIs (by the Brookmeyer-Crowley method), and 6-month and 12-month OS probabilities. Median duration of follow-up for PFS and OS, including quartiles, were estimated using the reverse Kaplan-Meier method. Confidence intervals for ORR were calculated using the exact method based on the F-distribution.[51]

Tumour responses were analysed in the response-evaluable population which included patients who received at least one dose of crizotinib, had an adequate baseline disease assessment (i.e., had a scan done no more than 35 days before the first dose of the study drug and had a scan showing disease that was evaluable per RECIST), and had either at least one post-baseline assessment at least 6 weeks after the first dose, or had withdrawn from the study or progressed or died without receiving a second scan at least 6 weeks after the first dose – patients who had withdrawn, progressed or died in this latter group were classified as non-responders.[51] The overall response-evaluable population included 143 patients; the remaining six patients did not have adequate baseline scans.[51]

Davis et al. (2015)

In Davis *et al.* (2015), PFS and OS were analysed using Kaplan-Meier methods. Patients without a progression event were censored at the time of initiation to a new therapy, death occurring more than 14 weeks after crizotinib completion, or the end of available medical records, whichever came first. In the analysis of OS, patients still alive at the time of data collection were censored at the date of the last available medical record.[133]

4.11.4 For non-randomised and non-controlled evidence such as observational studies, the potential biases should be identified before data analysis, either by a thorough review of the subject area or discussion with experts in the clinical discipline. Ideally these should be quantified and adjusted for.

PROFILE 1001

The limitations of PROFILE 1001 as a source of evidence with regards to this submission include:

- PROFILE 1001 was a phase I trial and was not designed to evaluate efficacy outcomes such as PFS

- As an open-label study biases may have been introduced in terms of the patient and investigator subjective decisions, including for example, assessments of tumour response
- As a non-controlled trial, the observed study outcomes can be less conclusively attributed to treatment with crizotinib
- The majority of patients included in PROFILE 1001 had been previously treated for advanced disease; only 24 patients (16%) received crizotinib in the first-line setting
- As discussed in Section 4.11.5, there were some differences in baseline characteristics between studies: patients included in PROFILE 1001 differed from those 'real-world' patients included in Davis *et al.* (2015) in terms of age, ECOG performance status and smoking status at baseline

Davis *et al.* (2015)

Potential biases that may have been introduced into the analysis of this study include:

- Patients selected for study inclusion represented a "convenience" sample, in that the records were obtained from physicians who were willing and available to participate in the study
- Information captured by the study's data-collection form was limited to information available in the patients' medical records held by the physicians participating in the study
- As this was a retrospective analysis, response criteria were not dictated by a protocol and assessments (imaging studies) were not done on a uniform schedule.

The few, notable differences in baseline characteristics between patients enrolled in the PROFILE clinical trials and the 'real-world' patients included in Davis *et al.* (2015) were also noted by UK clinical experts consulted at an advisory board whilst considering the generalisability of PROFILE 1014 to the UK population (see Section 4.13.2). These differences between the PROFILE trial populations and what is observed and/or expected in clinical practice have been explored and taken into account in the cost-effectiveness analysis (see Section 5.3.1.1).

4.11.5 In a table describe the characteristics of the participants at baseline for each of the studies. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between study groups. A suggested table format is presented below.

Patient disposition and reasons for discontinuation

In PROFILE 1001, 82/149 patients (55%) enrolled into the study, including those receiving crizotinib as a second- or subsequent-line therapy, were still ongoing treatment with crizotinib at the latest data cut-off date (1st June 2011).[51] Of these, 52 patients were yet to experience RECIST-defined progression. The median duration of treatment was 43.1 weeks (range, 0.1 to 138.6).[51]

In Davis *et al.* (2015), the median duration of treatment was not reported. The reasons for discontinuation of crizotinib treatment are presented in Table 28.

Table 28: Reasons for discontinuation of crizotinib treatment in Davis *et al.* (2015)

Reason for discontinuation of crizotinib treatment, n (%)	Patients receiving first-line crizotinib (n=137)
Death	1 (2.4)
Disease progression following initial response	90 (66.2)
Disease progression following no initial response	14 (10.3)
Treatment-related toxicity or side effect	2 (1.5)
Patient request	25 (18.4)
Other reason	4 (2.9)
Unknown	3 (2.2)

Source: adapted from Davis *et al.* (2015) – Table 2 [133]

Baseline characteristics

The baseline characteristics of patients included in PROFILE 1001 and Davis *et al.* (2015) are presented in Table 29.

The baseline characteristics of patients enrolled in PROFILE 1001 were broadly similar to those of patients included in PROFILE 1014 (see Table 20); patients in both trials had a median age of 52–54 years old, were predominantly never-smokers and typically had an ECOG performance status of 0 or 1. A notable difference between PROFILE 1001 and PROFILE 1014 was that patients in PROFILE 1001 were not all treatment-naïve; of those patients included in PROFILE 1001, only 24/149 patients (16%) received crizotinib in the first-line setting.

Compared to the baseline characteristics of patients in PROFILE 1001 and PROFILE 1014, in the study by Davis *et al.* (2015) of crizotinib treatment in a real-world setting, a higher proportion of patients treated in the first-line were male (68% in Davis et al versus 49% in PROFILE 1001 and 38% in PROFILE 1014) and former/present smokers (52%/10% in Davis et al versus 28%/<1% in PROFILE 1001 and 32%/4% in PROFILE 1014). In addition, patients were generally older (median age 60 years) and had higher ECOG performance status (22% ≥ ECOG 2 in Davis *et al.* [2015] versus 12%≥2 ECOG 2 in PROFILE 1001 and 5% in PROFILE 1014). A total of 137 out of 212 patients (65%) included in the medical chart review by Davis *et al.* (2015) received first-line crizotinib.

It should also be noted that this study was conducted entirely in the USA and Canada; no patients were from the UK. However, given the perceived generalisability of results from targeted therapies such as crizotinib due to the nature of the ALK translocation as the oncogenic driver in this indication, this study is still considered to be relevant for inclusion in this submission.

Finally, in both the PROFILE 1001 and Davis *et al.* (2015) studies, the vast majority of patients had tumours of non-squamous histology.

Table 29: Baseline characteristics of participants in PROFILE 1001 and Davis *et al.* (2015)

Characteristic	PROFILE 1001 Patients receiving crizotinib (n=149)*	Davis *et al.* (2015) Patients receiving first-line crizotinib (n=137)

Characteristic	PROFILE 1001 Patients receiving crizotinib (n=149)*	Davis *et al.* (2015) Patients receiving first-line crizotinib (n=137)
Age – years		
Median (range)	52 (21–86)	*[Academic / commercial in confidence information removed]*
Sex – n (%)		
Male	73 (49)	93 (68)
Female	76 (51)	*[Academic / commercial in confidence information removed]*
Ethnic origin – n (%)		
White	95 (64)	103 (75)
Asian	41 (28)	17 (12)†
Other	13 (9)	16 (12)‡
Smoking status – n (%)		
Never	106 (71)	51 (37)
Former	42 (28)	*[Academic / commercial in confidence information removed]*
Present	1 (<1)	*[Academic / commercial in confidence information removed]*
Histological findings – n (%)		
Adenocarcinoma	144 (97)	*[Academic / commercial in confidence information removed]*
Large-cell carcinoma	1 (<1)	*[Academic / commercial in confidence information removed]*
Squamous-cell carcinoma	2 (1)	*[Academic / commercial in confidence information removed]*
Other	2 (1)	*[Academic / commercial in confidence information removed]*
ECOG performance status – n (%)		
0	56 (38)	*[Academic / commercial in confidence information removed]*
1	75 (50)	*[Academic / commercial in confidence information removed]*
≥2	18 (12)	30 (22)

Characteristic	PROFILE 1001 Patients receiving crizotinib (n=149)*	Davis *et al.* (2015) Patients receiving first-line crizotinib (n=137)
Number of previous treatment regimens for advanced or metastatic disease – n (%)		
0	24 (16)	137 (100)
1	47 (32)	-
2	31 (21)	-
3	19 (13)	-
≥4	28 (19)	-

* Baseline characteristics for PROFILE 1001 are presented for the entire study population, including patients who received crizotinib as a second or subsequent line of therapy. Twenty-four patients received crizotinib in the first-line setting.
† Includes patients of Asian and Pacific Islander ethnicity
‡ Ethnicity for one patient was unknown; all 16 patients classified as 'Other' here were of African/Black ethnicity

Abbreviations: ECOG: Eastern Co-operative Oncology Group
Source: adapted from Camidge *et al.* (2012) – Table 1 for PROFILE 1001 [51]; and Davis *et al.* (2015) – Table 1 [133] and*[Academic / commercial in confidence information removed]*

4.11.6 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study identified in section 4.11.1 should be quality appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The quality assessment will be validated by the Evidence Review Group.

4.11.7 Describe the methods used for assessing risk of bias of individual studies (including whether this was done at the study or outcome level) and how this information is to be used in any data synthesis. For the quality assessments of non-randomised and non-controlled evidence, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). This includes information on a number of initiatives aimed at improving the quality of research reporting.

4.11.8 If there is more than 1 non-randomised or non-controlled study, tabulate a summary of the responses applied to each of the quality assessment criteria.

The study designs of PROFILE 1001 and Davis *et al.* (2015) were assessed using the Downs and Black checklist, which has been recommended as being suitable for use in systematic reviews that include non-randomised studies.[100, 138, 139]

The results of the quality appraisal of both studies are provided in **Error! Reference source not found.** in **Error! Reference source not found.**. As may be expected for a single-arm trial or retrospective analysis, neither PROFILE 1001 nor the study by Davis *et al.* (2015) scored highly in terms of internal validity mostly due to lack of blinding of participants and assessors. However, in all other respects, both studies were deemed to be of reasonably high quality.

Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

PROFILE 1001

At the time of the latest data cut-off (1st June 2011), the median duration of follow-up for PFS in PROFILE 1001 was 16.3 months (95% CI, 13.8 to 18.4) for all patients who received at least one dose of crizotinib (n=149).[51] Median PFS for patients who received first-line crizotinib was 18.3 months (95% CI, 8.3 to 'not reached').[51] It should be noted that the tails of the PFS curves in the whole population and in the 24 first-line patients appeared to demonstrate prolonged PFS in some patients, consistent with that seen for PROFILE 1014 (Section 4.7.1). However, these result should be considered in light of the small sample size of patients treated in the first-line setting (n=24).

Of those patients included in the response evaluable population, 22 patients in PROFILE 1001 had not received any prior systemic treatment for advanced or metastatic disease. The ORR for these previously untreated patients who received first-line crizotinib was 63.6% (95% CI, 40.7 to 82.28), as compared to 74% (95%, 67 to 81) reported in PROFILE 1014 (n=172).[51]

Davis et al. (2015)

The results of the medical chart review conducted by Davis et al. (2015) for patients who received crizotinib in the first-line setting were largely consistent with those reported in PROFILE 1014 (see Table 30), suggesting that the efficacy of crizotinib demonstrated in the context of the PROFILE 1014 clinical trial setting can be translated into clinical effectiveness for patients in a real-world setting. For example, ORR is similar between studies, with 69% and 74% patients achieving a best response of CR or PR in Davis et al. (2015) and PROFILE 1014, respectively.

Minor differences between study results may be due to the differences in patient baseline characteristics – with patients in PROFILE 1014 being typically younger, less likely to be current smokers and less likely to have an ECOG performance status of ≥2.

Kaplan-Meier plots for PFS and OS (from initiation of crizotinib) by treatment line from the study by Davis et al. (2015) are presented in **Error! Reference source not found.**.

Table 30: Clinical effectiveness results from Davis *et al.* (2015) and PROFILE 1014 – in patients who received first-line crizotinib

Outcomes	PROFILE 1014 (n=172)	Davis *et al.* (2015) (n=137)
Median PFS, months (95% CI)	10.9 (8.3 to 13.9)	*[Academic / commercial in confidence information removed]*
ORR, % (95% CI)	74 (67–81)	69 (N/A)
Median OS, years (95% CI)	Not reached	*[Academic / commercial in confidence information removed]*
1-year survival rate, % (95% CI)†	84 (77 to 89)	85 (79 to 91)
2-year survival rate, % (95% CI)†	Not reported	47 (35 to 60)

† Based on Kaplan-Meier estimates

Abbreviations: CI: confidence intervals; N/A: not applicable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.
Sources: data are presented from Davis *et al.* (2015) [133] *[Academic / commercial in confidence information removed] et al[Academic / commercial in confidence information removed]*and Solomon *et al.* (2014a) [2]

Summary of crizotinib safety and tolerability

- Crizotinib was well-tolerated by patients in PROFILE 1014; AEs from any cause associated with permanent discontinuation of study treatment occurred in 12% and 14% of patients in the crizotinib and chemotherapy groups, respectively.
- AEs that are known to occur with crizotinib can be primarily managed using dose reductions, allowing patients to continue benefiting from the clinical and HRQoL improvements associated with crizotinib.
- The safety profile of crizotinib is distinct to that of chemotherapy and an improved tolerability profile relative to chemotherapy may contribute to improved HRQoL with crizotinib treatment.

PROFILE 1014 safety analysis: crizotinib versus chemotherapy

- The most frequently reported AEs in the crizotinib group were vision disorders (71%); grade 3 or 4 vision disorders were reported in <1% of patients and were managed by dose reductions or interruptions.
- Grade 3 or 4 elevations in transaminase levels occurred at a higher incidence in the crizotinib group than the chemotherapy group (14% vs. 2%); in the majority of cases these were managed by dose reductions or interruptions.
- Treatment-emergent AE rates and discontinuation rates due to AEs were similar between treatment groups, despite longer treatment duration with crizotinib (median duration of treatment: 10.9 months vs. 4.1 months).

Pooled safety analysis from across clinical trials

- A pooled safety analysis provides data from 1,669 patients who have received crizotinib across four clinical trials.
- The safety profile of crizotinib is consistent across clinical trials; no new safety concerns emerged during PROFILE 1014.

4.12 Adverse reactions

4.12.1 Evidence from comparative RCTs and regulatory summaries is preferred, but findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse reactions commonly associated with the comparator, or that the occurrence of adverse reactions is not statistically significantly different to those associated with other treatments.

The incidence of AEs in patients receiving crizotinib in PROFILE 1014 is presented alongside AEs for patients in the chemotherapy group in Section 4.12.2. Safety analysis of crizotinib-treated patients in the phase I non-randomised trial PROFILE 1001 is also presented.

Pooled safety data for 1,669 patients who have received crizotinib across the respective clinical trial programme is also presented in Section 4.12.3, as reported in the SmPC.[6]

4.12.2 In a table, summarise adverse reactions reported in the studies listed in section 4.2. For each intervention group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.

Safety analysis in PROFILE 1014

In PROFILE 1014, the analysis of AEs was conducted in the as-treated (AT) population which included only those patients who had received at least one dose of the study drug they had been randomly assigned. 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.[102] In addition, only events that occurred prior to crossover were considered for patients who crossed over from the chemotherapy group to crizotinib.

The median duration of study treatment was considerably greater in the group of patients receiving crizotinib than in the chemotherapy group (see Table 31). Unless stated otherwise the analysis of safety in PROFILE 1014 was not adjusted for the duration of treatment.

Table 31: Median duration of study treatment in PROFILE 1014

Treatment group	Duration of study treatment, median (range)	Number of cycles started, median (range)
Crizotinib (n=171)	10.9 months (0.4 to 34.3)	16 cycles (1 to 50)
Chemotherapy (n=169)	4.1 months (0.7 to 6.2)	6 cycles (1 to 6)*

* A maximum of 6 cycles of chemotherapy was permitted.
Median duration of study treatment was defined as the total number of dosing days from date of first dose to date of last dose (or date of cut-off, whichever is earlier) +1, counting gaps for the crizotinib arm and including 21 days for last cycle for the chemotherapy arm.[3]

Source: adapted from information presented in Solomon *et al.* (2014a) [2]

Generally, crizotinib was well-tolerated by patients in PROFILE 1014; AEs from any cause that were associated with permanent discontinuation of study treatment occurred in 12% and 14% of patients in the crizotinib and chemotherapy groups, respectively.[2] Of those AEs associated with permanent discontinuations, 5% and 8% were judged to have been related to study treatment by the investigator, for each treatment group, respectively.[2] A summary of treatment-emergent AEs reported in PROFILE 1014 is presented in Table 32.

AEs of any cause which occurred in at least 15% of patients in either treatment group are presented in Table 33. The top three AEs of any grade reported in PROFILE 1014 for which the incidence was at least 5 percentage points greater in the crizotinib group than in the chemotherapy group included vision disorder (71% patients in the crizotinib group vs 9% in the chemotherapy group), diarrhoea (61% vs 13%), and oedema (49% vs 12%).[2] Conversely, the top three AEs of any grade that occurred with a frequency greater than 5% in the chemotherapy group than in the crizotinib group included fatigue (38% vs 29%), anaemia (32% vs 9%), and neutropenia (30% vs 21%) (see Table 33).[2] Vision disorders were the most commonly reported AE with crizotinib (71%); the majority of events were less than grade 3 in severity*[Academic / commercial in confidence information removed]* [3] Generally, crizotinib appeared to be associated with a safety profile that was distinct to that observed in the chemotherapy group.

All grade 3 or 4 AEs that occurred in at least 2% patients in either treatment group are presented in Table 34. Elevated levels of aminotransferases and neutropenia accounted for the majority of grade 3 and 4 events that occurred in the crizotinib group. Grade 3 and 4 elevations of aminotransferase levels that occurred in 24 (14%) patients in the crizotinib group and 4 (2%) patients in the chemotherapy group were managed primarily with dose interruptions or dose reductions.[2] Four hepatic events resulted in permanent discontinuation of study treatment in the crizotinib group: three events involved elevated aminotransferase levels only; and one event involved a grade 2 drug-induced liver injury that met the criteria for Hy's law.[2, 140] No deaths from hepatic dysfunction occurred. Grade 3 or 4 neutropenia occurred at a similar frequency in both treatment groups (11% in the crizotinib group and 15% in the chemotherapy group), with no cases of febrile neutropenia reported for patients receiving crizotinib.[2] Grade 3 or 4 events that occurred at a greater frequency in the chemotherapy group relative to the crizotinib group included anaemia (9% vs. 0), thrombocytopenia (7% vs. 0), leukopenia (5% vs. 2%), and hyponatremia (2% vs. 1%) (see Table 34).[108]

As noted above, reported results of the safety analyses have not been adjusted for the difference in duration of treatment exposure that occurred in the trial.

Table 32: Treatment-emergent adverse events in the AT population in PROFILE 1014

Adverse event, No. of patients (%)*	Crizotinib (n=171)*		Chemotherapy† (n=172)*	
	All causality	Treatment-related	All causality	Treatment-related
Number of patients:‡				
With AEs	170 (99.4)	168 (8.2)	168 (99.4)	157 (92.9)
With SAEs§	58 (33.9)	18 (10.5)	47 (27.8)	15 (8.9)
With Grade 3 or 4 AEs	97 (56.7)	60 (35.1)	87 (51.5)	66 (39.1)
With Grade 5 AEs	20 (11.7)	0	4 (2.4)	0
With AEs associated with:				
Permanent discontinuation	21 (12.3)	8 (4.7)	24 (14.2)	14 (8.3)
Dose reduction	11 (6.4)	9 (5.3)	14 (8.3)	14 (8.3)
Temporary discontinuation	70 (40.9)	59 (34.5)	58 (34.3)	51 (30.2)

* No. of patients in the AT population
† Only events that occurred before crossover to crizotinib are included
‡ Patients are only counted once per treatment in each row.
§ According to investigator assessment.
Incidence of AEs were unadjusted for duration of treatment.

Source: Pfizer Clinical Study Report (16th June 2015): adapted from Table 46 [3]

Table 33: Common adverse events from any cause in the AT population in PROFILE 1014

Adverse event, No. of patients (%)*	Crizotinib (n=171)*		Chemotherapy† (n=169)*	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Higher frequency in the crizotinib group				
Vision disorder‡	122 (71)	1 (1)	16 (9)	0
Diarrhoea	105 (61)	4 (2)	22 (13)	1 (1)
Oedema§	83 (49)	1 (1)	21 (12)	1 (1)
Vomiting	78 (46)	3 (2)	60 (36)	5 (3)
Constipation	74 (43)	3 (2)	51 (30)	0
Elevated aminotransferases§	61 (36)	24 (14)	22 (13)	4 (2)
Upper respiratory infection§	55 (32)	0	21 (12)	1 (1)
Abdominal pain§	45 (26)	0	20 (12)	0
Dysgeusia	45 (26)	0	9 (5)	0
Headache	37 (22)	2 (1)	25 (15)	0
Pyrexia	32 (19)	0	18 (11)	1 (1)
Dizziness§	31 (18)	0	17 (10)	2 (1)
Pain in extremity	27 (16)	0	12 (7)	0
Higher frequency in the chemotherapy group				
Fatigue	49 (29)	5 (3)	65 (38)	4 (2)
Neutropenia§	36 (21)	19 (11)	51 (30)	26 (15)
Stomatitis§	24 (14)	1 (1)	34 (20)	2 (1)
Asthenia	22 (13)	0	41 (24)	2 (1)
Anaemia§	15 (9)	0	54 (32)	15 (9)
Leukopenia§	12 (7)	3 (2)	26 (15)	9 (5)
Thrombocytopenia§	2 (1)	0	31 (18)	11 (7)
Similar frequency in the two treatment groups				
Nausea	95 (56)	2 (1)	99 (59)	3 (2)
Decreased appetite	51 (30)	4 (2)	57 (34)	1 (1)
Cough§	39 (23)	0	33 (20)	0
Neuropathy§	35 (20)	2 (1)	38 (22)	0
Dyspnoea§	30 (18)	5 (3)	26 (15)	4 (2)

Includes AEs that were reported in 15% or more of patients in either treatment group; higher frequency indicates a difference of 5 percentage points or more between groups; similar frequency indicates a difference of less than 5 percentage points between groups.
* No. of patients in the AT population
† Only events that occurred before crossover to crizotinib are included
‡ The category of vision disorder comprised a cluster of adverse events including (in descending order of frequency in the crizotinib group) visual impairment, photopsia, blurred vision, vitreous floaters, reduced visual acuity, diplopia, and photophobia.
§ This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes
Incidence of AEs were unadjusted for duration of treatment.

Source: adapted from Solomon *et al.* (2014a) – Table 3 [2]

Table 34: Grade 3 or 4 events from any cause in the AT population in PROFILE 1014

Grade 3 or 4 adverse event,	Crizotinib (n=171)* No. of patients (%)	Chemotherapy† (n=169)* No. of patients (%)
Higher frequency in the crizotinib group relating to Grade 3 or 4 adverse events		
Elevated transaminase‡	24 (14)	4 (2)
Decreased appetite	4 (2)	1 (1)
Diarrhoea	4 (2)	1 (1)
Electrocardiogram QC prolonged	4 (2)	0
Higher frequency in the chemotherapy group relating to Grade 3 or 4 adverse events		
Leukopenia‡	3 (2)	9 (5)
Hyponatremia	1 (1)	4 (2)
Anaemia‡	0	15 (9)
Thrombocytopenia‡	0	11 (7)
Similar frequency in the two treatment groups relating to Grade 3 or 4 adverse events		
Neutropenia‡	19 (11)	26 (15)
Pulmonary embolism‡	11 (6)	11 (7)
Dyspnoea‡	5 (3)	4 (2)
Fatigue	5 (3)	4 (2)
Pneumonia	4 (2)	2 (1)
Hypophosphatemia	4 (2)	2 (1)
Vomiting	3 (2)	5 (3)
Hypokalemia	3 (2)	4 (2)

Includes grade 3 or 4 AEs that were reported in 2% or more of patients in either treatment group; higher frequency indicates a two-fold or greater difference between groups; similar frequency indicates a less than two-fold difference between groups.
* AT population
† Only events that occurred before crossover to crizotinib are included
‡ This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes
Incidence of AEs were unadjusted for duration of treatment.

Source: adapted from Solomon *et al.* (2014a) – Supplementary material: Table S4 [108]

Deaths from any cause reported in PROFILE 1014 (before crossover)

Deaths that occurred from any cause between treatment start and 28 days after the last administration of study treatment are summarised in Table 35 (only deaths that occurred before crossover to crizotinib are included). The higher number of deaths due to disease progression in the crizotinib group that occurred whilst receiving study treatment may be explained by the greater duration of study treatment in this group. No deaths were considered to be related to study treatment with the exception of one patient who died of pneumonitis after crossing over to receive crizotinib.[2]

Table 35: Deaths from any cause in the AT population in PROFILE 1014

Grade 5 (death) adverse events, No. of patients (%)*	Crizotinib (n=171)*	Chemotherapy† (n=169)*
Disease progression	16 (9)‡	1 (1)
Other:		
Septic shock	2 (1)	0
Acute respiratory failure	1 (1)	0
Diabetic ketoacidosis	1 (1)	0
Cardiac arrest	0	1 (1)
Completed suicide	0	1 (1)
Haemoptysis	0	1 (1)
Total events	20 (12)	4 (2)

Includes grade 5 events (deaths) that occurred between the start of treatment and 28 days after the last administration of study treatment.
* AT population
† Only events that occurred before crossover to crizotinib are included; one patient died of pneumonitis after crossover to crizotinib which was considered to be treatment-related
‡ Two patients included although the grade 5 event occurred greater than 28 days after the last dose of crizotinib
Incidence of deaths were unadjusted for duration of treatment.

Source: adapted from Solomon *et al.* (2014a) – Supplementary material: Table S5 [108]

Safety analysis in PROFILE 1001

The reporting of AEs in PROFILE 1001 is included in the pooled safety analysis presented in the Section 4.12.3. The safety profile observed in PROFILE 1001 was consistent with that reported in PROFILE 1014 and across the crizotinib clinical trial program.

The most frequent AEs of any grade in PROFILE 1001 were visual effects (64%), nausea (56%) and diarrhoea (50%). The majority of treatment-related AEs were of low severity; grade 3 or 4 events occurring in 24% of patients. Ten patients (7%) required a dose reduction due to treatment-related AEs and three patients discontinued permanently due treatment-related AEs (one with grade 4 and one grade 2 pneumonitis, and one patient with grade 3 raised alanine aminotransferase levels). Out of the 46 deaths that occurred in PROFILE 1001, none were judged to be treatment related.[51]

Full details of treatment-related AEs that occurred in at least 10% of patients included in PROFILE 1001 are presented in **Error! Reference source not found.** in **Error! Reference source not found.**.

4.12.3 Provide details of any studies that report additional adverse reactions to those reported in section 4.2.

Pooled safety analysis of crizotinib clinical trials

The safety and tolerability of crizotinib in patients with ALK-positive, advanced NSCLC has been evaluated across the clinical trial program for crizotinib (see Table 36 for a description of trials). A pooled safety analysis of patients treated with crizotinib in these trials, as described in the SmPC, is presented below. Collectively, this analysis includes data from 1,669 patients who have received crizotinib and so provides substantial supportive evidence for the safety and tolerability of crizotinib.[6]

Table 36: Summary of crizotinib clinical trials from which pooled safety data are reported

Study name	Study design	Crizotinib line of treatment	Comparator
PROFILE 1014 [2]	Phase III randomised controlled trial	First-line	Pemetrexed plus either cisplatin or carboplatin
PROFILE 1007 [31]	Phase III randomised controlled trial	Second-line	Pemetrexed or docetaxel
PROFILE 1005 [50]	Phase II single-arm trial	Second-line or later	None
PROFILE 1001 [51]	Phase I single arm-trial – dose escalation study and expanded cohort	First, second and later lines*	None

* Only 24/149 patients included in PROFILE 1001 (at the latest 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.

The frequency of AEs reported across these four trials is presented in Table 37 by system organ class and frequency categories, defined using the following convention: very common (greater than or equal to 1/10); common (greater than or equal to 1/100 to less than 1/10), uncommon (greater than or equal to 1/1,000 to less than 1/100) or rare (greater than or equal to 1/10,000 to less than 1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequently reported AEs experienced by patients receiving crizotinib were vision disorders (62%), nausea (57%) and diarrhoea (54%), as was observed in PROFILE 1014. All-causality AEs associated with permanent treatment discontinuation across the four trials occurred in 298 (18%) patients of which the most frequent (≥1%) were interstitial lung disease (1.4%) and elevated transaminases (1%).[6] As noted in the CHMP's extension of indication variation assessment report: "*no major differences are highlighted in terms of AE frequency and severity when crizotinib is administered as first-line or in patients previously treated.*"[8]

Table 37: Adverse drug reactions based on pooled data from PROFILE 1001, 1005, 1007 and 1014

System Organ Class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Blood and Lymphatic System Disorders	Neutropenia* (22%) Anaemia* (15%) Leukopenia* (15%)		
Metabolism and Nutrition Disorders	Decreased appetite (30%)	Hypophosphataemia (6%)	
Nervous System Disorders	Neuropathy* (25%) Dysgeusia (21%		
Eye Disorders	Vision disorder* (62%)		
Cardiac Disorders	Dizziness* (25%) Bradycardia* (12%)	Cardiac failure* (1%) Electrocardiogram QT prolonged (4%) Syncope (3%)	
Respiratory, Thoracic and Mediastinal Disorders		Interstitial Lung Disease* (3%)	
Gastrointestinal Disorders	Vomiting (51%) Diarrhoea (54%) Nausea (57%) Constipation (43%) Abdominal pain* (21%)	Dyspepsia (8%)	Gastrointestinal perforation* (<1%)
Hepatobiliary Disorders	Elevated transaminases* (32%)	Blood alkaline phosphatase increased (7%)	Hepatic failure (<1%)
Skin and Subcutaneous Tissue Disorders	Rash (13%)		
Renal and Urinary Disorders		Renal cyst* (3%)	
General Disorders and Administration Site Conditions	Oedema* (49%) Fatigue (30%)		

* These items comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes

Source: SmPC – Table 3 [6]

4.12.4 Provide a brief overview of the safety of the technology in relation to the decision problem.

Safety data from PROFILE 1014 demonstrated that crizotinib is generally well-tolerated by patients receiving first-line crizotinib for ALK-positive, advanced NSCLC, with AEs from any cause associated with permanent discontinuation of study treatment occurring at a similar rate in both the crizotinib and chemotherapy groups (12% and 14%), respectively. This was supported by the opinion of four UK clinical experts consulted at an advisory board, who noted no particular concerns relating to AEs and stated that most of the AEs observed with crizotinib could be managed with dose reductions, whilst still maintaining the clinical and HRQoL benefits associated with crizotinib treatment.

The most common AEs that occurred in the crizotinib group in PROFILE 1014 were vision disorders; these were mostly Grade 1 or 2 in severity and could be managed with concomitant medication or subsequent dose reduction. Neutropenia (11%) and elevated aminotransferase levels (14%) accounted for the majority of grade 3 or 4 AEs in the crizotinib group and were primarily managed using dose interruptions or dose reductions.[2] Between-group comparisons of the incidence of AEs should be considered in light of the considerably longer treatment duration in the crizotinib group (see Table 31).

The safety profile of crizotinib observed in PROFILE 1014 is consistent with that observed in previous clinical trials with crizotinib, as demonstrated in the pooled safety analysis across four crizotinib trials (see Section 4.12.3). The most frequently reported AEs experienced by patients receiving crizotinib across these trials were vision disorders (62.2%), nausea (56.6%) and diarrhoea (54.3%), as was observed in PROFILE 1014.[6] No new safety concerns are therefore evident with crizotinib as a first-line treatment.[8]

Finally, the improved symptom-related PRO scores observed in PROFILE 1014 in the crizotinib group relative to chemotherapy (see Section 4.7.2) may be reflective of improved tolerability with crizotinib and a greater avoidance of toxicities that are associated with chemotherapy. Crizotinib therefore represents an alternative treatment option for patients with ALK-positive, advanced NSCLC that is associated with a distinct and improved safety profile in comparison to the current standard of care therapy.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 A statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Clinical benefits

PROFILE 1014 provides robust, randomised clinical data for the direct comparison of crizotinib versus pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin) for the first-line treatment of adults with ALK-positive advanced NSCLC. Pemetrexed plus platinum-based chemotherapy is considered to be the most relevant comparator for crizotinib in this patient population and is currently representative of routine clinical practice in the absence of targeted therapies within the first-line setting to treat the majority of typical ALK-positive NSCLC patients in the UK (see Section 3.3).

Progression-free survival

In PROFILE 1014, crizotinib was associated with prolonged PFS relative to pemetrexed plus platinum-based chemotherapy in patients with previously untreated ALK-positive, advanced NSCLC. Improvements in PFS were significant (HR, 0.45; 95% CI, 0.35 to 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).

Furthermore, in the study by Davis *et al.* (2015), the median PFS observed for ALK-positive patients receiving first-line crizotinib in a real-world setting were broadly aligned with those reported in PROFILE 1014 (9.6 months in first line patients in Davis *et al*. (2015) vs. 10.9 months in PROFILE 1014), suggesting that the clinical benefits of crizotinib are readily transferable to clinical practice.

Objective response rate

Crizotinib has demonstrable anti-tumour activity in ALK-positive tumours via the targeted inhibition of ALK fusion proteins and oncogenic variants.[62] In PROFILE 1014, the majority of patients treated with crizotinib achieved an objective response (74%) — this represented a significantly greater proportion of patients relative to pemetrexed plus platinum-based chemotherapy (45%) (P<0.001).[2] The response rate with crizotinib observed in PROFILE 1014 aligns with the ORR achieved by patients receiving first-line crizotinib in a real-world setting (69%), as reported by Davis *et al.* (2015).[133]

An improved tumour response was also reflected in the greater median best percentage reduction in target lesions achieved by patients treated with crizotinib in PROFILE 1014 compared to those treated with chemotherapy (*[Academic / commercial in confidence information removed]*).[39] 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.

Patient-reported outcomes and HRQoL

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, that is reflective of beneficial effects of greater tumour reduction. A positive association between tumour response and HRQoL in NSCLC has been proposed previously.[70, 141]

Overall survival

Median OS was not reached in PROFILE 1014 with only 26% of patients having died at the time of PFS analysis. Crizotinib was associated with a favourable hazard ratio at the data cut-off, though this was not statistically significant (unadjusted HR, 0.82; 95% CI, 0.54 to 1.26; P=0.36). However, the high-rate of crossover from the chemotherapy group to crizotinib (70%) is believed to have confounded estimates of OS in the chemotherapy group.

Crossover-adjusted analyses, conducted using methods recommended by NICE, showed a highly consistent range of HRs for death from 0.571 to 0.674, across nine parametric models

using three appropriate methods of analyses (RPSFTM, two-stage Weibull and IPE). The median value from this range is selected for the base case (HR = 0.624; 95% CI 0.405, 0.963; p=0.0158) as it best reflects the range in the absence of any methodological or clinical reason to select either of the extreme estimates in preference to the other. These results suggest that crizotinib is associated with improved survival relative to chemotherapy, which is explored further in survival analyses described in Section 5.3.4. The modelled estimates of median OS with crizotinib presented in Section 5.7.2 are comparable to those reported by Davis *et al.* (2015) for patients treated with first-line crizotinib in a real-world setting.

Adverse events

Crizotinib was generally well-tolerated by patients in PROFILE 1014. Vision disorders were the most common AEs in the crizotinib group in PROFILE 1014, but they were mostly grade 1 or 2 in severity and did not cause any permanent or temporary discontinuations to crizotinib treatment. Monitoring processes are already described for known hepatic events, and in PROFILE 1014 these were managed primarily with dose reductions and interruptions. The safety profile of crizotinib observed in PROFILE 1014 was consistent with that reported across four crizotinib trials (1,669 patients), as detailed in the pooled analysis presented in Section 4.12.3. As noted by UK clinical experts consulted at an advisory board, the majority of AEs known to be associated with crizotinib can be managed by dose reductions, thus allowing continuation of crizotinib treatment and the maintenance of the clinical benefits and improved HRQoL associated with crizotinib.

In conclusion, crizotinib has demonstrated a distinct safety profile from that of standard of care chemotherapy and the safety profile of crizotinib should be considered as supportive of the HRQoL improvements observed with use of crizotinib during the PROFILE 1014 trial.

End-of-life criteria

Evidence to support the consideration of first-line 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 38. The relevant sources and sections within this submission from which information has been derived are also detailed.

A benefit in OS with crizotinib relative to pemetrexed plus platinum-based chemotherapy has been demonstrated in crossover-adjusted analyses of PROFILE 1014 (see Section 4.7.2). Modelled estimates of OS using these crossover-adjusted analyses suggest that crizotinib is associated with an OS benefit of greater than 3-months compared to pemetrexed plus platinum-based chemotherapy, and that life-expectancy with first-line chemotherapy may be reasonably assumed to be less than 24-months (see Section 5.7.2), as is stipulated by NICE's end-of-life criteria.[42]

Moreover, survival data from previous studies and clinical estimates from UK clinical experts support the assumption that life-expectancy with first-line standard of care is less than 24-months for patients with ALK-positive, advanced NSCLC (see Table 10).

Table 38: 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 3.4, there is a paucity of estimates of OS with current chemotherapy (pemetrexed plus platinum-based therapy) in the ALK-positive NSCLC population specifically. Estimates from four UK clinical experts consulted at an advisory board suggested that for ALK-positive patients in the UK not receiving crizotinib, average life-expectancy is estimated at 15 months with current standard of care. In one retrospective analysis of previously treated and untreated ALK-positive patients, median OS from 36 crizotinib-naïve patients was 20 months undergoing treatment with various chemotherapy regimens.[30] Data from a number of studies in the NSCLC population, together with expert opinion, suggests that it is reasonable to assume that life expectancy with first-line pemetrexed plus platinum-based therapy ranges from 10.4 to 20 months (Table 10). In the PROFILE 1014 study of ALK-positive NSCLC patients, OS estimates for the chemotherapy group were confounded by high levels of crossover (see Section 4.5). Once adjusted for crossover, crizotinib exhibited a consistent estimate of relative OS benefit versus pemetrexed plus platinum-based therapy, with hazard ratios for death from multiple validated established crossover-adjusted models all lying in a narrow range (HR, 0.571 to 0.674) (see Section 4.7.2). Modelled estimates of OS with pemetrexed plus platinum-based chemotherapy suggest a median and mean life-expectancy of 13.8 and 17.9 months, respectively (see Section 5.7.2). Based on the available evidence, the life expectancy of previously untreated ALK-positive NSCLC patients is therefore expected to be below 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	As described above, crossover-adjusted analyses of OS in PROFILE 1014 showed a highly consistent range of HRs for death from 0.571 to 0.674, and thus demonstrated a difference in OS in favour of crizotinib versus chemotherapy (see Section 4.7.2). Modelled estimates of OS suggest a median and mean extension in life-expectancy of 7.9 and 11.1 months, respectively (see Section 5.7.2) with crizotinib versus pemetrexed plus platinum-based chemotherapy. In addition, a greater OS benefit with crizotinib is supported by the significant difference in PFS between treatment groups observed in PROFILE 1014. In the previous appraisal of crizotinib as a second-line therapy, it was acknowledged that PFS is considered a conservative estimate of OS: *"*[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."* **Source:** (NICE TA296) Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene [5]

	Crizotinib demonstrated clear benefits in terms of tumour response (see Section 4.7.2) in PROFILE 1014, 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 significant PFS benefit with crizotinib should be considered an absolute minimum estimate of overall survival benefit in light of a lack of certainty on overall survival estimates. This would therefore estimate a minimum benefit to survival associated with crizotinib of 3.9 months, which therefore meets the NICE criteria for end of life.
The treatment is licensed or otherwise indicated for small patient populations	Estimated from various sources – see Section 3.4. Estimated number of non-squamous, ALK-positive, advanced NSCLC patients expected to receive first-line crizotinib in England and Wales = 459 patients per year As detailed in Section 3.1, it is rare that an ALK-positive patient of squamous histology would present.

4.13.2 A discussion of the strengths and limitations of the clinical evidence base for the technology. This should include the following: A brief statement on the internal validity of the studies included in the clinical evidence base. A brief statement on the external validity of the studies included in the clinical evidence base. Include the relevance of the evidence base to the decision problem and the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice. Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The clinical evidence base for first-line crizotinib is largely drawn from the results of the phase III randomised controlled trial PROFILE 1014. The strengths and weaknesses of PROFILE 1014 as a source of evidence with regards to internal validity is discussed below.

Strengths of the evidence

PROFILE 1014 is an international, multicentre, randomised controlled trial and the first to investigate crizotinib as a first-line therapy for patients with ALK-positive, advanced NSCLC. The trial provides randomised evidence across a reasonably sized patient population (340 treated patients in total) and has been formally assessed as being of high quality – see Section 4.6.

The internal validity of PROFILE 1014 is supported by the following:

- Patients enrolled in PROFILE 1014 were appropriately assigned to treatment groups with randomisation stratified according to ECOG performance status, race, and presence or absence of brain metastases at baseline.
    - Baseline characteristics were similar between treatment groups
- Although blinding of study treatment was not possible due to the differences in drug administration, assessments of tumour response were evaluated by independent, central, radiological review which was blinded to treatment group
- The outcomes assessed in the PROFILE 1014 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

Supportive evidence for the clinical effectiveness of crizotinib as a first-line treatment in adults with ALK-positive NSCLC patients is presented in Section 4.11, and is based on phase I clinical trial data from PROFILE 1001 and a retrospective medical chart review of patients treated with first-line crizotinib in the USA and Canada (Davis *et al. [*2015]). These studies provide valuable supportive evidence for the use of first-line crizotinib in patients with ALK-positive, advanced NSCLC. In addition evidence from the chart review conducted by Davis *et al.* (2015) demonstrates that the outcomes observed in a real-world setting are similar to those observed within a trial environment.

The evidence base for crizotinib in terms of safety and tolerability is also supported by pooled safety data from 1,669 ALK-positive patients who have received crizotinib as part of the wider clinical trial programme.

Generalisability of PROFILE 1014 results to patients in the UK and the relevance of the evidence presented to the decision problem

PROFILE 1014 is highly relevant to the decision problem in terms of patient population, choice of comparator and outcomes considered, as detailed below:

- PROFILE 1014 included patients with previously untreated, confirmed ALK-positive, advanced NSCLC, which is the patient population under consideration in this submission. As the majority of patients encountered in clinical practice are expected to have non-squamous tumour histology (see Section 3.1), the inclusion of only non-squamous patients in PROFILE 1014 is considered to be reflective of the ALK-positive patient population in the UK.
- PROFILE 1014 provides direct comparative evidence for first-line crizotinib versus pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin). Pemetrexed-based chemotherapy is considered standard of care for the first-line treatment of non-squamous, advanced NSCLC in the UK – as validated by UK clinical experts consulted at an advisory board and recommended by NICE in TA181.[83] Given the predominance of non-squamous tumour histology in ALK-positive patients, pemetrexed plus platinum-based chemotherapy therefore represents the primary comparator for crizotinib in this submission and is listed in the final scope issued by NICE for this appraisal.[1]
- All outcomes listed in the final scope issued by NICE for this appraisal were reported in PROFILE 1014 and are presented here as part of this submission.[1] In addition, EQ-5D HRQoL data was collected directly from patients in the trial, as is preferred in the NICE reference case.[118]

Additional consideration of the external validity of PROFILE 1014 reflected on the dose of crizotinib that is used in PROFILE 1014 is consistent with the licensed dose described in the SmPC. Comparison of patient characteristics between patients included in PROFILE 1014 and those with ALK-positive, advanced NSCLC in the UK is limited by the paucity of UK-specific information on these patients. PROFILE 1014 did however include patients from eight study sites in the UK.[110] At an advisory board attended by UK clinical experts, the patient population studied in PROFILE 1014 was considered to be similar to patients in the UK, although the following was noted:

- Patients in PROFILE 1014 may be younger than in clinical practice

- Not many current smokers were included in PROFILE 1014
- The proportion of patients with ECOG performance status of 0 or 1 was higher than expected in clinical practice

With regards to the final point, it was acknowledged that researchers conducting a trial may be unwilling to administer pemetrexed in combination with cisplatin to patients with a performance score of 2 or higher due to the toxicity of chemotherapy. Similar differences between the PROFILE 1014 patient population and patients in clinical practice were also identified when comparing patients included in the crizotinib clinical trial and those included in the retrospective study by Davis *et al.* (2015) (see Section 4.11.5). Although the characteristics of the PROFILE 1014 trial are broadly generalisable to UK patients, the differences between the trial population and the real-world non-trial population have been taken into account in the modelled base case; this allows the model to provide results that are the most plausible and applicable patients presenting in the NHS (see Section 5.3.1.1 for more details).

The overall generalisability of results is supported by the notion that, for a targeted therapy, the key determinant of responsiveness to treatment is the presence/absence of the target ALK translocation. In PROFILE 1014, the improvements observed with first-line crizotinib were independent of stratification factors and baseline characteristics, including race (Asian vs. non-Asian), suggesting that most patients with confirmed ALK-positive NSCLC will respond positively to treatment with crizotinib independently of these characteristics (see **Error! Reference source not found.**).[2] Molecular testing for ALK-status is already available in the UK, thus allowing for the identification of patients with ALK-positive NSCLC who will most likely benefit from treatment with first-line crizotinib.

Limitations of the evidence

The internal validity of PROFILE 1014 is limited by the following:

- A crossover design was implemented to allow patients in the chemotherapy group to receive crizotinib following disease progression. Crossover was permitted for ethical reasons; however, estimates of OS are likely to be have confounded by the high proportion of patients (70%) in the chemotherapy group who subsequently received crizotinib (see Section 4.5). In order to account for potential confounding, multiple validated statistical methods to explore the effects of patient crossover on OS were employed; the crossover-adjusted analyses of OS are presented alongside unadjusted OS data in Section 4.7.2. Crossover adjusted analyses of OS were validated by UK clinical experts at an advisory board (see Section 5.10.1.3).
- At the time of PFS analysis, OS data for PROFILE 1014 was immature with only 26% of patients who were randomly assigned to study treatment having died at the latest data cut-off date (see Section 4.5). A follow-up OS analysis is planned for when median OS is eventually reached.
- Whilst overall the patient population studied in PROFILE 1014 were considered by clinicians to be similar to patients in the UK, key patient characteristics that differed included age, smoking status and ECOG PS. Therefore, an analysis of key covariates was conducted in order to evaluate the absolute effect of each of these factors on PFS and OS (see Section 5.3.4 for further details on the choice of covariates and the adjustments). In order to produce a set of robust and conservative results, the modelled base case within the economic evaluation calculates the results following an adjustment

of patient characteristics so that outcomes are more reflective of a “real” UK patient cohort.

As discussed in the points above, efforts have been made in this submission to reduce clinical uncertainty and produce a set of robust conservative results that have been clinically validated.

Finally, RCT data for first-line crizotinib is limited to PROFILE 1014.

4.14 Ongoing studies

4.14.1 Provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

PROFILE 1014 is closed to further enrolment and is currently in follow-up until median OS is reached.

PROFILE 1001 is an ongoing study; however, no further analyses are expected until *[Academic / commercial in confidence information removed]* when the publishing of final OS results is planned.

5 Cost-effectiveness

De novo cost-effectiveness model

- The cost-utility of crizotinib as a first-line treatment for patients with ALK-positive, advanced NSCLC was assessed with an area under the curve, partitioned survival model. The model included three health states: *progression free, progressed disease,* and *death*) and was similar to that presented in previous UK technology appraisals for advanced NSCLC.
- In the base case analysis, crizotinib was compared to pemetrexed plus platinum-based chemotherapy (cisplatin/carboplatin). An exploratory scenario analysis was undertaken in a squamous cell carcinoma population.
- OS and PFS estimates for crizotinib versus pemetrexed plus cisplatin/carboplatin were based on PROFILE 1014 trial data; covariate adjustments for patient characteristics from a real-world study were incorporated to better reflect the patient population expected in clinical practice and improve the face validity of results, based on discussion with oncologists.
- Health-state utilities were treatment-dependent in the *progression-free* state and reflected the worsening of patient condition upon disease progression. Disutilities for adverse events were considered already accounted for in the on-treatment utility.
- Input from oncologists who treat ALK-positive NSCLC in the UK was sought in order to validate the assumptions and parameter inputs.

Base case results

- In the base case analysis, crizotinib was associated with a deterministic ICER of *[Academic / commercial in confidence information removed]* at list price, and a probabilistic ICER of *[Academic / commercial in confidence information removed]*. Crizotinib was cost-effective with the PAS (results in a separate document) versus pemetrexed plus cisplatin/carboplatin.
- One-way sensitivity analyses indicated that the key drivers of the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact.

Sensitivity analyses

- The mean ICER from the probabilistic analysis was similar to that in the base case analysis; at a willingness to pay threshold of £50,000 per QALY gained crizotinib with the PAS was associated with a high probability of cost-effectiveness.
- In addition to probabilistically running the base case, 21 sensitivity analyses were explored where model assumptions were changed. Crizotinib remains cost-effective with the PAS despite alternative statistical survival approaches being considered. The modelled estimates for survival were credible as they were both externally validated and also in-line with existing literature.
- The modelled clinical outcomes are plausible and were validated. The model suggests a post-progression survival advantage with crizotinib, showing that the benefits of crizotinib extend beyond progression. This benefit can be explained by the greater tumour shrinkage associated with crizotinib whilst on treatment, improving the health status of patients from baseline.
- Crizotinib is an efficacious first-line treatment for adult patients with previously untreated ALK-positive, advanced NSCLC and results in improved outcomes compared with treatment with pemetrexed plus cisplatin/carboplatin, the main comparator in the submission.
- Conservative assumptions have been used and the uncertainty around the ICER has been rigorously investigated. The cost-effectiveness results are credible, robust and plausible; this treatment represents value for money to the NHS.

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

Search strategy

A systematic literature review was conducted to identify relevant cost-effectiveness studies for the first-line treatment of advanced or metastatic NSCLC. The objective was to both identify any existing estimates of the cost-effectiveness of crizotinib in the first-line setting but to also inform the development of a *de novo* model in the absence of previously conducted evaluations. Beyond searches within typical databases, further searches of health technology assessment (HTA) records and of the proceedings from relevant congresses were also carried out.

The following electronic databases were searched on the 17th July 2015 (MEDLINE, MEDLINE In-Process, Embase and EconLit) and 3rd August 2015 (Cochrane):

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (OVID)
- The Health Technology Assessment (HTA) Database
- The NHS Economic Evaluation Database (NHS-EED)
- EconLit (EBSCO)

The full search strategy for the literature review is presented in **Error! Reference source not found.**.

Inclusion of studies

To be included in the review, articles had to meet pre-defined eligibility criteria which are detailed in Table 39.

The citations found through the searches were first assessed by two independent reviewers for inclusion based on abstract and title. Full-text copies of studies that potentially met the initial inclusion criteria were then obtained and reviewed in more detail by the two independent reviewers. Studies that met the eligibility criteria after this second screening stage then had data extracted by a reviewer and checked by a second party. Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction table.

Table 39: Eligibility criteria used for the identification of relevant cost-effectiveness studies

Domain	Inclusion Criteria	Exclusion Criteria	Rationale
Population	Individuals with advanced/metastatic (stage IIIb/IV) NSCLC (*inclusion category 1*) Individuals with ALK positive advanced/metastatic (stage IIIb/IV) NSCLC (*inclusion category 2*)	-	The review focused on chemotherapy options in advanced NSCLC specifically, where chemotherapy is used as the primary therapy. ALK positive advanced/metastatic (stage IIIb/IV) NSCLC patients are particularly of interest because of the relevance of this population to the decision problem, but this was not an essential inclusion criteria.
Country	UK All countries (*only for inclusion category 2*)	All other countries (*unless study qualifies for inclusion category 2*)	The aim of the review was to assess the evidence relevant for decision making in the UK. Very few studies have been conducted in the UK on ALK positive patient populations. Therefore, the inclusion criteria for studies in this patient population was extended to countries other than the UK.
Intervention(s) and comparator(s)	Any pharmacological intervention(s) and comparator(s), provided that they are evaluated as first-line therapy. These include (but are not limited to): • Afatinib • Bevacizumab • Crizotinib • Docetaxel • Erlotinib • Gefitinib • Gemcitabine • Paclitaxel • Pemetrexed • Vinorelbine	Studies not evaluating at least one pharmacological intervention (eg. comparing two non-pharmacological interventions) Studies evaluating maintenance therapies, including first-line maintenance therapy.	The aim of this review was to specifically consider interventions in first-line therapy.
Outcomes	Outcomes of relevant study designs, including: • Costs • Life years • Quality-adjusted life years (QALYs) • Incremental costs and QALYs • Incremental cost-effectiveness ratios (ICERs)	-	The aim of the review was to examine cost-effectiveness data.
Study design	Economic evaluations, specifically one of the following analysis types: • Cost-effectiveness	-	The aim of the review was to examine cost-effectiveness data.

	• Cost-utility • Cost-benefit • Cost-minimisation • Cost-consequence		
Publication type	HTAs, original economic evaluations and systematic reviews of economic evaluations (the reference lists of the latter will be hand-searched for further, relevant publications).	• Comments • Letters • Editorials • Non-systematic/ narrative reviews	The aim of the review was to examine empirical cost-effectiveness data.
Other considerations	English language Human subjects	Non-English language articles Articles not on human subjects	The aim of the review was to assess the evidence relevant for decision making in the UK.

Abbreviations: ALK: anaplastic lymphoma kinase; HTA: health technology assessment; ICER: incremental cost-effectiveness ratio; NSCLC: non-small cell lung cancer; QALY: quality-adjusted life-year; UK: United Kingdom.

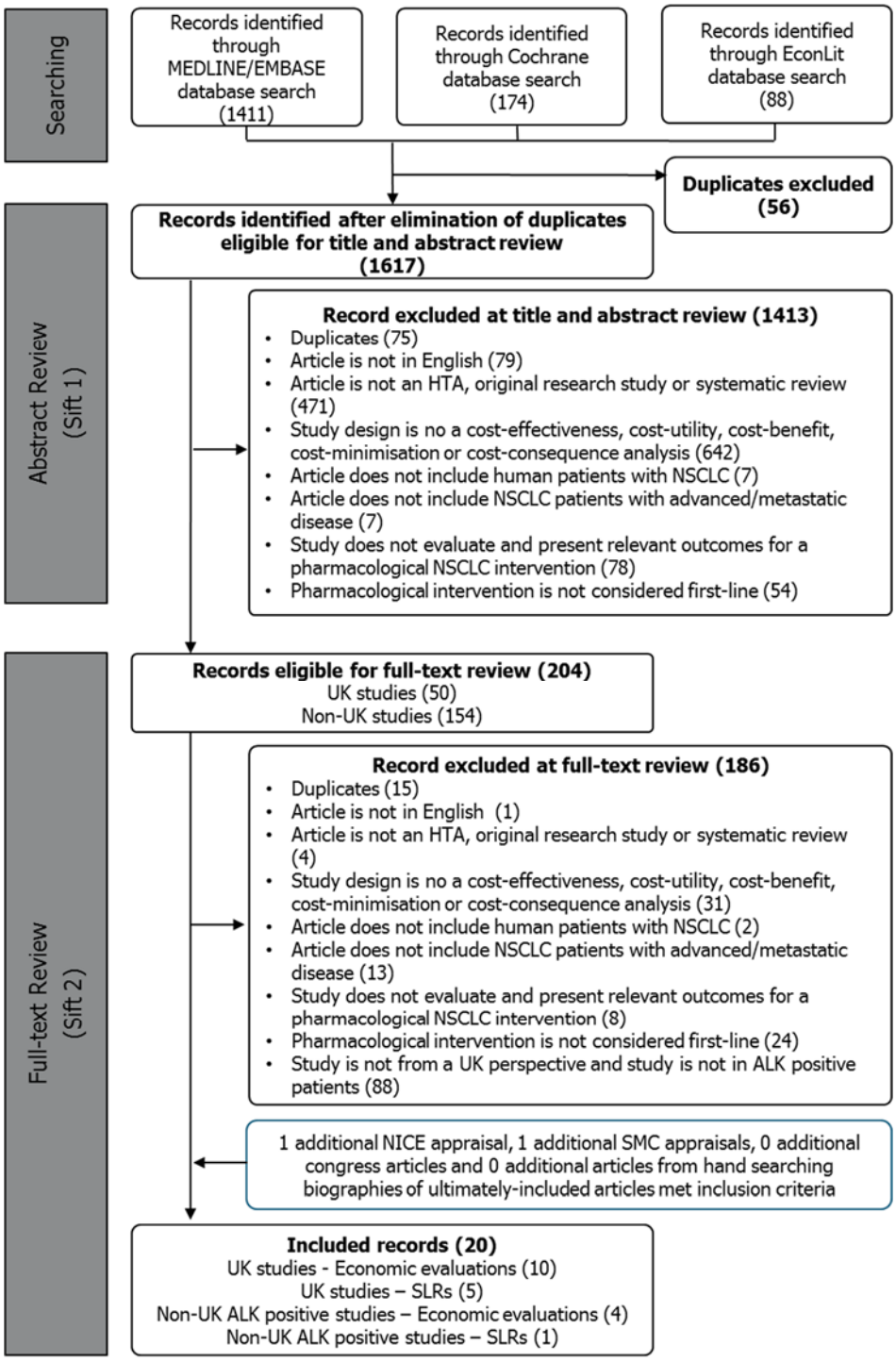
5.1.2 Description of identified studies

A total of 1,673 articles were identified from the database searches. Following deduplication of database results, 1,617 abstracts were reviewed at the title/abstract stage, of which 204 articles were identified as being potentially relevant. A total of 18 articles subsequently met the eligibility criteria following a full-text review: 13 studies relevant to decision making in the UK (5 economic evaluations, 5 systematic reviews and 3 HTAs) and 5 studies from outside the UK but in ALK-positive patients (4 economic evaluations and 1 systematic review). No additional articles to those captured through the database searches were identified through congress searching and through hand searching of the bibliographies of the ultimately included articles. However, two additional and relevant technology appraisals were identified from searches of the NICE and SMC websites, bringing the total to 20 articles for inclusion. The flow of studies through the review process is presented in Figure 16.

Of the 20 included articles, 10 studies were economic evaluations relevant to decision making in the UK (including 4 HTAs). Of the 6 studies not appraised by HTA bodies, two were cost-minimisation analyses comparing vinorelbine with various comparators; two were cost-effectiveness analyses exploring coupled cisplatin regimens and palliative care; and two were cost-utility analyses exploring combinations of platinum based chemotherapy from the UK health sector perspective. Of the four HTA appraisals identified, three were conducted by NICE (TA192, TA181 and TA258) and one was an SMC submission evaluating the cost-effectiveness of pemetrexed in combination with cisplatin (ID 531/09). However, of the identified studies, none evaluated crizotinib in the first-line setting that could be used to establish existing estimates of crizotinib's cost-effectiveness, and none examined a patient population that was specifically ALK-positive.

Please refer to **Error! Reference source not found.** for further details of the included studies in this review (**Error! Reference source not found.**), including a summary of results from each included study (**Error! Reference source not found.**).

Figure 16: PRISMA flow diagram of articles identified and included in the review of cost-effectiveness studies



5.1.3 Quality assessment of included cost-effectiveness studies

A critical appraisal of each included cost-effectiveness study identified in the literature review was conducted using the Drummonds *et al.* (1996) checklist.[142] The results of these quality assessments are presented in **Error! Reference source not found.** in **Error! Reference source not found.**.

5.2 *De novo analysis*

5.2.1 Patient population

This economic evaluation provides estimates for cost-effectiveness for adult patients with previously untreated, advanced NSCLC presenting with the ALK translocation. This population matches the licensed indication for crizotinib based on the positive CHMP opinion, however the evaluation models the clinical data which are from a non-squamous population.[8]

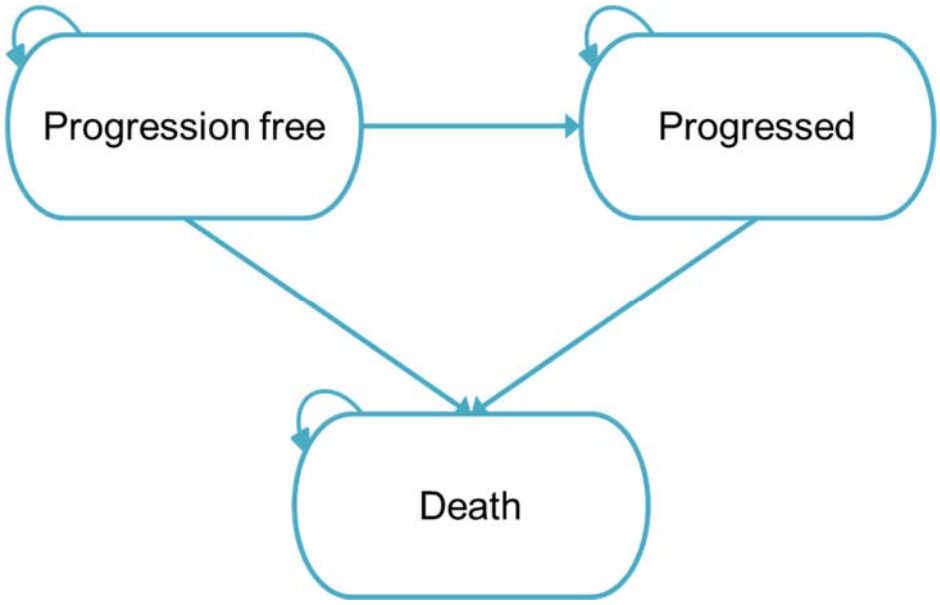
The incidence of ALK-positivity in a squamous NSCLC population is estimated at 0.08%, as derived in Section 3.1. The identification of patients with ALK-positive squamous NSCLC would therefore be extremely rare in the UK. Although the phase III first-line trial for crizotinib (PROFILE 1014) included only non-squamous patients, a scenario analysis is presented to estimate the cost-effectiveness in the squamous population (see Section 5.2.4 for details).

5.2.2 Model structure

The cost-effectiveness model was developed in Microsoft Excel® using an "area under the curve" structure in both a deterministic and probabilistic (Monte Carlo simulation) framework.

The model structure schematic is presented in Figure 17. The model is based on three health states: *progression free, 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*. The model therefore captures the changes in quality of life between pre- and post-progression.

Figure 17: Model structure



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 4.3.1). This model structure and the health states utilised are typical of modelling in oncology and have been utilised previously in numerous NICE technology appraisals, including for NSCLC.[5, 80, 81, 84, 85] It contains the three most relevant disease related health states from a patient, clinician and NHS perspective:

- *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 the PROFILE 1014 trial, and therefore subsequently in the model, using Response Evaluation Criteria in Solid Tumours (RECIST). Patients in this state are assumed to incur costs associated with treatment, including drug costs for crizotinib and pemetrexed plus cisplatin/carboplatin, costs of drug administration, and costs associated with medical management of the condition and the management of Grade 3/4 adverse events. Patients also experience a higher utility weighting compared with *progressed disease*, as their tumour and related symptoms are controlled, and this utility weighting is treatment specific (based on observed treatment utilities in the PROFILE 1014 trial).
- *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) and then third-line best supportive care (BSC) before death. This treatment pathway was discussed with clinical experts who treat ALK-positive NSCLC in the wider UK.
    - The current assumption in the model is that second-line therapy post-progression is docetaxel for both treatment arms. This is aligned with routine clinical practice in England and Wales and reflects the existing NICE recommendation for docetaxel for NSCLC within the second-line setting.
    - Whilst it is acknowledged that crizotinib as a second-line agent is available via the CDF, at the time of submission, this was not considered a treatment option due to the current uncertainty of future funding with the CDF transition arrangements. Therefore we have not considered this as representative of routine clinical practice. Additionally, crizotinib as a second-line agent is not funded, and hence not standard of care, in Wales.

  Patients may continue to incur costs associated with medical management (see Section 5.5.6) and will experience a lower utility weighting than in the *progression free* state (see Section 5.4.7). Progression to docetaxel treatment is delayed by 3.1 months (set to 4 cycles in the model to allow for crizotinib wastage costs) for 73% of crizotinib patients to reflect treatment beyond progression that took place in the PROFILE 1014 trial (see Section 4.5.1).
- *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 5.3.4).

ALK-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' ALK status is known upon entry into the model. The costs of screening for ALK-positivity have been included in the model as per the testing strategy recommended as a "cost-effective approach" in the ESMO guidelines (IHC test, with positive tests being confirmed by FISH).[24] It is understood from discussions with clinical experts at an advisory board that this is a commonly used strategy in the

UK. This is applied in the model in terms of the expected cost per patient to identify an ALK-positive patient from a cohort of all patients with non-squamous NSCLC. A sensitivity analyses removes the cost of ALK-testing.

5.2.3 Features of the de novo analysis

The analysis was conducted from a National Health Service (NHS) and personal social services (PSS) perspective in England and Wales using 30-day model cycles. A time horizon of 15 years was chosen in line with the maximum life expectancy of the cohort predicted by parametric survival analysis and clinically it is unlikely for patients with ALK-positive NSCLC to survive beyond 15 years; in the deterministic model base case all patients had died prior to the time horizon being reached. 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.[118] A half cycle correction was applied.

The features of the de novo analysis undertaken are presented in Table 40.

Table 40: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	15 years	15 years is sufficiently long that the majority of patients in the model have died by the end of the modelled time horizon.
Cycle length	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.
Were health effects measured in QALYs; if not, what was used?	Yes	Consistent with the NICE reference case.[118]
Discount of 3.5% for utilities and costs	Yes	Discounting follows the NICE reference case.[118]
Half cycle corrected?	Yes	Half cycle correction follows the NICE reference case.[118]
Perspective (NHS/PSS)	Yes	The perspective follows the NICE reference case.[118]

Abbreviation: NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal social services; QALYs: Quality-adjusted life years.

5.2.4 Intervention technology and comparators

Crizotinib will be utilised within the economic evaluation for adults with treatment naïve non-squamous ALK-positive advanced NSCLC. A scenario is explored for squamous patients, as detailed in Section 5.8.3.

The final scope for this appraisal includes the following comparators:

1. Pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin) for patients with non-squamous tumour histology.

2. A third-generation drug in combination with platinum chemotherapy (cisplatin or carboplatin) for patients with squamous tumour histology.

3. Single-agent chemotherapy with a third-generation drug (for example, gemcitabine or vinorelbine) for patients with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate.

Consultation with treating UK clinical experts at an advisory board highlighted that the main comparator in clinical practice is pemetrexed in combination with either cisplatin or carboplatin and is offered to the majority of ALK-positive patients; head-to-head data are available for this comparator in the control arm of the PROFILE 1014 trial. The base case analysis models this comparison.

The above-listed second comparator (a third-generation drug in combination with platinum chemotherapy) is listed as a treatment for patients with ALK-positive squamous tumour histology. This treatment for these patients would be used very rarely as the incidence of ALK-positive squamous NSCLC is estimated to be only 0.08% (see Section 5.2.1 for more details). Consequently, the data available for treating these patients in the first-line are extremely limited. In order to estimate the cost-effectiveness of crizotinib in this population the approach that was suggested at the NICE Decision Problem meeting for this appraisal has been followed in a scenario analysis. The outcomes and costs from the non-squamous population in the model versus pemetrexed plus cisplatin/carboplatin are extrapolated to the squamous population, and are still presented versus the non-squamous comparator. However, the way this scenario differs is that the additional ALK diagnostic testing that needs to be conducted in order to identify a rarer squamous patient (due to the lower incidence) is now included in the crizotinib model arm, which increases the ICER. It should be noted that the ICER in this scenario reflects a situation in which every squamous NSCLC patient is tested for ALK; however, discussions at the clinical expert advisory board indicate that in practice, squamous patients would likely only be tested if they were identified as having typical ALK-positive characteristics (such as being young, and a non-smoker), if they are tested at all. Consequently, this scenario in the model presents a very conservative ICER as it assumes every squamous NSCLC patient in the UK is ALK-tested.

The third comparator listed in the scope refers to those patients unable to tolerate a platinum agent. However, consultation with the clinical experts at the advisory board revealed that these patients eligible for this treatment is very small, around 1-2% of crizotinib's potential patient population. Due to absence of data in this population, together with the small patient numbers expected, the economic evaluation does not consider a comparison versus single-agent therapy.

5.2.5 Treatment discontinuation rules

Treatment with crizotinib should be stopped in the case of disease progression or unacceptable toxicity. However, as treating beyond progression was permitted in the PROFILE 1014 trial, the model considers the cost and benefit of this (see Section 5.4.6.2).

The model assumes treatment beyond progression to occur (and the corresponding costs and effects) for a duration in line with what was observed in the PROFILE 1014 trial (where 73% of crizotinib patients received treatment beyond progression for a median of 3.1 months).[2]

Although the base case includes treating beyond progression which yields a conservative ICER, a sensitivity analysis is explored that excludes treating beyond progression and its effect on cost and utility (presented in Section 5.8.3).

5.3 Clinical parameters and variables

5.3.1 Clinical data incorporated into the model

5.3.1.1 Patient characteristics

As was discussed in Section 4.13.2, the baseline characteristics of patients included in the PROFILE 1014 trial are considered to be largely representative of the ALK-positive patient population in the UK; however it was noted on consultation with clinical experts at the advisory board that a non-trial population may be slightly less healthy population (explicitly a lower proportion of patients with ECOG performance status 0 or 1 at baseline, and 5 to 10 years older) would be expected to present in clinical practice. The extrapolated survival curves for the cohort from the PROFILE 1014 study were discussed (both adjusted and unadjusted for crossover) with the clinical experts, and it was felt that projected median OS was being over-estimated for both the crizotinib and the crossover-adjusted pemetrexed cohorts, compared to patients that would present in UK clinical practice (see Section 5.3.5). In addition to differences in patient characteristics, the over-estimation of this extrapolated OS from the trial data may be also due to the immaturity of the survival data on which the extrapolated curves are based, as only 26% of patients having died at the time of data cut, which makes the data further along the survival curves uncertain beyond the end of the existing Kaplan-Meier data.

Adjusting patient characteristics to obtain a more realistic estimate of clinical efficacy is a technique which has been published previously.[143, 144] The majority of examples are ones in which the evidence comes from single-arm Phase II studies where patients selected are fitter than patients which might be selected in Phase III studies or seen in clinical practice to increase the chances of observing good outcomes or where efficacy for an historical control arm comes from a single-arm study.

A retrospective real-world cohort study conducted by Davis *et al.* (2015) provides data on the demographics of real-world patients in non-trial population that is also in a Western cohort (see Section 4.11.5).[133] These patients are considered to be more representative of patients seen in current UK clinical practice, who would be expected to be less healthy (slightly older and with worse ECOG performance status on average), compared to the observed characteristics of patients enrolled in PROFILE 1014 (see Table 42 for a comparison of patient characteristics).

Therefore, an analysis of key covariates has been conducted by fitting Cox regression models to the patient-level trial data in order to evaluate the absolute effect of each of these factors on PFS and OS (see Section 5.3.4.2 and **Error! Reference source not found.** for further details on the choice of covariates and the adjustments). The modelled base case calculates the results following an adjustment of patient characteristics in order to match the Davis *et al.* (2015) data (considering the covariate effect) so that outcomes are more reflective of a “real” patient cohort. This analysis is used in the modelled base case for the following reasons:

1. The adjustment for real-world patient characteristics allowed for a modelled cohort more similar to that which is expected to present for treatment in the UK.

2. This method maintains the relative treatment effect established in the trial, but generates more conservative absolute estimates within each arm.

3. Furthermore, the adjustment produced OS estimates that were more in line with what is expected based on both published literature and clinical expert opinion (see Table 10).

The adjustment for real-world patients was removed in a sensitivity analysis (presented in Section 5.8.3), where data for all demographic and baseline patient characteristics were taken from the PROFILE 1014 Phase III trial. The distribution of patients for the included covariates is provided in Table 42. Further details of the stepwise covariate selection are given in Section 5.3.4.2.

5.3.1.2 Other clinical data used in the model

Data from the Phase III randomised-controlled PROFILE 1014 trial were used to estimate the proportion of patients in each health state (based on PFS and OS data which were adjusted for patient characteristics from real-world evidence), the proportion of patients experiencing treatment-related AEs and treatment-dependent utility values for the progression free health state. PROFILE 1014 provided a head-to-head comparison of crizotinib against pemetrexed plus cisplatin or carboplatin, the standard of care comparator for this submission.

5.3.2 Estimation of transition probabilities from the clinical data

The area under the curve model was populated by fitting survival curves to PROFILE 1014 trial data for PFS and OS. 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.

5.3.3 Transition probabilities over time

Examination of survival functions from PROFILE 1014 and other oncology RCTs 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.

5.3.4 Extrapolation of data

For both PFS and OS, standard multivariable parametric curve fitting for data from the PROFILE 1014 trial was conducted to estimate PFS and OS in the long-term (beyond the end of the trial) for both crizotinib and pemetrexed plus cisplatin/carboplatin. The parametric survival models included covariates for potentially important prognostic factors. Furthermore, rather than fitting separate models/curves for each treatment, the models also included a covariate for treatment, hence assuming a constant treatment effect (see Section 5.3.4.2). Survival curve fitting was conducted in line with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[145, 146]

5.3.4.1 Overall survival data

As described in Section 4.7.2, crossover methods were employed to adjust the chemotherapy arm to estimate overall survival treatment effects in the trial had crossover not been permitted.

Adjusted survival times were estimated using three approaches: the RPSFT method, the IPE method, and the two-stage method. These methods were the most suitable given the data, with *[Academic / commercial in confidence information removed]* However, due to the methodological similarities between the RPSFT and IPE methods (i.e. both methods maintained randomisation between treatment arms and assumed a common treatment effect), only the RPSFT (pre-specified in the clinical trial protocol) and two-stage models were considered for use in the parametric modelling (as noted in Section 4.7.2). The corresponding treatment effects for the five methods employed using the RPSFT and two-stage models are presented in Table 41.

Table 41: Overall Survival Crossover Adjustment Methods Use in Parametric Modelling, with Treatment Effect Estimates

Crossover adjustment method	Analysis	Abbreviation	Crizotinib versus pemetrexed plus cisplatin/carboplatin Hazard Ratio (95% CI)
Two-stage	Adjusted for treatment switching and additional covariates (ECOG sensitivity imputation)	TS A	0.624 (0.405, 0.963)
	Adjusted for treatment switching and additional covariates (base case ECOG imputation)	TS B	0.649 (0.421, 1.000)
	Adjusted for treatment switching	TS C	0.610 (0.395, 0.942)
RPSFT	Wilcoxon text method	RW	0.604 (0.265, 1.420)
	Log-rank test method	RL	0.674 (0.283, 1.483)

Abbreviation: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; RL: rank-preserving structural failure time log-rank test method; RPSFT: rank-preserving structural failure time; RW: rank-preserving structural failure time Wilcoxon method; TS: two-stage.

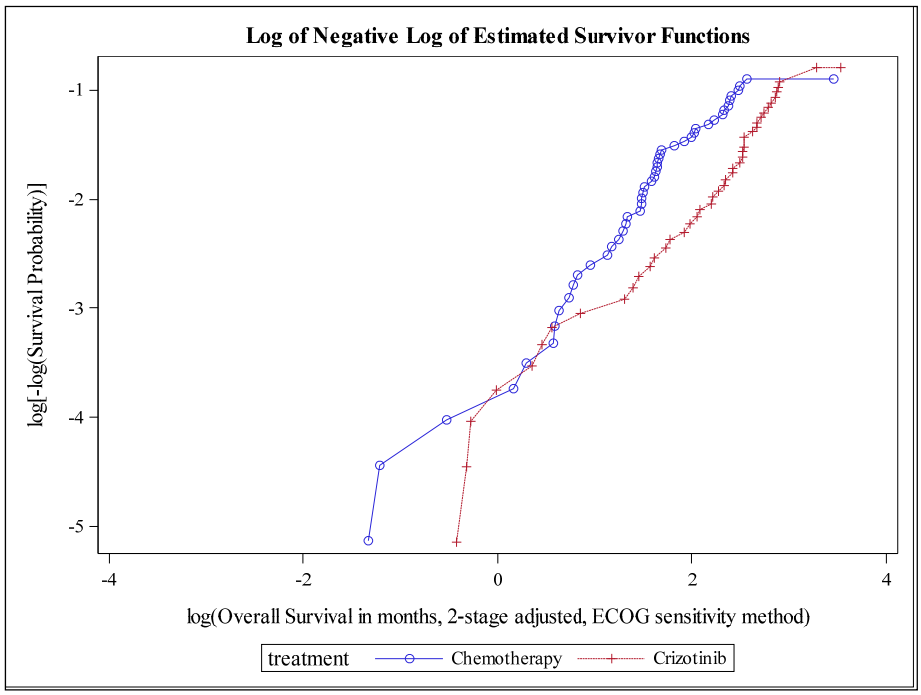
The results demonstrate a strong, consistent estimate of clinical benefit across the different crossover adjustment methods. The counterfactual survival times estimated using method 'TSA' were chosen for use in the base case set of overall survival curves as this method yielded the median treatment effect estimate. In the absence of any methodological or clinical reason to select either of the extremes in preference to the other, the median value has been chosen for the modelled base case. Parametric curves are also available for the other four crossover adjustment approaches. The differences between the three two-stage approaches, TSA, TSB and TSC, are explained in Section 4.4 and in further detail in **Error! Reference source not found.**.

5.3.4.2 Covariate adjustment with real world evidence

Covariate-adjusted parametric models were fit for both PFS and OS, including a covariate for treatment, and a series of other covariates known to be potentially prognostic factors.

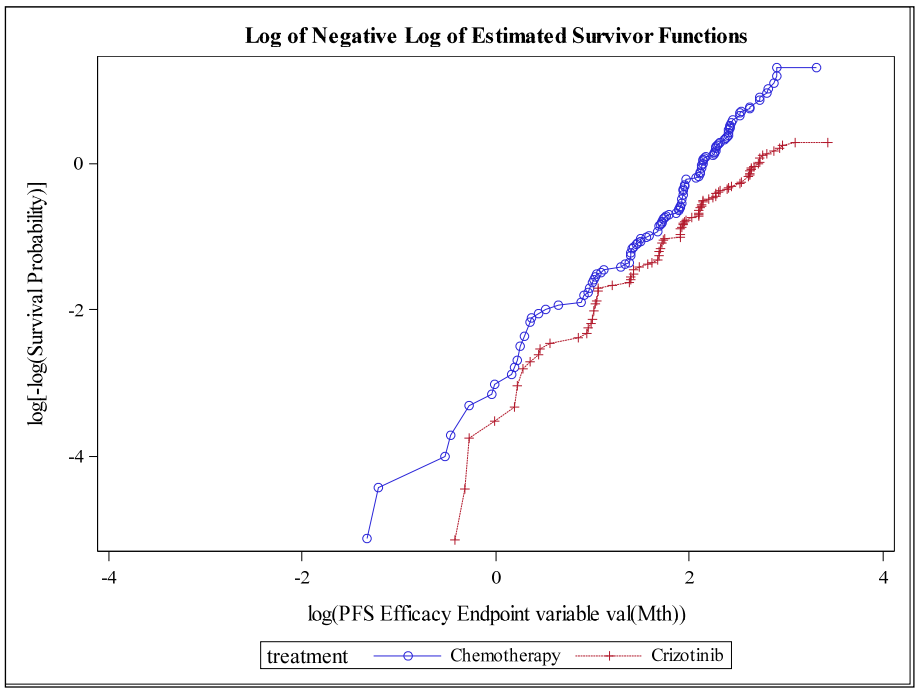
Inclusion of treatment as a covariate in the parametric models allows the fitting of one parametric model to estimate separate curves (using the treatment effect estimate) whilst adjusting for the common effects of the prognostic factors. This requires an assumption of a constant treatment effect. This assumption was assessed by inspecting the plot of log hazards by log time for OS and PFS separately. Both plots, Figure 18 and Figure 19, did not yield large departures from parallel lines, except in the extremes where data are limited, therefore the assumption of a constant treatment effect was made for both analyses.

Figure 18: Assessing constant treatment effect for overall survival (using crossover method TSA)



Abbreviation: ECOG: Eastern Cooperative Oncology Group.

Figure 19: Assessing constant treatment effect for progression free survival



Abbreviation: ECOG: Eastern Cooperative Oncology Group; PFS: progression-free survival.

Other covariates included in the models were the three randomisation stratification variables (race [Asian vs. non-Asian], Eastern Cooperative Oncology Group [ECOG] status [2 vs. 1 or 0], and brain metastases [yes vs. no]), together with age group (≥65 vs. <65), sex (male vs. female), smoking status (never smoked vs. former smokers or current smoker), and adenocarcinoma (yes vs. no). Further details on covariate selection are given in **Error! Reference source not found.**.

The distribution of patients for the included covariates is provided in Table 42. For model fit checking purposes, the covariate estimates by treatment arm were used; for prediction in the economic model, estimates from real-world data were used in the base case and estimates for the pooled population from PROFILE 1014 were used in a sensitivity analysis, as discussed in Section 5.3.1.

Table 42: Baseline demographics and patient characteristics for covariate-adjusted PFS and OS

Covariate	Real-world data (Davis *et al.* [2015]) [133]	Crizotinib (PROFILE 1014) [2]	Pemetrexed plus cisplatin/ carboplatin (PROFILE 1014) [2]	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	51.8%	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.

5.3.4.3 Parametric models fit

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 against covariate-adjusted 'Kaplan-Meier' estimates; i.e. survival predictions from a Cox proportional hazards model,
- 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. Similarly, different proportions of patients for each covariate could be and were used to predict curves for different populations. The survival curves are estimated for each treatment separately by setting the treatment covariate effect to 1 or 0 depending on which treatment's curve is being predicted.

5.3.4.4 Progression-free survival estimates

The AIC and BIC for the PFS curves (including covariates for treatment and prognostic are provided in Table 43; lower values are preferred for best fit. The PFS curve fits for crizotinib are shown in

Figure 20 and the PFS curve fits for pemetrexed plus cisplatin/carboplatin are shown in Figure 21 along with their respective Kaplan-Meier curves, which have each been adjusted for the same covariates as the parametric curves were.

Table 43: AIC and BIC for PFS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	1619.10	1653.63
Generalised gamma	1593.36	1635.58
Gompertz	1610.75	1649.12
Log-logistic	1603.05	1641.43
Log-normal	1607.92	1646.30
Weibull	1591.86	1630.24

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Figure 20: PFS parametric curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm

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Figure 21: PFS parametric curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm

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For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; PFS: progression-free survival.

The AIC and BIC indicate that there is no great difference between different curve fits in terms of fit to the data; however, the generalised gamma and Weibull curves had the lowest values, and therefore best fit to the observed Kaplan-Meier data. The generalised gamma curve was selected for the base case as it had a good fit to the observed data (based on the AIC, BIC and visual inspection) and provided the most plausible extrapolation; i.e. the fitted curve predicts nearly all pemetrexed plus cisplatin/carboplatin patients to have progressed by 30 months, and other curves predict longer, unrealistic PFS times.

The base case PFS curves for crizotinib and for pemetrexed plus cisplatin/carboplatin, adjusted to the real-world data patient characteristics, are presented in Figure 22.

Figure 22: PFS – selected curves: Generalised gamma model (estimated using real-world data for patient characteristics)

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Curves estimated using the fitted survival model patient characteristics from real-world data.

The parameter estimates shown in Table 44 are model estimates estimated in, and output from the R function 'flexsurvreg' in the R library 'flexurv'. Care should be taken interpreting these parametric survival equations, as different statistical packages have different model parameterisations and use different terminology for similar parameters.

Table 44: Estimated model parameters for progression free survival

	Exponential	Weibull	Gompertz	Log Normal	**Generalised gamma**	Log logistic
Fixed model parameters						
Q	n/a	n/a	n/a	n/a	**0.847**	n/a
Sigma	n/a	n/a	n/a	n/a	**-0.253**	n/a
Sdlog	n/a	n/a	n/a	-0.009	n/a	n/a
shape	n/a	0.303	0.039	n/a	n/a	0.587
Linear combination parameters						
[Academic / commercial in confidence information removed]	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
[Academic / commercial in confidence information removed]	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
[Academic / commercial in confidence information removed]	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
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[Academic / commercial in confidence information removed]	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*

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[Academic / commercial in confidence information removed]	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

The chosen base case model is indicated in bold.

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

For the generalised gamma model, we estimated a treatment effect of pemetrexed plus cisplatin/carboplatin vs crizotinib of -0.629, standard error=0.103, p-value=<0.0001; thus implying there is a significant difference between the treatments with respect to PFS. As the generalised gamma parametric curve is an accelerated failure time model, this can be interpreted in terms of a ratio of mean PFS estimates (pemetrexed plus cisplatin/carboplatin / crizotinib) of 0.53 (i.e. exp(-0.629)).

Sensitivity analyses have been conducted using alternative PFS curves to assess the impact of these on the cost-effectiveness of crizotinib. The curves used in sensitivity analyses are the Weibull and Gompertz curves as these provided a similar extrapolation to the generalised gamma curve. These curves are presented in **Error! Reference source not found.**.

5.3.4.5 Overall survival estimates

The counterfactual survival times estimated from the 'TSA' approach to crossover adjustment were used for the base case overall survival analyses, and are presented within this section. As the range of crossover adjusted hazard ratios were so consistent, the selection of TSA in the base case is a suitable and realistic choice that reduces uncertainty as it is the median estimates in a range where there is no methodological rationale to select either of the extremes in preference to the other. Nevertheless, the model estimates and curve fits for the other methods of crossover adjustment were also explored, and are presented in **Error! Reference source not found.**. The AIC and BIC for the OS curves (including covariates for treatment and prognostic factors) are provided in Table 45. The OS curve fits for crizotinib are shown in

Figure 23, and the OS curve fits for pemetrexed plus cisplatin/carboplatin are shown in Figure 24, along with their respective 'Kaplan-Meier (KM) curves' which have been adjusted for the same covariates as the parametric curves.

Table 45: AIC and BIC for OS (using crossover method TSA) (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	831.59	866.13
Generalised gamma	833.87	876.09
Gompertz	833.55	871.93
Log-logistic	832.90	871.27
Log-normal	836.60	874.98
Weibull	832.24	870.61

Abbreviation: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 23: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm

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Figure 24: OS (using crossover method TSA) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm

[Academic / commercial in confidence information removed]

For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

The AIC and BIC indicate that there is no great difference between different curve fits in terms of fit to the data. The Weibull curve had a good fit to the observed data (based on the AIC, BIC and visual inspection) and provided median survival for crizotinib of 41.4 months. This is still higher than would expected in a real-world setting, however it provides the most plausible extrapolation as it yields the lowest estimated median survival, therefore allowing for a decision based on the most conservative estimate possible.[133] The same issue was observed with the pemetrexed plus cisplatin/carboplatin curve. As such, the Weibull curve was selected in the base case.

The base case OS curves for crizotinib and for pemetrexed plus cisplatin/carboplatin, adjusted to the real-world data patient characteristics (see Section 5.3.1), are presented in Figure 25.

Figure 25: OS (using crossover method TSA) – selected curves: Weibull model (estimated using real-world data for patient characteristics)

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Curves estimated using the fitted survival model patient characteristics from real-world data.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 46: Estimated model parameters for overall survival (using crossover method TSA)

	Exponential	**Weibull**	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Sigma	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Sdlog	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
shape	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
scale	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*

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meanlog	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
mu	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
>=65 vs <65 years	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Male vs Female	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*

	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
ECOG 2 vs 1 or 0	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

The chosen base case model is indicated in bold.

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

For the Weibull model, a treatment effect was estimated of pemetrexed plus cisplatin/carboplatin vs. crizotinib of *[Academic / commercial in confidence information removed]* standard error=*[Academic / commercial in confidence information removed]* p-value=*[Academic / commercial in confidence information removed]*; thus implying there is a significant difference between the treatments with respect to OS. This treatment effect can be converted to a hazard ratio (crizotinib / pemetrexed plus cisplatin/carboplatin) of *[Academic / commercial in confidence information removed]*.

A sensitivity analysis has been conducted using an alternative OS curve to assess the impact of this on the cost-effectiveness of crizotinib. The Gompertz curve was used in sensitivity analysis as this provided a similar extrapolation to the Weibull curve. This is presented in **Error! Reference source not found.**.

5.3.5 Input from clinical experts

In all cases, assumptions were made in a manner consistent with published literature and previous NICE appraisals wherever possible. An advisory board of four UK clinical experts with ALK-positive treatment experience was held to gain clinical expert input.

While overall the patient population studied in PROFILE 1014 was considered by the clinical experts to be generalisable to patients in the UK, key patient characteristics may differ with those presenting in practice, namely age, smoking status and ECOG status.

The extrapolated survival curves for the cohort from the PROFILE 1014 study were discussed (both adjusted and unadjusted for crossover) with the clinical experts, and it was felt that projected median OS was being over-estimated for both the crizotinib and the crossover adjusted pemetrexed cohorts, compared to patients that would present in UK clinical practice.

Opinion at the advisory board stated expected OS when treating with pemetrexed plus cisplatin/carboplatin would be around 15 months (see Table 10).

The clinical opinion on both patient characteristics and expected OS drove the decision to explore the use of real-world patient characteristics in the modelled base case (Section 5.3.1.1), which produced estimates of OS similar to expert opinion and historical data for pemetrexed plus cisplatin/carboplatin, and similar to real-world first-line data for crizotinib.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality of life data from clinical trials

Utility was collected in PROFILE 1014 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.[116, 117]

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.[118]

To calculate the mean progression-free 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) pre-progression utility of*[Academic / commercial in confidence information removed]* for crizotinib *[Academic / commercial in confidence information removed]* for pemetrexed plus cisplatin/carboplatin.[3]

5.4.2 Mapping

Mapping was not used within this economic evaluation.

5.4.3 Details of studies in which health-related quality of life was measured

Search strategy

To inform the utility estimates that are used in the model, an update of a previous systematic review in 2012 was carried out to identify the HRQoL and utilities associated with advanced/metastatic lung cancer; this previous review was used to inform HTA submissions in the UK for crizotinib for the treatment of previously-treated ALK-positive NSCLC, which included NICE TA296.[5] The 2012 systematic review was in-turn conducted as an update of another, original review, performed in 2011 to inform the manufacturer’s NICE submission for erlotinib in advanced or metastatic NSCLC (TA258).[81] This review was chosen for update as it is a recent, high-quality systematic review in a similar but broader population and has previously been appraised through prior HTA processes.

The updated systematic review process adhered to the CRD guidance for undertaking systematic reviews in health care and the PRISMA reporting checklist to ensure transparency and a reproducible method of conducting and reporting data from systematic reviews.[100, 101]

The following electronic databases were searched on the 31st July 2015, except the Cochrane database which was searched on 3rd August 2015:

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (OVID)
- The Cochrane Library, incorporating;

    - The Health Technology Assessment (HTA) Database
    - The NHS Economic Evaluation Database (NHS-EED)
- EconLit (EBSCO)

A lower date limit of the 13th June 2012 was applied to the searches of MEDLINE, MEDLINE In-Process and Embase to update searches in concordance with the previous systematic review described above. In the EBSCO search of EconLit and the search of the Cochrane Library, a date limit of 2012 was applied. To retrieve further studies not identified through the electronic database search, reference lists of included articles were scanned, and searches for grey literature, as well as completed and on-going trials, were also carried out.

Full search strategies for the HRQoL review are provided in **Error! Reference source not found.**.

Eligibility criteria

Citations found through the searches were assessed by two independent reviewers for inclusion based on abstract and title. Full-text copies of studies that potentially met the initial criteria were then obtained and reviewed against the inclusion criteria by two independent reviewers. Studies that met the eligibility criteria when the full texts were reviewed at the second screening stage then had their data extracted by a reviewer and checked by a second party.

The inclusion and exclusion criteria used to select relevant studies are outlined in Table 47. Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction table.

Table 47: Eligibility criteria used in the search strategy for identification of HRQoL studies

Inclusion criteria	**Participants**	Adult patients with metastatic or advanced lung cancer
	Interventions	Any
	Comparators	Any
	Outcomes	• Health related quality of life • QALY • Quality adjusted life year • SF-36 • SF-12 • EQ-5D • EQ-5D-5L • EUROQOL • Time trade off • Standard gamble • Utilities
	Study design	Any
Exclusion criteria		• Not English language • Not in humans • Not in adult metastatic/advanced lung cancer patients • Not HRQoL related • No useful HRQoL data or utilities reported (e.g. use of VAS/rating scale alone, or methodological papers) • Article published prior to June 2012 • If not a primary study, article reports only data published prior to June 2012

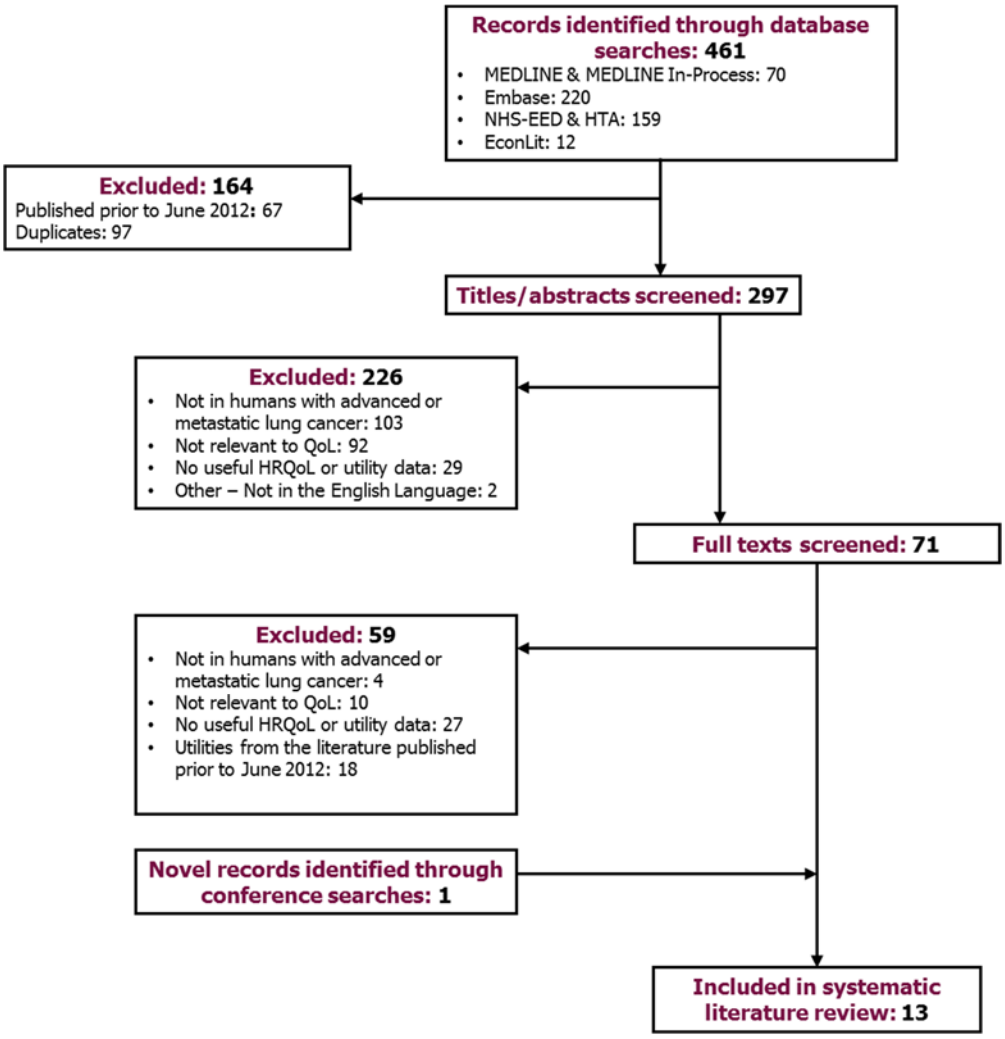
Summary of identified studies and results

The updated systematic literature review identified 13 unique citations; 8 full text publications and 5 conference abstracts.

A summary of the design and key results of included studies reporting HRQoL data are presented in **Error! Reference source not found.** in **Error! Reference source not found.**. Studies identified from the previous systematic literature reviews (of which this described review is an update of) are presented in **Error! Reference source not found.**.

A PRISMA flow diagram of identified studies in the HRQoL systematic literature review is presented in Figure 26.

Figure 26: PRISMA flow diagram of identified studies



5.4.4 Key differences between the values derived from the literature and those reported in the clinical trials

Following review of the included studies, no studies were deemed to be superior in terms of relevance to this submission than HRQoL results collected in PROFILE 1014 which collected on-treatment EQ-5D data for both the intervention and standard of care comparator (see Section 5.4.1). Furthermore, PROFILE 1014 was the only identified study that provided HRQoL data in previously untreated ALK-positive, advanced NSCLC. Therefore, HRQoL data from PROFILE 1014 were used exclusively in the base case analysis.

A comparison of the utility values obtained from PROFILE 1014 (ALK-positive NSCLC) and those in the literature (NSCLC) showed that results in this population were broadly similar with chemotherapy, however it the utilities in PROFILE 1014 are higher than values previously reported (see **Error! Reference source not found.** in **Error! Reference source not found.**). Crizotinib has a higher utility value than chemotherapy, but this is expected, as it is a targeted, innovative therapy with a superior response, symptom improvement and well-managed toxicity profile versus chemotherapy (Section 4.5.1). This is consistent with the utilities reported in the PROFILE 1007 for crizotinib in the second-line indication. The slightly higher reported on-

treatment utilities for chemotherapy likely reflect the patient characteristics of ALK-positive patients.

5.4.5 Adverse reactions

A number of 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.[147] 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.[57] 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 48).

Table 48: 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) [57]

Thomas *et al.* (2011) reported that a Common Terminology Criteria for Adverse Events (CTCAE) score of >2 was associated with a greater risk of worsening HRQoL.[148] However, as this publication was available only as a congress abstract at the time of writing this submission, further information on the methodology used and the results are limited. Another 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.[149]

5.4.6 Health-related quality of life data used in cost-effectiveness analysis

5.4.6.1 Progression-free utilities

The HRQoL of a patient with NSCLC is affected by pain, mobility functionality and symptom burden.[92] 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.[68] 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.[68]

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.[147]

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.[83]

Within the cost-effectiveness model, patients are expected to incur different utility values in the *progression free* health state dependent on the first-line treatment received. Patients receiving crizotinib are expected to have higher utility than patients receiving pemetrexed plus cisplatin/carboplatin (0.81 vs. 0.72 as observed in PROFILE 1014). This is likely because crizotinib reduces symptoms of the disease more than does chemotherapy, and is associated with fewer and less severe side effects. These are shown in the difference in outcomes in quality of life between the treatment arms in PROFILE 1014, as set out in Section 4.7.2.

5.4.6.2 Sustained utility during treatment beyond progression

Based on PROFILE 1014, a proportion of patients are assumed to receive crizotinib treatment beyond progression. The rationale for a treating clinician to do so is because they perceive a continued benefit to a patient's HRQoL; this may be in the form of limiting the speed of disease progression or to allow the patient to continue to benefit from the superior toxicity profile of crizotinib compared with the next line of treatment (docetaxel). In order to reflect this benefit, a 'sustained' utility is applied for the duration of treatment beyond progression (4 cycles) for the proportion of patients in the model assumed to receive it. Due to some degree of disease progression and potential symptom worsening, it is unlikely patients would achieve the same utility score as pre-progression, however it is similarly unlikely their utility score would decrease to that of a second-line patient (as this defeats the point of treating beyond progression). Hence, the model assumes that the 73% of patients treated beyond progression with crizotinib have a utility score that is the midpoint between first-line and second-line utility (Table 49 and Figure 27).

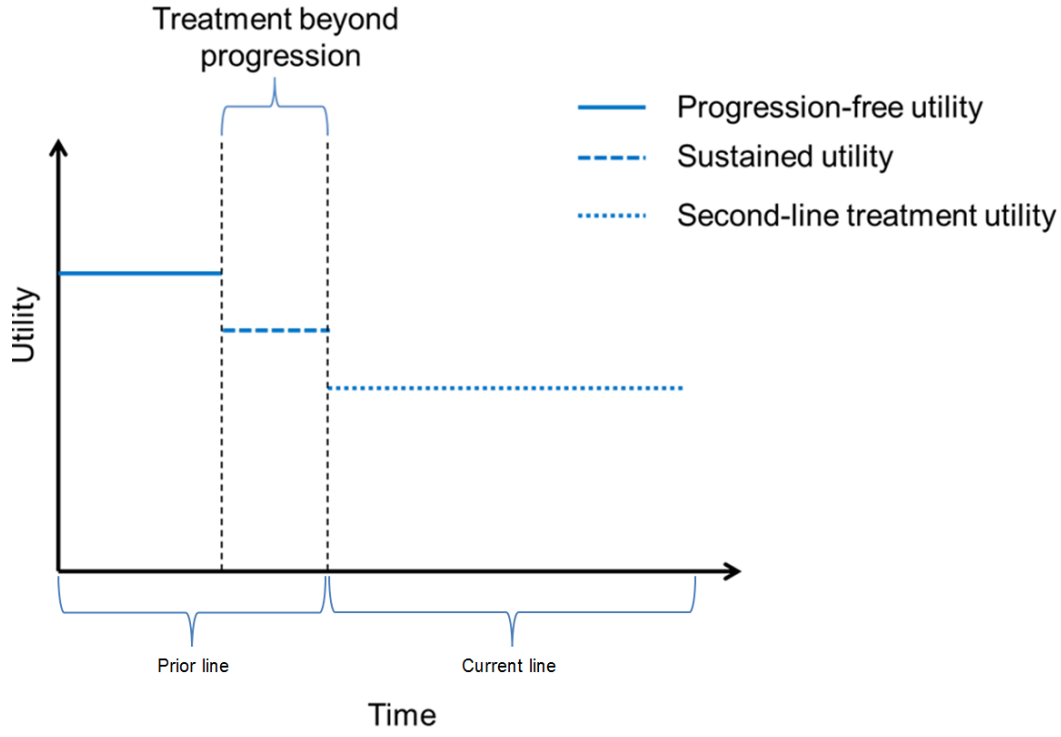
Table 49: Sustained utility applied in the model during treatment beyond progression

Patients	Utility before progression	Sustained utility value during TBP	Utility on second-line docetaxel chemotherapy
Following crizotinib (treatment beyond progression)	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	0.66

	removed]	*removed]*	

Following the completion of treatment beyond progression, patients then move to the utility for second-line treatment with docetaxel. This assumption was validated as plausible in discussions with clinical experts who confirmed that the utility, although impacted, will not immediately drop to expected levels until after initiation of second-line therapy. The sensitivity of the model results with regards to this assumption is explored in a sensitivity analyses (see Section 5.8.3).

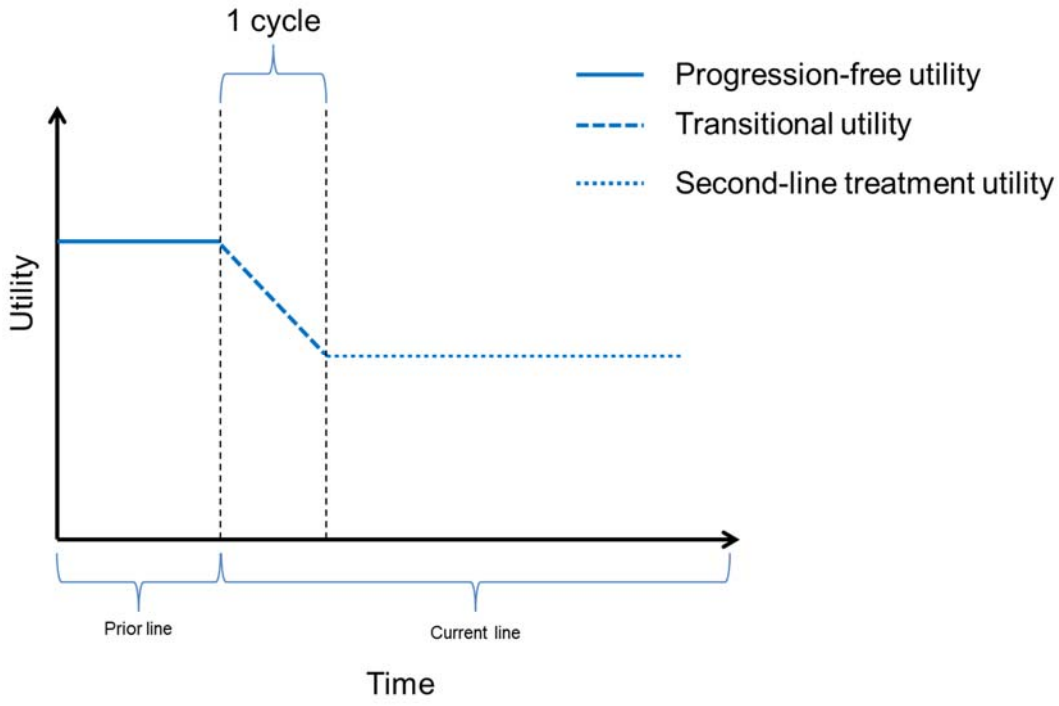
Figure 27: Sustained utility during treatment beyond progression



5.4.6.3 Transitional utility following progression between lines of treatment

In the base case analysis, a 'transitional' utility is applied when moving between health states, during the first cycle following progression in order to best reflect the patient pathway in reality. The value of this transitional utility is a value in between the utility in pre-progressions and the utility in post-progression. This rule is applied when transitioning between first-line and second-line treatment, but is also applied between second-line and third-line treatment. This is intended to represent that, following progression between lines of treatment, it is implausible that a patients' utility will drop immediately to the utility associated with the next line of treatment on the first day following confirmation of progressed disease; it is logical and clinically rational to assume there is a period of transition in HRQoL between states. Figure 28 illustrates this transitional utility when moving between states.

Figure 28: Transitional utility following progression



A sensitivity analysis is presented whereby the transitional utility is removed and patients' utility drops immediately to that of the next treatment line following progression.

5.4.6.4 Progressed disease utilities

HRQoL decreases with disease progression. Nafees *et al.* (2008) used SG techniques to elicit preferences of members of the UK general population for health states associated with metastatic NSCLC.[57, 93] It was shown that progressive disease showed lower utility (0.483) compared with stable disease with no toxicity (0.653).[93] In order 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 second-line therapy after progressing, thus allowing the differences in modelled results to be reflective of the incremental differences in first-line therapy only. Discussions with the UK clinical experts at the advisory board highlighted that docetaxel would be a common second-line therapy, so for the duration of second-line treatment, the utility for patients receiving second-line treatment with docetaxel in ALK-positive NSCLC were obtained from the PROFILE 1007 trial.[150] In order to model the treatment pathway of a patient in UK practice, the duration of docetaxel 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, it was understood from the UK clinical experts that patients would not be offered chemotherapy when progressed into the third-line, hence the utility for patients beyond this point (who were receiving BSC) was assumed to be consistent with the utility for progressive disease following second-line treatment from Nafees *et al.* (2008).[57]

5.4.6.5 Adverse event disutilities

As the HRQoL estimates included in the PROFILE 1014 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. Hence, the utility estimates included in the economic model for the crizotinib and pemetrexed plus cisplatin/carboplatin arms are already expected to include any disutility incurred through adverse events. Therefore, in the base case, no disutility due to adverse events is applied as it would be double-counting. This assumption in the base case produces a more conservative ICER as crizotinib has a more favourable adverse event profile compared with pemetrexed plus cisplatin/carboplatin, thus benefits incremental when disutilities are introduced for these events.

A sensitivity analysis is provided whereby disutilities from adverse events are applied to each treatment arm during cycle 1, based on the disutilities presented in Table 50 and the incidence of adverse events (see Table 58). Adverse events were included if they were of Grade 3/4 and occurred in ≥5% of either treatment arm in PROFILE 1014. Incidences of grade 1 and 2 adverse events were not considered as these would not be expected to require active intervention or have a large impact on quality of life.

The calculated total disutility from the adverse event profiles are 0.01 for crizotinib patients and 0.03 for pemetrexed plus cisplatin/carboplatin patients.

Table 50: Disutilities due to adverse events

Health state	Utility decrement	Reference
Elevated transaminases	0.00	Assumed to not have a disutility
Neutropenia	0.09	Nafees *et al.* (2008) [57]
Anaemia	0.07	Nafees *et al.* (2008) [57]- assumed same as fatigue, as per TA181 [83] and TA192 [82]
Leukopenia	0.09	Nafees *et al.* (2008) [57] - assumed same as neutropenia. As per TA296 [5]
Thrombocytopenia	0.09	Nafees *et al.* (2008) [57] - assumed same as fatigue, as per TA181 [83]

Including adverse event disutilities in addition to EQ-5D utility estimates as a sensitivity analysis has been explored because it is possible that some patients in the PROFILE 1014 trial could have missed treatment visits due to adverse events and therefore not have completed the EQ-5D. Additionally, an adverse event could be experienced but then also treated between the time-points at which the EQ-5D questionnaire was administered in the PROFILE 1014 trial (treatment visits), therefore at the time of the EQ-5D measurement, the effect of the adverse event may not be picked up. This sensitivity has minimal impact on the results of the analysis due to the small proportions of patients experiencing adverse events, and the small utility decrement associated with these.

5.4.7 Health-related quality of life over time

Within the cost-effectiveness model, HRQoL is assumed to decrease over time as patients experience disease progression on first-line treatment and then on second-line treatment, as described above. Within each disease sate (*progression free*, *progressed disease* on docetaxel and *progressed disease* on BSC), an 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.

5.4.8 Baseline health-related quality of life

No single baseline HRQoL was used within the economic model.

5.4.9 Adjustments to health state utility values

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

5.4.10 Health effects excluded from the cost-effectiveness analysis

The impact of adverse events on utilities has not been considered in the base case analysis, as discussed in Section 5.4.6.

No other health effects were identified that were excluded from the cost-effectiveness analysis.

5.4.11 Summary of utility values chosen for the cost-effectiveness analysis

The utility values used within the economic model base case are shown in Table 51.

Table 51: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission	Justification
Progression free				
Progression free – crizotinib	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	Section 5.4.1	Observed in PROFILE 1014; specific to first-line treatment of ALK-positive NSCLC with crizotinib and pemetrexed plus cisplatin/carboplatin
Progression free – pemetrexed plus cisplatin/carboplatin	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	Section 5.4.1	
Progressed disease				
Treatment beyond progression with crizotinib: Sustained utility for 3 cycles	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	Section 5.4.6.2	There is expected to be a benefit to patient's HRQoL compared with moving them to second-line therapy immediately that justifies the choice to continue treatment beyond progression
Progressed disease: second-line treatment with docetaxel	0.66 (0.04)	(0.58, 0.74)	Section 5.4.6.4	PROFILE 1007 provides utility values for second-line treatment of ALK positive NSCLC with docetaxel [150]
Progressed disease: third-line treatment with BSC	0.47 (0.05)	(0.38, 0.57)	Section 5.4.6.4	Nafees *et al.* (2008) provides utility values for third-line treatment of NSCLC [57]

Abbreviation: ALK: anaplastic lymphoma kinase; BSC: best supportive care; NSCLC: non-small cell lung cancer; CI: confidence interval; SE: standard error.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Parameters used to estimate cost-effectiveness

In line with recent NICE technology appraisals of NSCLC treatments and published literature, the following range of cost inputs were considered in the modelling undertaken:

- Drug acquisition cost for crizotinib and comparator treatments. Dose intensity for crizotinib has not been included, which follows a conservative approach.
- Administration cost of intravenous chemotherapy.
- No administration costs were assumed for crizotinib in the base case (the cost of oral chemotherapy administration was applied as a one-off cost in a scenario analysis only)
- NHS resource use associated with routine medical management and best supportive care.
- Treatment for adverse events related to crizotinib and its comparators.
- ALK-testing costs were applied to the crizotinib arm of the model.

All costs are further described below.

5.5.2 Resource identification, measurement and valuation studies

Search strategy

A systematic review update was carried out to identify costs and resource use data from the literature in a population with advanced/metastatic ALK-positive NSCLC. The previous review (from which this update is based) was used to inform HTA submissions in the UK for crizotinib for the treatment of previously-treated ALK-positive NSCLC (e.g. NICE TA296).[5] The 2012 systematic review was in turn conducted as an update of another, original review, performed in 2011 to inform the manufacturer's NICE submission for erlotinib in advanced or metastatic NSCLC (TA258).[81] This review was chosen for update as it is a recent, high-quality systematic review in a similar but broader population and has previously been appraised through prior HTA processes.

The updated systematic review process adhered to the CRD guidance for undertaking systematic reviews in health care and the PRISMA reporting checklist to ensure transparency and a reproducible method of conducting and reporting data from systematic reviews.[100, 101]

In line with the previous resource use and cost studies reviews, updates to two separate searches were conducted:

- Search 1: Identification of general costs and resource use studies on patients with advanced/metastatic lung cancer
- Search 2: Identification of costs and resource use particularly associated with molecular or diagnostic testing for genetic mutations in patients with advanced/metastatic lung cancer.

Both searches were conducted on the 31st July 2015 (MEDLINE, MEDLINE In-Process, Embase and EconLit) and 3rd August 2015 (The Cochrane Library databases):

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (OVID)
- The Cochrane Library, incorporating;
    - The Health Technology Assessment (HTA) Database
    - The NHS Economic Evaluation Database (NHS-EED)
- EconLit (EBSCO)

The searches of MEDLINE, MEDLINE In-Process and Embase were run with a lower date limit of the 13th June 2012 to update searches conducted for a previous systematic review conducted as a part of NICE TA296. Similarly, in the EBSCO search of EconLit and the search of the Cochrane Library, a date limit of 2012 was applied. To retrieve further studies not identified through the electronic database search, reference lists of included articles were scanned, and searches for grey literature as well as completed and on-going trials, were also carried out.

Full search strategies and the screening process for the costs and resource use review is provided in **Error! Reference source not found.**.

Eligibility criteria

Citations found through the searches were assessed by two independent reviewers for inclusion based on abstract and title. Full-text copies of studies that potentially met the initial criteria were then obtained and reviewed against the inclusion criteria by two independent reviewers. Studies that met the eligibility criteria after the second screening stage were extracted by a reviewer and checked by a second party.

The inclusion and exclusion criteria used to select relevant studies are outlined in Table 52. Studies which met the eligibility criteria after the second screening stage were extracted by a reviewer and checked by a second party. Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction table.

Table 52: Eligibility criteria used in the search strategy for identification of HRQoL studies

		Search 1: Resource use associated with advanced or metastatic lung cancer	Search 2: Resource use associated with molecular and/or diagnostic testing
Inclusion criteria	**Participants**	Adult patients with metastatic or advanced lung cancer	Adult patients with metastatic or advanced lung cancer*
	Interventions	Any	Any
	Comparators	Any	Any
	Outcomes	Costs and resource use from a UK NHS perspective	Costs and resource use: Associated with molecular and/or diagnostic testing for genetic mutations From a UK NHS perspective
	Study design	Any	Any
Exclusion criteria		Not in humans Not English-language Not in metastatic/advanced lung cancer Not UK-specific Not a public health care perspective Publications/studies published prior to 2012 Non-primary publications/studies published since June 2012, but which present only costs and resource use data previously published prior to June 2012	Not in humans Not English-language Not in metastatic/advanced lung cancer Resource use related exclusively to procedures associated with biopsy or staging of lung cancer Not UK-specific Not a public health care perspective Publications/studies published prior to June 2012 Non-primary publications/studies published since June 2012, but which present only costs and resource use data previously published prior to June 2012

Summary of identified studies and results

Search 1 of the updated systematic literature review identified 23 unique citations including 8 full-text publications and 2 conference abstracts. The majority of identified citations were horizon scanning assessments conducted by the Horizon Scanning Centre of the National Institute for Health Research (NIHR) (n=13).

Search 2 of the systematic literature review update was conducted to identify costs and resource use particularly associated with molecular and/or diagnostic testing for genetic mutations in patients with advanced/metastatic lung cancer. Given the limited scope of the review, only 29 articles were identified through the electronic database searches and one was ultimately deemed eligible for inclusion. However, it is worth noting that costs specifically associated with diagnostic testing, in particular EGFR tests, were identified in Search 1.

A summary of the methodology and results of the identified studies are presented in **Error! Reference source not found.**, along with a summary of the studies identified in the previous reviews upon which this update is based.

PRISMA flow diagrams of identified studies in Search 1 and Search 2 of the cost and resource systematic literature review are presented in Figure 29 and Figure 30, respectively.

Figure 29: PRISMA flow diagram of identified studies (Search 1)

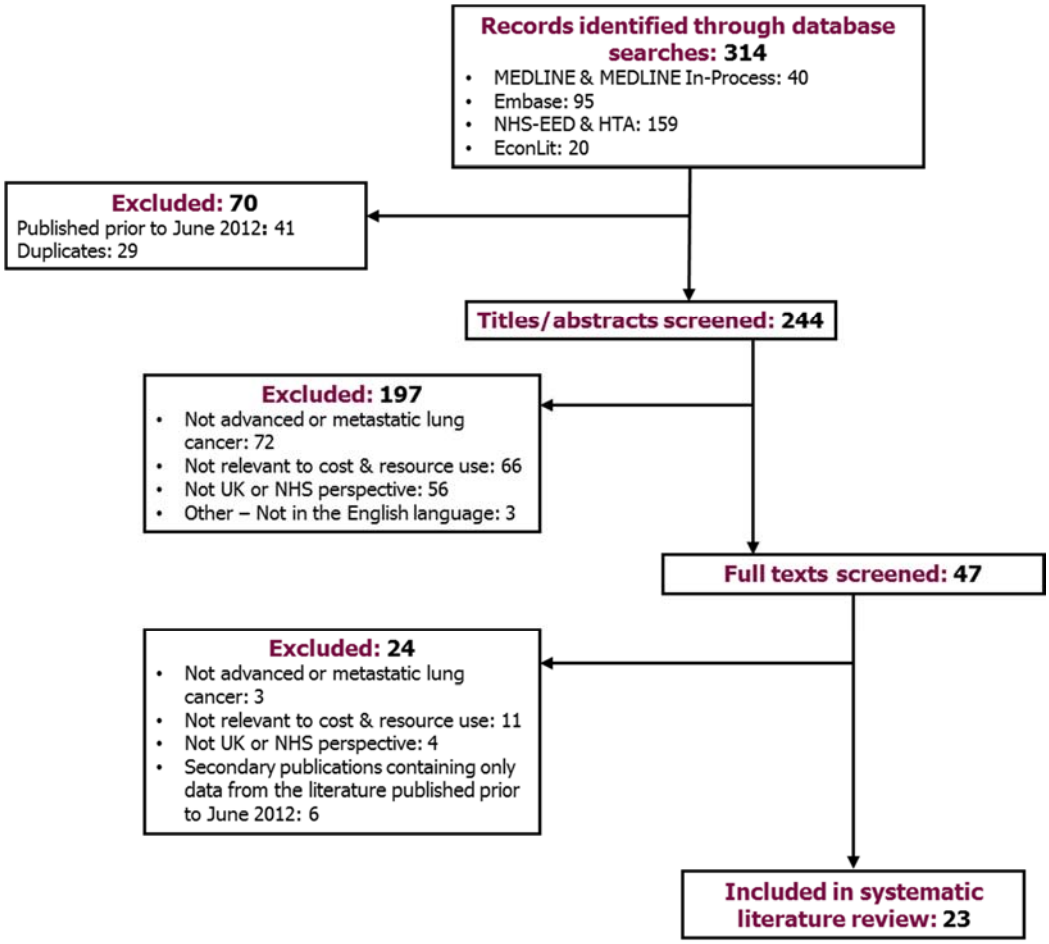
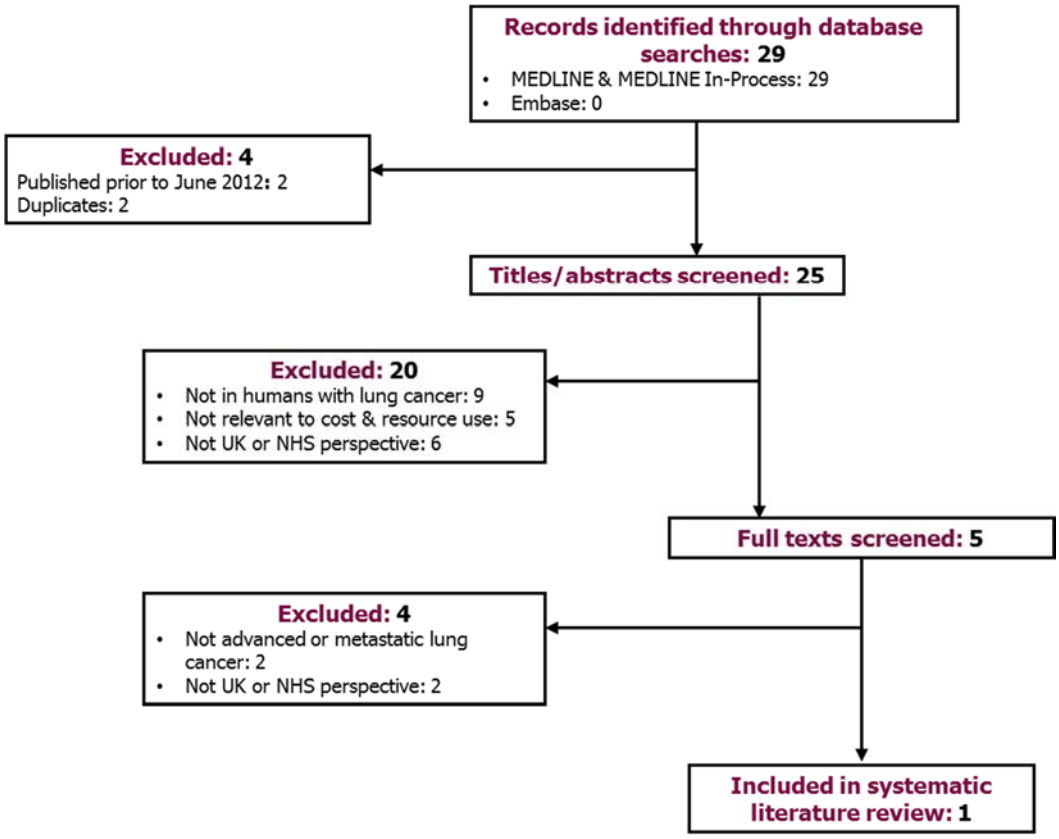


Figure 30: PRISMA flow diagram of identified studies (Search 2)



5.5.3 Unit cost identification and source

Resource use items were obtained using clinical expert opinion, and unit costs were derived from the latest NHS reference costs. The NHS reference costs used include medical oncologist visits, outpatient parenteral administration for chemotherapy, and the costs of tests (chest X-ray, blood count, biochemistry tests, and computed tomography). The appropriate Healthcare Resource Groups for each resource are provided in Section 5.5.6.

5.5.4 Clinical expert input

Assumptions around resource use based around UK clinical input are made that suggest health state costs that are not treatment specific (*e.g.* monitoring) are the same for first-line patients as with second-line patients. Clinical input was sought from the four UK clinical experts at the advisory board who confirmed this was an appropriate assumption.

Moreover, expert clinical opinion was also provided to inform assumptions around diagnostic testing (including testing strategy), and the management of adverse events. Furthermore, the treatment of patients following progression from first-line treatment was discussed with the clinical experts to identify and agree appropriate what second-line treatment options.

5.5.5 Intervention and comparators' costs and resource use

The acquisition costs associated with each treatment are presented in Table 53. Prices were taken from the Monthly Index of Medical Specialities (MIMS) for branded products, and the electronic market information tool (eMit) for generic products.[151, 152]

For the pemetrexed plus cisplatin/carboplatin treatment arm, the distribution of patients across the two platinum regimens is assumed to be as per PROFILE 1014, where patients were eligible to receive either cisplatin or carboplatin based on the investigator's choice. The split observed in the study was therefore expected to reflect clinical practice, where clinicians will be able to choose from either of the two platinum regimens. In PROFILE 1014, 46.15% of patients received pemetrexed plus carboplatin, and 53.85% received pemetrexed plus cisplatin. Clinical experts attending an advisory board expressed opinion that in some centres, up to three-quarters of patients may receive carboplatin instead of cisplatin. A sensitivity analysis is presented in Table 74 that examines the effect on the ICER whereby 75% of patients received pemetrexed plus carboplatin, and 25% received pemetrexed plus cisplatin; the impact was minimal.

With respect to the acquisition cost of crizotinib, Pfizer have proposed a confidential PAS to the Patient Access Scheme Liaison Unit (PASLU) and the Department of Health (DH) which is still under consideration. The proposed confidential discount is stated in the supporting PAS results document to this submission.

Dosing for pemetrexed and cisplatin were based on the body surface area (BSA), which is assumed to be 1.73 m^2 based on patients in PROFILE 1014. Carboplatin dosing is based on a target area under the curve (AUC) of 5–6. In the absence of data from PROFILE 1014 to estimate the target AUC, previous NICE submissions were reviewed for their assumptions regarding the dosing of carboplatin. TA181 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.[83, 153] The dose of 500 mg was selected in the base case as a conservative assumption as this results in the lower cost for carboplatin. The model does not assume any impact on efficacy.

Drug wastage was included in the base case analysis, as this is more likely to reflect the use of therapies in practice. Costs for chemotherapies were calculated assuming that clinicians will use the optimum combination of vial sizes to reach the required dose, rounding up to the nearest full vial. It was assumed that a whole pack of crizotinib would be issued at the beginning of every 30-day treatment cycle. When the cost of treatment beyond progression is included for crizotinib, four cycles worth of cost are incorporated in the model as patients who treated beyond progression did so for a median of 3.1 months, implying significant wastage in the fourth cycle.

In addition to acquisition cost, the cost of administration was included for chemotherapy based regimens (Table 54). 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 for pemetrexed due to the more complex administration required for cisplatin.[83]

Crizotinib is an oral therapy and does not require hospital administration. This assumption is consistent with a previous appraisal of oral therapies (TA347).[153] A one-off cost of oral administration for crizotinib during the first model cycle has been explored as a sensitivity analysis to reflect a situation where patients are given instructions on how to take the tablets by a nurse the first time they receive them. Following administrations are assumed only require the patient to collect their prescription during regular check-ups and therefore are assumed to carry no cost.

As discussed in Section 5.2.5, crizotinib is modelled allowing treatment beyond progression for 4 cycles (3.1 months) in 73% of patients, based on PROFILE 1014. The median PFS in PROFILE

1014 was 10.9 months (equivalent to 11 cycles of crizotinib). However, a sensitivity analysis was conducted whereby crizotinib is modelled as treat to progression.

In the base case analysis, up to 6 cycles of chemotherapy are assumed (pemetrexed plus cisplatin/carboplatin), based on the median number of cycles of pemetrexed plus cisplatin/carboplatin received in the PROFILE 1014 trial where up to 6 cycles were allowed.[3] The SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy.[96] A sensitivity analysis is presented assuming only 4 cycles of pemetrexed plus cisplatin/carboplatin are given; this sensitivity is conservative as it assumes no change to efficacy.

Table 53: Unit costs of intervention and comparator treatment components

Treatment	Unit	Unit cost (list price)	Reference	Dose per cycle (treatment cycle length)	Cost per treatment cycle (cost with PAS)
Crizotinib	60 x 200mg tablets	£4,689.00	MIMS, accessed 13/01/2016 [151]	2x 250mg per day (30 days)	£4,689.00
	60 x 250mg tablets	£4,689.00			
Pemetrexed	100mg vial	£160.00		500 mg/m^2 = 500/1.73 = 866 mg (21 days)	£1,440.00 with wastage £1,385.40 without wastage
	500mg vial	£800.00			
Cisplatin	10mg (10ml vial)	£3.24	eMit, accessed 13/01/2016 [152]	75mg/m^2 = 75/1.73 =130mg (21 days)	£47.00 with wastage £25.72 without wastage £19.98 without wastage
	50mg (50ml vial)	£6.97			
	100mg (100ml vial)	£12.53			
Carboplatin	50mg (5ml vial)	£4.36		Target AUC = 5, dose = 500 mg (21 days) [83]	£34.18 with wastage £28.27 without wastage £22.41 without wastage
	150mg (15ml vial)	£9.90			
	450mg (45ml vial)	£29.82			
	600mg (65ml vial)	£33.92			

Abbreviation: eMit: electronic market information tool; MIMS: Monthly Index of Medical Specialities

Table 54: Administration costs for intervention and comparator treatment components

Treatment	Setting	Cost code	Description	Unit cost
Crizotinib (base case)	N/A	N/A	No cost	£0.00
Crizotinib (sensitivity analysis)	Outpatient	SB11Z	Deliver exclusively Oral Chemotherapy (first cycle only)	£163.85
Pemetrexed plus cisplatin	Day case and regular day/night	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£413.58
Pemetrexed plus carboplatin	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£325.94

Source: NHS reference costs 2014-15.[154]

The costs associated with treatment are summarised in Table 55.

Table 55: Unit costs associated with the technology in the economic model base case

Items	Crizotinib (confidence interval)	Pemetrexed plus cisplatin /carboplatin (confidence interval)	Reference in submission
Technology **Cost per treatment cycle**	£4,689.00 list price	£1,467.76 (£1,467.56, £1,467,95)	Table 53
Mean cost of technology treatment	£51,579.00; assuming median duration of treatment is 11 cycles (accounts for wastage) of 30 days	£8,806.54 (£8,805.37, £8,807.71); assuming median duration of 6 cycles of 21 days	Section 5.5.5
Administration **Cost per treatment cycle**	£0	£373.13 (£228.08, £399.85)	Table 54
Mean cost of technology administration	£0	£2,238.79 (£1,368.46, £2,399.08)	Section 5.5.5
Monitoring cost	N/A – monitoring is expected to be based on health state rather than treatment	N/A – monitoring is costed in the health state	Section 5.5.6
ALK-testing, cost per treated patient	£*[Academic / commercial in confidence information removed]*	N/A – no testing costs are required for pemetrexed treatment	Section 5.5.8.2
Total	**£53,223.60** (£52,917.11, £53,561.22) with PAS]	**£11,045.33** (£10,173.83, £11,206.78)	

Abbreviation: N/A: not applicable

5.5.6 Health-state unit costs and resource use

The details of the health state costs are described in Table 56. 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

Clinical experts confirmed that resource utilisation is expected to be the same for patients receiving first-line and second-line treatment for NSCLC. Resource utilisation assumptions were derived from TA296, which used values from TA162 and TA258.[5, 81, 155] 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 Evidence Review Groups (ERGs) and appraisal committees on three previous occasions and, although not all specifically focusing on patients with an ALK mutation, are applicable for second-line NSCLC patients receiving treatment with an oral agent.

The unit costs for all resource items, other than drugs, were updated to most recently available values (2014-2015).

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 & Bardsley (2014).[156] 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 £7,253 (see Table 57).

Table 56: 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	TA296	£158.54	NHS reference costs 2014-15 Outpatient Attendances Data - medical oncology (370) [154]
	GP visit	10% of patients per month		£50.00	Curtis (2014) Clinic consultation lasting 17.2 minutes without qualification costs [157]
	Cancer nurse	20% of patients receive 1 per month		£66.42	NHS reference costs 2014-15Nurse cancer relate adult face-to-face (N10AF) [154]
	Complete Blood Count	0.75 per month		£3.01	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS05) [154]
	Biochemistry	0.75 per month		£1.19	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS04) [154]
	CT scan	30% patients receive 0.75 per month		£132.18	NHS reference costs 2014-15Direct Access: Pathology Services (RA13Z) [154]
	Chest X-ray	0.75 per month		£30.23	NHS reference costs 2014-15Direct Access Plain Film (DAPF) [154]
Total cost per month (first- and second-line treatment)				**£192.75**	

Health State	Resources Required	Frequency	Reference (frequency)	Unit cost	Reference
Patients in progressed disease health state receiving third-line treatment	Oncologist Visit	1 visit	TA296	£158.54	NHS reference costs 2014-15Outpatient Attendances Data - medical oncology (370) [154]
	GP visits	28% patients (1 visit)		£50.00	Curtis (2014) Clinic consultation lasting 17.2 minutes without qualification costs **[REF**38] [157]
	Cancer nurse	10% patients (1 visit)		£66.42	NHS reference costs 2014-15Nurse cancer relate adult face-to-face (N10AF) [154]
	Complete Blood Count	All patients, 1 per month		£3.01	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS05) [154]
	Biochemistry	All patients, 1 per month		£1.19	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS04) [154]
	CT scan	5% of patients, 0.75 per month		£132.18	NHS reference costs 2014-15Direct Access: Pathology Services (RA13Z) [154]
	X-ray	30% of patients, 0.75 per month		£30.23	NHS reference costs 2014-15Direct Access Plain Film (DAPF) [154]
Total cost per month, Progressed Disease				**£195.13**	

Abbreviation: CT: computed tomography; GP: general practitioner; NHS: National Health Service

.

Table 57: Cost of palliative care

Cost	Unit cost (confidence interval)	Reference
District nurse	£278 (£226, £335)	Georghiou and Bardsley (2014) [156]
Nursing and residential care	£1,000 (£814, £1,205)	
Hospice care – inpatient	£550 (£448, £663)	
Hospice care – final 3 months of life	£4,500 (£3,661, £5,424)	
Marie Curie nursing service	£550 (£448, £663)	
Total cost	*£6,878, then inflated to 2014/15 in line with PSSRU [157]* **£7,253 (£5,901, £8,742)**	

5.5.7 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 either treatment arm in PROFILE 1014 were considered for incorporation into the model, as 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 either treatment arm of PROFILE 1014 were elevated transaminases, neutropenia, anaemia, leukopenia and thrombocytopenia.

For adverse events occurring with crizotinib, clinical expert opinion presented in TA296 indicated that neither elevated transaminases or neutropenia caused by crizotinib treatment would require pharmacological intervention, as 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.[158]

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.[83] There were no incidences of anaemia or thrombocytopenia caused by crizotinib treatment. Consequently, there is no cost associated with treatment of adverse events due to crizotinib treatment as the adverse events considered in the model are managed with dose reduction/interruption. To be conservative, we have not altered 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 chemotherapy treatment have been costed to be consistent with the costings used in previous NICE technology appraisals, 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 58. The costs associated with treating adverse events are described in Table 59.

Table 58: Proportions of patients experiencing each adverse event

Adverse event	% patients with adverse event	
	Crizotinib	Pemetrexed plus cisplatin/carboplatin
Elevated transaminases	14.04%	2.37%
Neutropenia	11.11%	15.38%
Anaemia	0.00%	8.88%
Leukopenia	1.75%	5.33%
Thrombocytopenia	0.00%	6.51%

Abbreviation: NR: not reported.
Source: Crizotinib: PROFILE 1014 [2]; pemetrexed plus cisplatin/carboplatin: PROFILE 1014 [2]

Table 59: Cost of treating adverse events due to chemotherapy with pemetrexed

Adverse event	Resource required	Reference	Unit cost	Total cost	Reference for unit cost
Anaemia	1.7 hospitalisation days	Consistent with TA296	£220.16 per day	£374.27	NHS reference costs 2014-15; Iron Deficiency Anaemia with CC Score 0-1 SA04L [154]
Thrombo-cytopenia	2.0 hospitalisation days		£375.05 per day	£758.50	NHS reference costs 2014-15; Thrombocytopenia with CC Score 0-1 SA12K [154]
Neutropenia	Managed by dose reduction		-	-	-

Abbreviation: TA: technology appraisal.

The costs associated with treating adverse events are described in Table 59 and the total cost of treating adverse events for crizotinib and each comparator treatment are summarised in Table 60, which are based on the proportion of patients experiencing each adverse event. These were applied within the model as a one-off cost during the first cycle of the model for simplicity. As discussed above, adverse events due to crizotinib are assumed to be managed by dose reduction/interruption and hence not to incur any cost.

Table 60: Total cost of adverse events, by treatment

Treatment	One-off total cost of treating adverse events
Crizotinib	£0.00
Pemetrexed plus cisplatin/carboplatin	£163.20

The model was tested with the adverse event costs set to £0 in the pemetrexed arm and this had minimal impact on the deterministic ICER (a change of only £128).

5.5.8 Miscellaneous unit costs and resource use

5.5.8.1 Treatment received following disease progression

Following progression of disease all patients were expected to receive second-line treatment with docetaxel, based on expert clinical opinion which stated that this is the most reflective of clinical practice. 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.[158] Following treatment with docetaxel all patients were assumed to receive best supportive care (consisting of monitoring only) until death. The unit cost and administration cost of docetaxel are provided in Table 61 and Table 62.

Table 61: Unit costs of treatment following progression

Treatment	Unit	Unit cost	Reference	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Docetaxel	20 mg (1 ml Vial)	£4.55	eMit [152]	75 mg/m^2 (21 days)	£21.49 with wastage £19.44 without wastage
	80 mg (4 ml Vial)	£12.39			
	140 mg (7 ml Vial)	£20.95			
	160 mg (16 ml Vial)	£44.84			

Abbreviation: eMit: electronic market information tool.

Table 62: Administration costs for treatment following progression, per chemotherapy cycle

Treatment	Setting	Cost code	Description	Unit cost
Docetaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£325.94

Source: NHS reference costs 2014-15 [154]

5.5.8.2 ALK-testing

In the base case the expected cost per patient to identify one ALK-positive patient from a cohort of all patients with NSCLC is applied to the crizotinib treatment arm, as crizotinib is only licensed for use in ALK-positive patients. This is the cost of one test multiplied by the number of patients needed to be tested to identify one ALK-positive patient. Only acquisition costs of the tests were considered, as the NHS already has the infrastructure in place to perform and analyse such tests.

The model assumes that the testing strategy will be to test with IHC first and then to confirm equivocal results of 1 or 2 with a FISH test, based on a recommendation that this is a "cost-effective" approach to testing in the ESMO guidelines, published in 2014.[24]

The most reliable incidence figure identified for ALK-positivity is 3.4%.[48] Therefore, 29 non-squamous patients would have to be tested to identify one ALK-positive patient (= 1 / 3.4%). Please see Section 3.1 for a more detailed discussion on the incidence of ALK-positivity.

To calculate the cost per ALK-positive patient of testing for ALK-status, concordance tables were considered that show the distribution of NSCLC patients according to their IHC and FISH test results. Concordance data from high risk populations, which have a higher prevalence of ALK-positive patients than the general NSCLC population, were mapped to the expected ALK-positivity incidence of 3.4%. Two antibodies are most commonly used for ALK-testing: the Novacastra and Dako antibodies. The pooled concordance estimates from two studies for the Novacastra antibody (Table 63) were used in this analysis, as the Novacastra antibody has been shown to be slightly more accurate than the Dako antibody.

Table 63: Expected distribution of NSCLC patients according to IHC and FISH tests with Novacastra antibody – pooled data from 2 sources

IHC	FISH: ALK-positive	FISH: ALK-negative	Any FISH
0	0.00%	91.98%	91.98%
1+	0.47%	2.11%	2.59%
2+	2.26%	0.91%	3.17%
3+	2.26%	0.00%	2.26%
Any IHC	5.00%	95.00%	100.00%

Abbreviation: ALK: anaplastic lymphoma kinase; FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry.
Sources: data was pooled from 2 sources [159-161]

For the IHC validation strategies, the model divides the cost of IHC (*[Academic / commercial in confidence information removed]*) by the prevalence of ALK patients (3.4%) to calculate the cost of testing a full cohort with IHC to identify one patient.[48, 162] It then adds on the cost of FISH testing for equivocal IHC cases, calculated by dividing the cost of FISH (£120) by the probability of getting a positive FISH test if there is an equivocal IHC test (37.7%, assuming that IHC 1+ and 2+ will be confirmed by FISH) and then multiplying by the prevalence of ALK-positive patients who received a FISH test (1.9%) divided by the overall prevalence of ALK (3.4%).[163] The calculation for the probability of getting a positive FISH test if there is an equivocal IHC test is as follows: Sum of the probabilities of FISH+ for IHC1+ and IHC2+ (0.47% + 2.26%; Table 63), divided by the sum of the probabilities of IHC1+ and IHC2+ (2.59% + 3.17%; Table 63).

The respective costs calculated per patient are *[Academic / commercial in confidence information removed]* (Table 64). It should be noted that costs may be different when considering the price of the testing kit as purchased from the manufacturer of that test, and the overall cost to the NHS per test (overheads, laboratory costs, etc). It is assumed from the source documentation that the price of the FISH cost covers the total cost to the NHS as it is stated "prices apply to the NHS". It is more difficult to estimate what the difference between the exact cost of the testing kit and the total cost to the NHS of testing with the IHC is due to the lack of publically available data on the cost of IHC ALK-testing.

Table 64: Testing costs applied in the model

Test	Cost per test	Cost per ALK-positive patient identified
IHC 1+ and 2+ confirmed by FISH (base case)	IHC: *[Academic / commercial in confidence information removed]* [162] FISH: £120 [163]	*£[Academic / commercial in confidence information removed]*

Abbreviation: ALK: anaplastic lymphoma kinase; FISH: fluorescence in situ hybridization; IHC: immunohistochemistry.

5.6 Summary of base case de novo analysis inputs and assumptions

5.6.1 Summary of base case de novo analysis inputs

A full summary of model parameters is provided in **Error! Reference source not found.** in **Error! Reference source not found.**.

5.6.2 Assumptions

Table 65: Assumptions in the modelled base case

Assumptions	Assumption description	Justification
Time horizon	Lifetime (15 years)	The economic model runs for 15 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 cisplatin is 500mg	TA181 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 750mg.[83, 153] in the base case the target dose was assumed to be 500mg.	The dose of 500mg was selected in the base case as a conservative assumption as this results in the lower cost for cisplatin.
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 for pemetrexed, due to the more complex administration required for cisplatin.

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.	This is based on the median number of cycles of pemetrexed plus cisplatin/carboplatin 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.
No administration cost for crizotinib	Crizotinib is assumed to incur no administration cost in the base case.	Crizotinib is an oral therapy and does not require hospital administration. This assumption is consistent with a previous appraisal of oral therapies (TA347).[153] A one-off cost of oral administration for crizotinib during the first model cycle has been explored as a sensitivity analysis to reflect a situation where patients are given instructions on how to take the tablets by a nurse the first time they receive them. Following administrations are assumed only require the patient to collect their prescription during regular check-ups and therefore are assumed to carry no cost.
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 who treat ALK-positive NSCLC in the UK.
Adverse event costs	Adverse events were assumed not to incur a cost for crizotinib patients.	Clinical opinion in TA296 indicated that adverse events resulting from crizotinib would be managed through dose reduction, dose interruption, or “watch and wait” monitoring.[158]
Treatment beyond progression	Treatment with crizotinib beyond progression is modelled in 73% of patients for 3.1 months in the base case, so is costed for this period.	The PROFILE 1014 trial allowed treatment beyond progression with crizotinib at the investigator’s discretion. A sensitivity analysis has been included whereby crizotinib is given until progression.
Second-line treatment	It is assumed second-line treatment is docetaxel in all cases.	The clinical experts confirmed that docetaxel would be the second line treatment option in a world without crizotinib or pemetrexed in the second line. In order to compare the incremental differences between first-line treatment, it was decided to offer the same treatment to all patients in the second-line, so that factors outside the first-line setting are held constant for both arms.
ALK-testing	The cost of ALK-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 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.[24]

Real-world data	The characteristics of an ALK-positive patient in the model were taken from a retrospective cohort study of real-world patients with ALK-positive NSCLC in the USA and Canada in the base case. These difference in patient characteristics to the clinical trial considered an estimation of covariate-adjusted parametric survival models.[133]	Discussions with clinical experts in the UK around the demographic characteristics of a typical ALK-positive patient bared a strong similarity with real-world patients that have been studied in the US and Canada. Determining the effect of covariate characteristics on efficacy outcomes allowed the use of baseline patient characteristics from the US and Canadian real-world data in the model. This adjustment produced more clinically plausible extrapolations of OS in both treatment arms and more face valid results than the extrapolated PROFILE 1014 trial OS data which was immature. This adjustment increased the ICER making crizotinib less cost-effective; these results are presented in the base case to allow for a more conservative evaluation, hence reducing the uncertainty in decision making. The unadjusted characteristics taken directly from the Phase III PROFILE 1014 trial have also been modelled and are presented in a sensitivity analysis.
Proportional hazards	A common treatment effect is assumed for both PFS and OS	This assumption was assessed by inspecting the plot of log hazards by log time for OS and PFS separately. Neither plot yielded large departures from parallel lines, except in the extremes where data are limited.
PFS curve	The generalised gamma curve was selected as the base case curve for PFS.	The generalised gamma curve was selected for the base case as it had a good fit to the observed data (based on the AIC, BIC and visual inspection) and provided a plausible extrapolation; i.e. the fitted curve predicts nearly all pemetrexed plus cisplatin/carboplatin patients to have progressed by 30 months, and other curves predict longer, more unrealistic PFS times. The Weibull and Gompertz curves have been used in sensitivity analyses to explore uncertainty.
OS curve	The Weibull curve was selected as the base case curve for OS.	The Weibull curve had a good fit to the observed data (based on the AIC, BIC and visual inspection) and provided the most plausible extrapolation (and other curves predict longer, more unrealistic OS times), and this curve was therefore selected in the base case. The Gompertz curve has been used in a sensitivity analysis to explore uncertainty.
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 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 and pemetrexed plus cisplatin/carboplatin arms are taken directly from patients on treatment in the PROFILE 1014 trial, 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', however its inclusion was explored in a sensitivity analysis.

HRQoL is assumed constant over time in a given state	It was assumed that HRQoL in each disease state (progression free, progressed disease on docetaxel and progressed disease on BSC) 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.
Treatment beyond progression	Treatment with crizotinib beyond progression is modelled in 73% of patients for 3.1 months in the base case, so patients' treatment-related utility is assumed to be sustained as first-line crizotinib is much more tolerable than second-line docetaxel.	Utility is a function of both symptoms and toxicity. When disease progression occurs, it is reasonable to assume that utility falls as symptoms have worsened. However, second-line treatment (docetaxel) is far more toxic than crizotinib (reflected in its poorer EQ-5D score), so the utility of patients treating beyond progression would benefit in part from continued use of crizotinib rather than docetaxel. This 'sustained' utility is assumed to be the midpoint between crizotinib's utility in first-line and docetaxel's utility in second-line, thus reflecting the worsening symptoms from disease progression, yet maintaining benefit from lower toxicity. The sustained utility is applied for the duration of treatment beyond progression (4 cycles including wastage) for those who continue to receive treatment, after which it will be followed by a drop to the utility for second-line treatment with docetaxel.
Transitional utility	A transitional utility is applied for the first cycle following progression from first-line to second-line treatment and also from second-line to third-line treatment, to reflect the gradual change in a patient's utility. In this first cycle, a patient's utility will be at the mid-point between the utility of the two states.	This is intended to represent that, following progression between lines of treatment, it is implausible that a patients' utility will drop immediately to the level of utility associated with the next line of treatment on the first day following confirmation of progressed disease. Therefore it is logical to assume there is a short transitional period between cycles as patients' utility changes transit down. The utility in the one transitional cycle is equal to the utility for prior line of treatment, plus 50% of the difference between the utility for the current line of treatment and the utility for the prior line of treatment).

Abbreviations: 1L: first-line; 2L: second-line; AIC: Akaike information criterion; ALK: anaplastic lymphoma kinase; AUC: area under the curve; BIC: Bayesian information criterion; BSC: best supportive care; EQ-5D: EuroQoL-5 dimensions; ESMO: European Society for Medical Oncology; FISH: fluorescence *in situ* hybridisation; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; IHC: immunohistochemistry; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; TA: technology appraisal; USA: United States of America.

5.7 Base case results

5.7.1 Base case incremental cost-effectiveness analysis results

The deterministic base case results are presented in Table 66 for crizotinib at list price. Probabilistic results are provided in Section 5.8.1. These indicate that at a willingness to pay threshold of £50,000 per QALY gained, crizotinib is becomes a cost-effective treatment option when it is provided with the PAS, producing an ICER of *[Academic / commercial in confidence information removed]*per QALY at list price.

Table 66: Base case results – crizotinib at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/carboplatin	£21,480	1.49	*[Academic / commercial in confidence information removed]*				
Crizotinib	£79,884	2.42	*[Academic / commercial in confidence information removed]*	£58,404	0.93	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

5.7.2 Clinical outcomes from the model

The clinical outcomes from the modelled base case are presented in Table 67 for crizotinib and Table 68 for pemetrexed plus platinum based chemotherapy (cisplatin/carboplatin).

The tables also present outcomes data from previously published studies. As the modelled outcomes incorporate the adjustment of patient characteristics to reflect those of real-world patients, outcomes from a crizotinib prospective real-world study (Davis *et al.* [2015]) are presented, and outcomes from a pemetrexed plus platinum prospective real-world study (FRAME) are presented.[94, 133] For further comparison, the tables also provide outcomes from the pivotal phase III trials for both crizotinib (PROFILE 1014) and pemetrexed plus platinum (JMDB; Scagliotti *et al.* [2008]).[2, 74]

A discussion of how these comparative data validate the modelled results is presented in Section 5.10.1.

Table 67: Clinical outcomes (in months) from the model versus published first-line studies – crizotinib

Outcome	Crizotinib		
	Model result (adjusted for real-world patients)	PROFILE 1014 phase III trial [2]	Davis *et al.* (2015) real-world data [133]
Median PFS (months)	9.9	10.9	9.6
Median OS (months)	21.7	Not reached	24
Mean OS (months)	29.0	Data not mature	NR

Table 68: Clinical outcomes (in months) from the model versus published first-line studies – pemetrexed plus platinum based chemotherapy

Outcome	Pemetrexed plus cisplatin/carboplatin			
	Model result (adjusted for real-world patients)	PROFILE 1014 phase III trial [2]	JMDB trial phase III trial [74]	FRAME real-world data [94]
Median PFS (months)	5.9	7.0	5.3	5.6
Median OS (months)	13.8	Not reached	11.8	10.6
Mean OS (months)	17.9	Data not mature	NR	NR

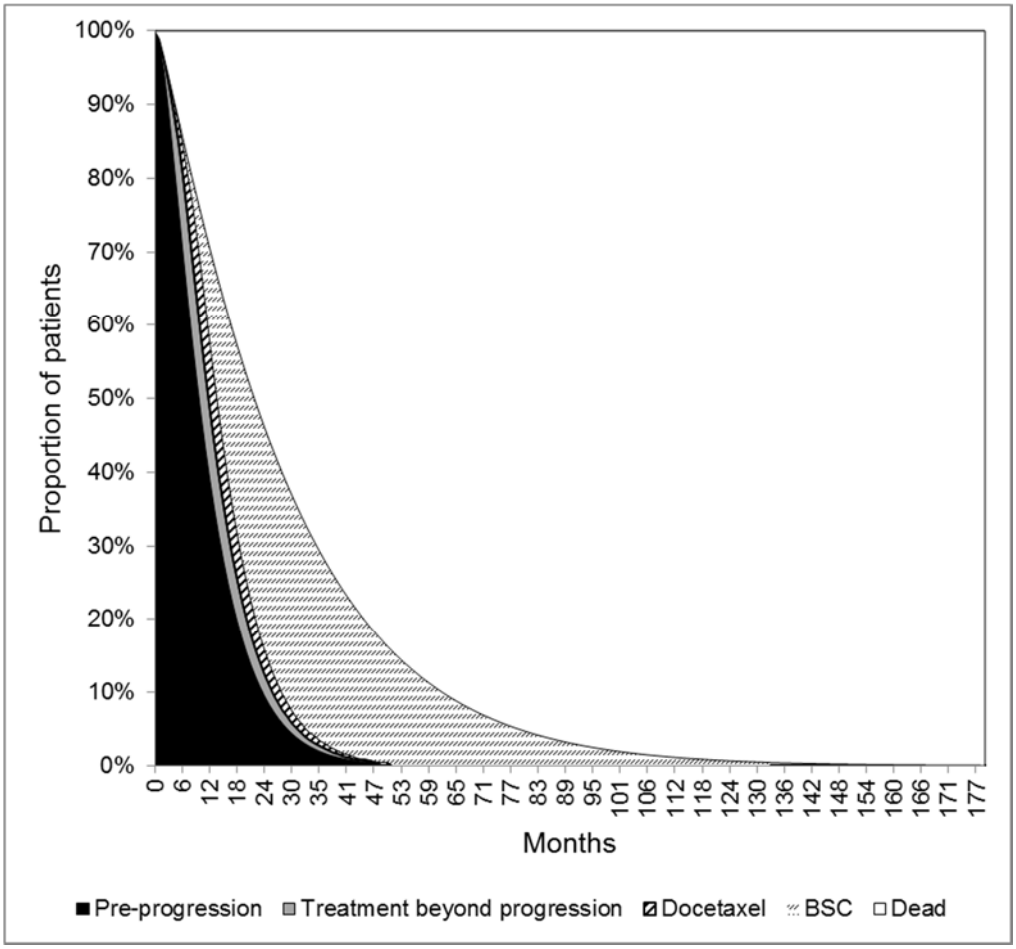
The Markov traces for crizotinib and pemetrexed plus platinum show the proportion of the cohort in each health state over time (Figure 31 and Figure 32). These highlight the time spent in the post-progression survival state in the model is higher for patients who received crizotinib compared with patients who received pemetrexed plus platinum.

This result is expected, based on the observed clinical evidence in PROFILE 1014. In the study, crizotinib demonstrates a greater tumour response and increases the degree to which the tumour shrinks relative to the pemetrexed plus platinum comparator (see Section 4.7.2). This improvement in tumour shrinkage is reflected through crizotinib's statistically significant improvement in symptom related HRQoL versus pemetrexed plus platinum (see Section 4.7.2). At the point when a crizotinib patient does progress, the result of having an improved tumour

response and superior HRQoL from their time on treatment puts a crizotinib patient in a healthier position as they enter the post-progression survival stage; this rationale was also confirmed with the clinical experts at the UK advisory board. The effect of this is that crizotinib patients entering the post-progression state are likely to experience longer post-progression survival as they begin this state in a healthier position. This extended benefit was also recognised in prior health technology appraisals for crizotinib as a second-line therapy.[5]

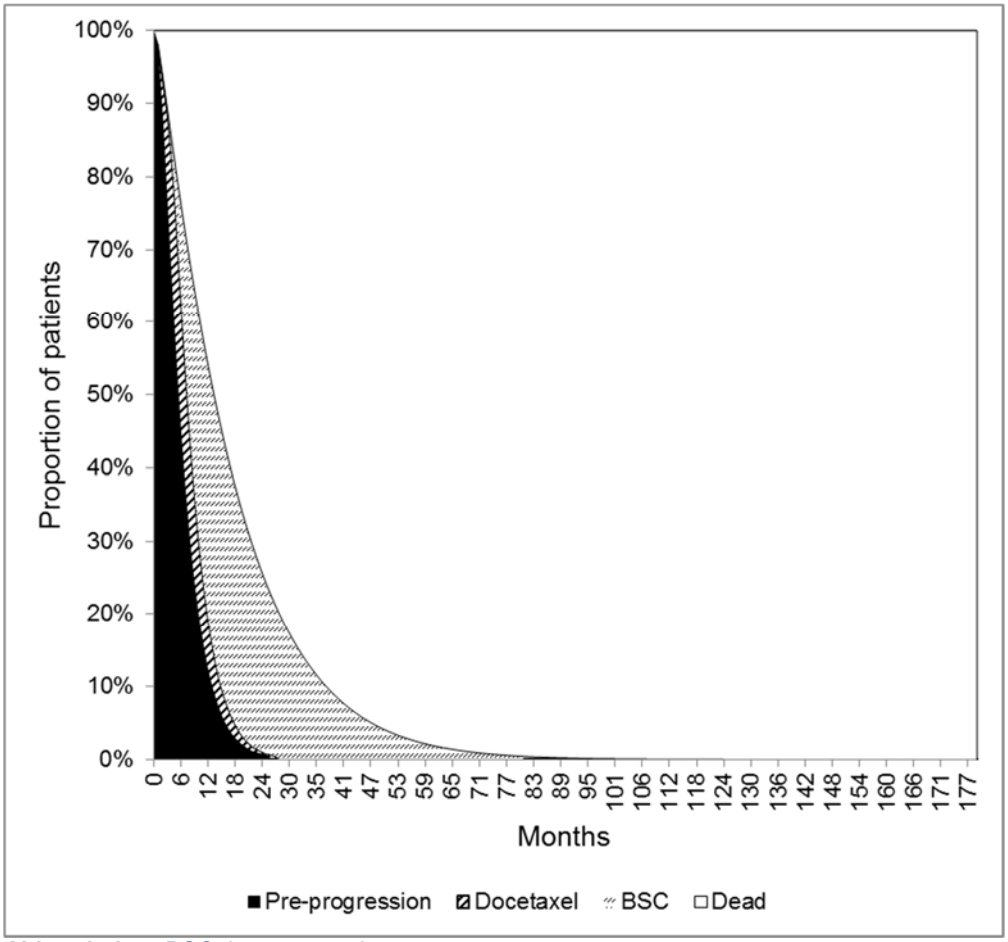
As the model results reflect crizotinib's post-progression survival benefit, the results of the cost-effectiveness evaluation can be said to be in line with not only the PFS and OS outcomes observed in clinical data, but also the tumour response and HRQoL observed outcomes.

Figure 31: Markov trace – crizotinib



Abbreviation: BSC: best supportive care

Figure 32: Markov trace – pemetrexed plus cisplatin/carboplatin



Abbreviation: BSC: best supportive care

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Disaggregated results are presented in Table 69 for the QALY gain by health state, Table 70 at list price, and Table 71 for the resource use by category of cost at list price. These demonstrate that treatment with crizotinib results in increased QALYs in pre- and post-progression states. This is likely due to the improved quality of life for crizotinib patients observed in the progression-free state, and the improved PFS and OS seen for crizotinib over pemetrexed.

Table 69: Summary of QALY gain by health state

Health state	QALY: Crizotinib arm	QALY: Pemetrexed plus cisplatin/ carboplatin arm	Increment	Absolute increment	% absolute increment
Pre-progression	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Post progression	*[Academic /*	*[Academic / commercial in*	*[Academic /*	*[Academic / commercial*	*[Academic / commercial*

	commercial in confidence information removed]	*confidence information removed]*	*commercial in confidence information removed]*	*in confidence information removed]*	*in confidence information removed]*
Total	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.
Abbreviation: QALY: quality-adjusted life year.

Table 70: Summary of costs by health state - crizotinib at list price

Health state	Cost: Crizotinib arm	Cost: Pemetrexed plus cisplatin/ carboplatin arm	Increment	Absolute increment	% absolute increment
Pre-progression	£61,085*	£11,478	£49,607	£49,607	84.94%
Post progression	£18,799	£10,003	£8,797	£8,797	15.06%
Total	**£79,884**	**£21,480**	**£58,404**	**£58,404**	**100%**

* ALK-testing is performed at the initiation of treatment, and therefore has been included in the pre-progression costs for crizotinib.
* Includes the costs of treatment beyond progression for crizotinib treatment arm.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 71: Summary of predicted resource use by category of cost – crizotinib at list price

Item	Cost: Crizotinib arm	Cost: Pemetrexed plus cisplatin/ carboplatin arm	Increment	Absolute increment	% absolute increment
Drug cost*	£65,266	£8,077	£57,190	£57,190	90.52%
Administration cost*	£785	£2,877	-£2,092	£2,092	3.31%
[Academic / commercial in confidence information removed]	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Adverse event cost	£0	£82	-£82	£82	0.13%
[Academic / commercial	*[Academic / commercial*	*[Academic / commercial in*	*[Academic / commercial*	*[Academic /*	*[Academic / commercial*

in confidence information removed]	*in confidence information removed]*	*confidence information removed]*	*in confidence information removed]*	*commercial in confidence information removed]*	*in confidence information removed]*
[Academic / commercial in confidence information removed]	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Total	**£79,884**	**£21,480**	**£58,404**	**£63,177**	**100.00%**

*Includes costs associated with first- and second-line treatment.

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To determine the number of probabilistic simulations required to obtain approximately stable results from probabilistic analysis, 10,000 simulations were run (please see **Error! Reference source not found.** for the probabilistic sensitivity analysis diagnostics). Following this, it was observed that in fact 5,000 was a suitable number for obtaining reliable results as the total costs and QALYs estimated from the two runs are very similar (but will never be identical as different random numbers are used). This test was performed several times. The total costs and QALYs for crizotinib and pemetrexed plus cisplatin/carboplatin obtained from each simulation were recorded and averaged over an increasing number of simulations; this was repeated 5 times.

The incremental results from the probabilistic analyses are presented in Table 72 for crizotinib at list price. The probabilistic ICERs indicate that at a willingness to pay threshold of £50,000 per QALY, crizotinib is a cost-effective treatment option when it is provided with the confidential PAS. These results are very similar to the deterministic base case results with both the PAS and at list price *[Academic / commercial in confidence information removed]*. This similarity in results provides confidence that the most plausible estimate of the ICER is below £50,000 per QALY threshold.

Table 72: Probabilistic mean pairwise cost-effectiveness analysis results – crizotinib at list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/carboplatin	£21,850	*[Academic / commercial in confidence information removed]*			
Crizotinib	£82,647	*[Academic /*	£60,797	*[Academic / commercial*	*[Academic / commercial*

		commercial in confidence information removed]		*in confidence information removed]*	*in confidence information removed]*

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Figure 33 shows the scatter plot of incremental costs and QALYs for crizotinib vs. pemetrexed plus cisplatin/carboplatin from 5,000 probabilistic simulations when crizotinib is provided at list price. Crizotinib consistently results in higher costs and higher QALYs compared with pemetrexed plus cisplatin/carboplatin.

Figure 33: Cost-effectiveness plane: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib at list price

[Academic / commercial in confidence information removed]

Abbreviation: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 34 shows the cost-effectiveness acceptability curves for crizotinib vs. pemetrexed plus cisplatin/carboplatin on the incremental NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY when crizotinib is provided at list price.

Figure 34: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib at list price

[Academic / commercial in confidence information removed]

5.8.2 Deterministic sensitivity analysis

The tornado diagram showing the key drivers of cost-effectiveness in the comparison of crizotinib and pemetrexed plus cisplatin/carboplatin is presented in Figure 35 when crizotinib is provided at list price.

Figure 35: Tornado diagram of the ten most influential parameters: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib at list price

[Academic / commercial in confidence information removed]

Abbreviation: BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year.

In Figure 35 it can be seen that eight of the top ten key drivers in the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact. It is unsurprising that this parameter is the most influential as this parameter drives the incremental difference in OS between the two treatment arms, and therefore affects the overall QALYs and costs attributed to each treatment arm.

In addition to the covariates attributed to the calculation of overall survival, other model driver are the utility applied to 3rd line treatment with BSC and the discount rate for QALYs, as seen in the tornado diagrams. As a crizotinib patients have a longer post progression survival period, then inevitably spent longer in the BSC (third line) stage than chemotherapy patients; the utility gain in this state therefore impacts the ICER, although observing the tornado diagram shows this impact is minor.

5.8.3 Probabilistic scenario and sensitivity of assumption analyses

A number of parameters and assumptions that have been varied in probabilistic sensitivity analyses (5,000 simulations) are outlined in Table 73.

The results of the analyses exploring the sensitivity of assumptions (numbers 1-21) are set out in Table 74 with the results of the scenario analysis exploring crizotinib's cost-effectiveness versus in the squamous population (number 22) set out in Table 75 for crizotinib at list price. Crizotinib remains cost-effective with the PAS at a threshold of £50,000/QALY across the majority of these extensive sensitivity analyses. Full results of the sensitivity analyses are presented in **Error! Reference source not found.**.

Alternative crossover adjustment methods were explored but these had a small effect on the ICER. The other two-stage models beyond the model used in the base case changed the ICER by a small degree. Selecting different combinations of survival curves in the model did not have a large impact on the ICER at either list or PAS price.

Allowing the patient characteristics to be those of the PROFILE 1014 trial lowers the ICER to *[Academic / commercial in confidence information removed]* at list price. Therefore we are confident that the cost-effectiveness estimate that we have produced is conservative and represents the upper bound of the likely ICER.

The ICERs in Table 74 are all probabilistic calculations. In addition to these, the effect on the deterministic ICER was investigated around the cost of AE management. The cost for managing AEs was set to £0 in the comparator arm and this changed the deterministic ICER by £128, suggesting the cost of AEs do not drive the results.

Table 73: Full list of sensitivities undertaken and their respective settings

	Description	Base case setting	Sensitivity setting
1	**Excluding wastage for pemetrexed plus cisplatin/carboplatin**	Include wastage	Exclude wastage
2	**Excluding ALK-testing costs**	Include	Exclude
3	**Alternative crossover adjustment: TSB**	TSA	TSB
4	**Alternative crossover adjustment: TSC**		TSC
5	**Alternative crossover adjustment: RPSFT-Wilcoxon**		RPSFT-Wilcoxon
6	**Alternative crossover adjustment: RPSFT-Log-rank**		RPSFT-Log-rank
7	**Patient characteristics as per PROFILE 1014**	Real-world data (Davis *et al.* [2015]) [133]	PROFILE 1014
8	**Alternative survival models: (PFS=Gamma, OS=Gompertz)**	PFS=Gamma, OS= Weibull	PFS=Gamma, OS=Gompertz
9	**Alternative survival models: (PFS=Weibull, OS=Weibull)**		PFS=Weibull, OS=Weibull
10	**Alternative survival models: (PFS=Weibull, OS= Gompertz)**		PFS=Weibull, OS= Gompertz
11	**Alternative survival models: (PFS= Gompertz, OS=Weibull)**		PFS= Gompertz, OS=Weibull
12	**Alternative survival models: (PFS= Gompertz, OS= Gompertz)**		PFS= Gompertz, OS= Gompertz
13	**Sustained utility not applied between progression from 1L to 2L and from 2L to 3L**	Yes - Applied to TBP and following progression	Yes - But only applied to TBP
14	**Alternative split of cisplatin (25%) and carboplatin (75%) with pemetrexed**	46.15%	75.00%
15	**4 cycles of chemotherapy to represent clinical practice**	6	4
16	**Applying a one-off cost for crizotinib administration**	No cost	One-off
17	**Including utility decrements due to AEs**	No	Yes
18	**Time horizon: 1 year**	15	1
19	**Time horizon: 5 years**		5
20	**Time horizon: 10 years**		10
21	**Time horizon: 20 years**		20
22	**Squamous population (crizotinib vs. pemetrexed)**	Non-squamous population	Squamous population*

*This analysis extrapolates the outcomes in terms of costs and clinical outcomes of the model from the non-squamous population, and amends the incidence of ALK-positive NSCLC to reflect the lower incidence observed in the squamous population as this is the only parameter for which data were available for the squamous population.

Abbreviation: 1L: first-line; 2L: second-line; 3L: third-line; AEs: adverse events; ALK: Anaplastic lymphoma kinase; OS: overall survival; PFS: progression-free survival; RPSFT: Rank Preserved Structural Failure Time; TSA: two-stage method A; TSB: two-stage method B; TSC: two-stage method C.

Table 74: Summary table of probabilistic sensitivity analyses undertaken – crizotinib at list price

No.	Description	Incremental costs (£)	Incremental QALYs	ICER
1	**Excluding wastage**	£61,416	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
2	**Excluding ALK-testing costs**	£59,383	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
3	**Alternative crossover adjustment: TSB**	£60,977	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
4	**Alternative crossover adjustment: TSC**	£61,304	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
5	**Alternative crossover adjustment: RPSFT-Wilcoxon**	£61,328	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
6	**Alternative crossover adjustment: RPSFT-Log-rank**	£60,731	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
7	**Patient characteristics as per PROFILE 1014**	£76,593	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information*

				removed]
8	**Alternative survival models: (PFS=Gamma, OS=Gompertz)**	£60,983	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
9	**Alternative survival models: (PFS=Weibull, OS=Weibull)**	£60,982	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
10	**Alternative survival models: (PFS=Weibull, OS= Gompertz)**	£61,168	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
11	**Alternative survival models: (PFS= Gompertz, OS=Weibull)**	£61,981	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
12	**Alternative survival models: (PFS= Gompertz, OS= Gompertz)**	£62,194	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
13	**Transitional utility not applied between progression to subsequent line of treatment**	£60,845	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
14	**Alternative split of cisplatin (25%) and carboplatin (75%) with pemetrexed**	£60,800	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
15	**4 cycles of pemetrexed to represent clinical practice**	£64,168	*[Academic / commercial*	*[Academic /*

			in confidence information removed]	*commercial in confidence information removed]*
16	**Applying a one-off cost for first crizotinib administration**	£60,981	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
17	**Including additional utility decrements due to AEs**	£60,804	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
18	**Time horizon: 1 year**	£38,267	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
19	**Time horizon: 5 years**	£59,711	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
20	**Time horizon: 10 years**	£60,698	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
21	**Time horizon: 20 years**	£60,767	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

Abbreviation: 1L: first-line; 2L: second-line; 3L: third-line; AEs: adverse events; ALK: Anaplastic lymphoma kinase; OS: overall survival; PFS: progression-free survival; RPSFT: Rank Preserved Structural Failure Time; TSA: two-stage method A; TSB: two-stage method B; TSC: two-stage method C.

Table 75: Exploratory probabilistic scenario analyses undertaken – crizotinib at list price

No.	Description	Incremental costs (£)	Incremental QALYs	ICER
22	**Squamous population (crizotinib vs. pemetrexed)**	£135,149	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

An exploratory analysis was included for squamous patients in order to reflect the scope. The ICER for the squamous population is not cost-effective in Table 75, however these results should be considered with the number of squamous patients that would present. The ICERs represent a worst case scenario for cost where every squamous NSCLC patient is ALK-tested with the increased cost of testing that needs to be conducted to identify rarer squamous patients impacts the ICER heavily. However, in clinical practice it is expected that squamous patients would only be tested if they were identified as having typical ALK-positive characteristics (such as being young and a non-smoker for example). Henceforth, the number of squamous patients expected to be tested in practice in order to identify one squamous ALK-positive patient is much lower than every single NSCLC patient as is suggested in this scenario analysis; this would result in reduced testing costs and an improved ICER. However, this is difficult to quantify in absolute terms.

5.8.4 Summary of sensitivity analyses results

- The mean ICERs obtained from probabilistic analysis were consistent with those obtained from deterministic analyses. Crizotinib's probabilistic ICER versus the standard of care is lower than the £50,000/QALY threshold when provided with a PAS.
- One-way sensitivity analysis indicated that the key drivers of the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact.
- Crizotinib remained cost-effective across the majority of probabilistic sensitivity analyses when provided with a PAS. Allowing the patient characteristics to be those of the PROFILE 1014 trial (i.e. not adjusting for age or ECOG status at baseline) lowers the ICER and makes crizotinib more cost-effective.

5.9 Subgroup analysis

No subgroup analyses are presented as part of this submission. Although the pre-specified subgroup analyses (see Section 4.8) identified groups of patients that had better outcomes than others (for example PFS and OS outcomes for patients with ECOG performance status 0-1 were better than for patients with ECOG performance status 2), any differences in the relative efficacy between treatment arms across subgroups were minimal.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

5.10.1.1 Consistency with previous appraisals and trial or literature outcomes - PFS

Previous trial and literature PFS outcomes are presented alongside the model's PFS in Table 67 for crizotinib and Table 68 for pemetrexed plus platinum based chemotherapy (cisplatin/carboplatin).

In the crizotinib model arm, the median PFS is similar to that reported in the Davis *et al.* (2015) real-world data study (0.3 months difference).[133] The similarity of the Davis *et al.* (2015) study's PFS face validates the modelled PFS. Crizotinib's phase III trial PFS is higher than the model's PFS, but this is expected as the patient cohort in the trial is healthier than patients in the model which is reflective of current UK clinical practice.[2]

When considering the pemetrexed plus platinum treatment arm, the model's PFS is comparable to that reported in the FRAME study (0.3 months difference).[94] This similarity again provides face validity for the modelled PFS. Pemetrexed plus platinum's PFS in the PROFILE 1014 trial is higher than the model's PFS, but again this is expected as the patient cohort in the trial is healthier than the population included in the model.[2]

Pemetrexed plus platinum's modelled PFS is also similar to pemetrexed's phase III JMDB trial (which is the pivotal trial for pemetrexed which has been accepted within TA181 by NICE), but the slight differences here may be due to the comparison of ALK-positive patients in the model with more general non-squamous patients from the publications.[74] This point may also be applicable to the FRAME study.[94] Nevertheless, multiple data sources support the modelled PFS for pemetrexed plus platinum arm.

The proportional differences in PFS between crizotinib and pemetrexed plus platinum across Table 67 and Table 68 suggests consistency in the treatment effect observed in the trial and the real-world setting, reflected by the model's clinical outcome results.

Table 76: Observed vs. modelled PFS

Proportion of patients in progression-free	Pemetrexed		Crizotinib	
	Observed time (months) from crossover-adjusted Kaplan-Meier	Modelled time (months) using PROFILE 1014 patient characteristics	Observed time (months) from Kaplan-Meier	Modelled time (months) using PROFILE 1014 patient characteristics
90%	1.4	1.8	2.8	3.2
75%	3.6	3.4	6.73	6.2
50% (median)	6.9	6.4	11.1	11.6
25%	10.1	10.8	18.8	19.8

Figure 21 illustrates that all of the fitted curves (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma) consistently under-predict PFS for pemetrexed at the median point when the PROFILE 1014 patient characteristics are used, however at later time-points all of the fitted curves consistently over-predict the observed PFS for pemetrexed. Therefore making a comparison of outcomes at one particular time-point difficult and may not present the most accurate information of the comparative efficacy between crizotinib and pemetrexed (see Table 76).

5.10.1.2 Consistency with previous appraisals and trial or literature outcomes - OS

Previous published trial data and supplemental publications for OS outcomes are presented alongside the model's OS in Table 67 for crizotinib and Table 68 for pemetrexed plus platinum based chemotherapy (cisplatin/carboplatin).

A comparison of the median OS in the modelled base case shows that the model provides a more conservative estimate of median OS when compared to the real-world data reported in Davis *et al.* (2015) (21.7 months versus 24 months).[133] A comparison of median OS from the model to PROFILE 1014 is not possible as median OS was not reached in the PROFILE 1014 trial.[2]

In the pemetrexed plus platinum treatment arm, the difference between the modelled OS and observed real-world data in the FRAME study was of similar magnitude, however the model provides the higher estimate in this case (13.8 months vs. 10.6 months).[94] As was seen with the PFS, pemetrexed plus platinum's OS is slightly higher than observed in its phase III JMDB trial.[74] Again, this may be due to the comparison of ALK-positive patients versus more general non-squamous patients.

Pemetrexed plus platinum's modelled OS is in line with the expected OS in UK practice that was estimated at the clinical expert with experience treating ALK-positive patients in the UK (around 15 months) (see Table 10). As with PFS, the comparisons between the modelled OS and previously published estimates suggest that the model outcomes are supported by multiple data sources.

The proportional differences in OS between crizotinib and pemetrexed plus platinum across Table 67 and Table 68 suggests consistency in the treatment effect observed in the trial and the real-world setting, reflected through the model's results.

5.10.1.3 Clinical expert validation

The projected overall survival curves were shown to the clinical experts at the advisory board, with general agreement that the crossover-adjusted curves were predicting a higher median survival in the ALK-positive NSCLC population than they would have expected in practice. The clinical experts also reviewed the patient characteristics of the PROFILE 1014 trial and, although it was agreed that the trial population was not vastly dissimilar to UK patients, it was felt that ALK-positive patients in the UK would in general be older and would have a worse average ECOG performance score at baseline, compared to the characteristics of the patients enrolled in PROFILE 1014. Given this, patient characteristics from real-world data in the US and Canada incorporated into the model, as these patients were older and had a worse average ECOG performance score than the trial population, as well as having a higher proportion of Caucasian race patients than the PROFILE 1014 trial, which is more representative of the UK patient pool (see Section 5.3.1).

The clinical experts additionally validated resource use assumptions, indicating that they would expect monitoring requirements to be the same for patients receiving first- or second-line treatment and confirmed which treatments would be relevant in current clinical practice.

5.10.2 Quality control

A number of quality control measures were undertaken to validate the model findings included in this submission. Internal quality control was undertaken by the developers of the model on behalf of the manufacturer. In addition, the model was critiqued by an external independent health economist with a full review of model structure, parameter inputs, and core assumptions, as well as results produced. Lastly, the outcomes produced by the model in the base case were reviewed and ratified by clinical experts to confirm face validity and clinically plausibility, and one clinical expert from the original advisory board meeting was also followed up to discuss the approach in which real-world data are used to provide more plausible results and to compare the estimates of survival from the modelled trial data and the modelled real-world data.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Comparison with published economic literature

To our knowledge this is the first economic evaluation comparing crizotinib with pemetrexed plus cisplatin/carboplatin in patients with treatment-naïve ALK-positive NSCLC.

5.11.2 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.

5.11.3 Generalisability of the analysis

The analysis is relevant and generalisable to clinical practice in the UK. The relative treatment effect was established from the PROFILE 1014 trial which included a total of 343 patients across a number of locations. Discussions with clinical experts who treat ALK-positive patients in the UK suggested that, although the patient population is felt to be representative of clinical practice, the reality in the non-trial UK patients who present with NSCLC is that they are often less healthy. The adjustment of the characteristics of the patient cohort in the model to reflect this makes the

results generalisable to clinical practice outside the confines of a global clinical trial. The results of this approach were validated as plausible through expert opinion.

In the base case analysis, only patients with non-squamous tumour histology were included, in line with the trial population of PROFILE 1014. Nearly all ALK-positive patients are non-squamous (97.7%). A separate exploratory scenario analysis was undertaken of squamous cell patients.

The model was developed using the NHS Reference costs and costs from previous technology appraisals presented to NICE as a source of cost inputs.[151, 152, 154, 157] 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.

5.11.4 Strengths of the economic evaluation

The model has been developed to incorporate patient-level data from the pivotal Phase III randomised controlled PROFILE 1014 trial where possible.[2] The trial provided direct head-to-head evidence for crizotinib compared to pemetrexed plus cisplatin/carboplatin, a relevant comparator for the patient population under consideration. Utility data have, where possible, also been taken directly from the PROFILE 1014 (first-line) or PROFILE 1007 (second-line) trials which included the EQ-5D, the generic, preference-based utility measure which is preferred by NICE. The base case modelling approach, including structure and costs included, is consistent with those accepted in previous technology appraisals for treatments of NSCLC, hence allowing consistency and comparability across evaluations.

Despite immature survival data from PROFILE 1014 and the extensive of crossover in the trial, a key strength of the evaluation is that is has produced clinically plausible results that have been validated through expert opinion and with EMA, in terms of the results produced for both crizotinib and pemetrexed. We are confident in the relative clinical effectiveness between these treatments and the low uncertainty seen by the tight range of crossover-adjusted estimates of OS (HR, 0.571 to 0.674).

As discussed in Section 5.10.1, the greater OS benefit observed with crizotinib versus pemetrexed-cisplatin/carboplatin is indicative of both the PFS benefit and the post-progression survival benefit predicted (arising from tumour response; see Section 4.7.2). This is also consistent with the clinical benefits observed and accepted as part of the prior appraisal for crizotinib as a second-line therapy, TA296, where a higher number of months was accepted as OS benefit than compared to PFS benefit.[5]

Given the utmost importance for the model to have face validity, the use of real-world patient characteristics in this evaluation not only provides a set of results that are reflective of clinical practice (Section 5.7.2), but also produces a more conservative upper bound estimate of the ICER for crizotinib in the base case analysis.

A further strength of the economic evaluation is the extensive sensitivity analyses which have been conducted in-depth to test the model's sensitivity to the key drivers of the model. The results of sensitivity analyses demonstrated that the ICER was consistently below the £50,000 per QALY threshold.

5.11.5 Limitations of the economic evaluation

A key limitation of the analysis is that both PFS and OS data had to be extrapolated as neither were complete (i.e. not all patients had experienced the corresponding event) at the data cut-off of the PROFILE 1014 trial. Despite this, by extrapolating based on the observed data in the PROFILE 1014 trial, the best available evidence has been taken into account. The modelled curves varied in their extrapolations, indicating that there is uncertainty in the long-term outcomes for these patients. However, we have undertaken a number of different approaches to estimate the survival benefit and reduce this uncertainty in an attempt to counter this limitation:

- All curves which were considered to have a clinically plausible extrapolation were tested in sensitivity analyses and the curve selection was shown to have minimal impact on the results.

- Acknowledging the uncertainty in extrapolated data, the face validity of the model results was carefully considered and evidence from real-world data was introduced in order to present results with the most face validity. The modelled results were subsequently validated as plausible through expert opinion.

- The approach used throughout the economic evaluation has been conservative, and we are therefore confident in the clinical and cost-effectiveness results produced.

The overall survival outcomes for pemetrexed plus cisplatin/carboplatin observed in PROFILE 1014 are confounded by crossover, and therefore are subject to limitations and uncertainty. This has been explored in sensitivity analyses whereby alternative crossover adjustment methods have been used. These had some impact on the results, but were not the main drivers of cost-effectiveness.

Utilities were only collected prior to progression in the PROFILE 1014 trial. Utilities for docetaxel as a second-line treatment were available from the PROFILE 1007 trial, however no trial-based utilities were available for patients receiving third-line best-supportive care. Therefore utilities from the literature which have been used in previous technology appraisals for NSCLC were used within the model for best supportive care.

5.11.6 Further analyses

Longer-term follow-up of patients with treatment naïve ALK-positive NSCLC receiving crizotinib and pemetrexed plus cisplatin/carboplatin without crossover would improve the robustness of the economic evaluation presented here; however it is recognised that such analyses would be impossible for the comparator given the ethical constraints, and would not be attainable from the PROFILE 1014 trial.

Further follow-up on the PROFILE 1014 trial will enable the OS to mature, allowing a more mature crossover adjusted analysis to be conducted in order to determine the OS benefit. However, despite the issues with crossover, the model has already generated a relative OS benefit that has been externally validated as plausible through UK clinical expert consultation. Consequently, it is expected that future data might only make the estimates of absolute OS more certain, whereas the relative benefit is already established.

5.11.7 Conclusions

Crizotinib is an efficacious treatment for patients with treatment naïve ALK-positive NSCLC and results in improved outcomes compared with treatment with pemetrexed plus cisplatin/carboplatin. When crizotinib is provided with the PAS, it is a cost-effective treatment option for patients with treatment naïve ALK-positive NSCLC and represents value for money to the NHS. The results presented are a conservative upper bound estimate of the ICER and the relative clinical effectiveness of crizotinib versus the UK standard of care has been validated through clinical expert opinion.

6 Assessment of factors relevant to the NHS and other parties

6.1 How many patients are eligible for treatment? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The calculations for the number of ALK-positive patients in England and Wales are presented in the flow diagram (Figure 4) in Section 3.4. It is expected that 459 patients with non-squamous, ALK-positive, advanced, NSCLC would be diagnosed. Based on the population size, it is expected that 434 of these patients would be identified in England, and the remaining 25 in Wales.

This number of new patients per annum is expected to remain constant over the next 5 years, with an estimated 459 new patients developing ALK-positive NSCLC in each of these years. However, if only a proportion of non-squamous NSCLC patients are ALK-tested, then only a proportion of these 459 patients will be identified.

It is very rare that a patient of squamous histology would be eligible for crizotinib as the incidence of ALK-positivity within the non-squamous NSCLC population is estimated at only 0.08% (derived in Section 3.1). The expected number of squamous patients identified each year would thus be very few, considering further that squamous patients are unlikely to be routinely tested for ALK (see discussion in Section 5.8.3).

6.2 What assumption(s) were made about current treatment options and uptake of technologies?

At the advisory board, the four UK clinical experts indicated that current standard of care is pemetrexed plus cisplatin or carboplatin.

Discussions at the advisory board revealed that if crizotinib were an available treatment in the first-line setting, then all identified ALK-positive patients would be offered crizotinib. It is thus assumed that the uptake of crizotinib would be in every patient who is identified as ALK-positive. Hence, the future proportionate use of crizotinib is assumed to be in 100% of identified patients.

6.3 What assumption(s) were made about market share (when relevant)?

In the future market share, the uptake of crizotinib is assumed to be 100%, but this is impacted by the proportion of patients that are ALK-tested. Some ALK-positive patients may not be identified if they had not had an ALK-test at baseline diagnosis. Although these patients may be ALK-positive, if they have not had a test, or there was a delay in test results reaching the treating oncologist, the patients would not be offered crizotinib as their ALK-status would be unknown. The estimate of 459 ALK-positive patients above in Section 6.1 is thus the figure should 100% of patients receive an ALK-test and all 100% have their ALK-status known before treatment initiation. If testing rates are below 100%, then those patients missing the tests would continue to be offered pemetrexed plus cisplatin/carboplatin. In this section's calculations, it is assumed that the testing rate is 100% (every patient receives an ALK-test) as this presents the upper limit of the potential budget impact to the NHS.

Consequently if crizotinib is recommended, it is essential to avoid regional variations in ALK-testing rates as this would lead to inequitable access to crizotinib in the UK, significantly impacting patients' quality of life and life expectancy in the final years of their life.

Any recommendation for crizotinib should specify a national requirement for testing to avoid such regional variations.

6.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The cost of administering treatments is considered in this analysis. Crizotinib is an oral medication that is taken by the patient at home without healthcare resource use. On the other hand, the pemetrexed regimens are intravenously administered and require healthcare resource use at each administration.

The cost of ALK-testing is also incorporated, but is only applied to crizotinib's costs, in line with the economic model's base case.

The costs of monitoring depend on the health state a patient is in (*progression free, post progression, death*). The incorporation of these costs into the modelling of budget impact would thus require efficacy to be modelled in conjunction, as the time spent in these states depends on the PFS and OS associated with each treatment. In order to keep this analysis restricted solely to budget impact and not cost-effectiveness, these costs are not included. Likewise, the costs of adverse events are also not considered in the budget impact analysis, but these are displayed in Table 60 for consideration.

6.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Treatment acquisition unit costs are presented in Table 53 in Section 5.5.5. Administration unit costs are presented in Table 54 in Section 5.5.5.

Using the treatment duration from the economic model, the costs with wastage included are presented in Table 77. The costs presented in this table are all sourced from the data inputs in the model, cited in Section 5, and are in line with the inputs in the economic model. The cost of ALK-testing is taken from Table 64.

Table 77: Cost per patient for the treatments in the budget impact analysis

Treatment	Treatment duration from model	Number of cycles (inc wastage)	Drug cost per patient	Total cost of administration in all cycles	ALK-testing costs per ALK-positive patient
Crizotinib	9.9 months	11	£51,579	£0	*[Academic / commercial in confidence information removed]*
Pemetrexed plus cisplatin/ carboplatin	6 cycles	6	£8,807	£2,239	-

Abbreviations: ALK: anaplastic lymphoma kinase; inc: including.

6.6 Were there any estimates of resource savings? If so, what were they and when would they be made?

Crizotinib introduction is expected to result in administration cost savings for patients currently receiving chemotherapy. As crizotinib is an oral therapy it will not require chemotherapy chair time, staffing costs or pre-medication. This cost offset has been included in Table 78 and is estimated at £1,026,654 per year across the 459 patients.

6.7 What is the estimated annual budget impact for the NHS?

The current budget impact to the NHS to treat the 459 ALK-positive patients is estimated at £5,065,210 before the introduction of crizotinib. This includes the drug acquisition costs (£4,038,556) and treatment administration costs (£1,026,654).

Assuming 100% of patients receive an ALK-test and the uptake of first-line crizotinib will be in all of these patients, the new budget impact is estimated at *[Academic / commercial in confidence information removed]* with crizotinib at list price. This includes the drug acquisition costs, treatment administration costs, and also the cost of ALK-testing. The cost of ALK-testing comprises *[Academic / commercial in confidence information removed]* of the total annual costs. This budget impact is assumed to be constant each year over the next 5 years due to no change in the assumed market shares and/or the incidence of disease.

Table 77 displays the breakdown of costs in the current and future scenarios. This budget impact only provides the estimate with the list price of crizotinib, and without the PAS.

Table 78: Current versus future budget impact

Treatment	Current budget impact	Future budget impact (annual figures, same for years 1, 2, 3, 4 and 5)
Crizotinib		
Drug acquisition cost	£0	£23,653,424
Administration costs	£0	£0
ALK-diagnostic testing costs	£0	*[Academic / commercial in confidence information*

		removed]
Pemetrexed plus cisplatin/carboplatin		
Drug acquisition cost	£4,038,556	£0
Administration costs	£1,026,654	£0
ALK-diagnostic testing costs	-	-
Total budget impact	**£5,065,210**	*[Academic / commercial in confidence information removed]*

Abbreviations: ALK: anaplastic lymphoma kinase.

6.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Additional resource savings are expected outside the NHS within the wider economy. ALK-positive patients are younger than typical NSCLC patients and are more often of working age. As crizotinib not only delays disease progression, but often reduces the size of the tumour and improves symptoms and HRQoL for patients whilst on treatment, the result is that patients of working age may be able to return to work and become economically productive again.

This improvement in patients' health status also alleviates carer burden.

These benefits are discussed in more detail in Section 2.5.1.

6.9 Highlight the main limitations within the budget impact analysis.

The budget impact was conservative in nature for several reasons, and as such may overestimate the actual future budget impact to the NHS:

- ALK-testing is assumed to be 100%. If it is less than this and some patients do not receive an ALK test, then these patients will not incur the cost of crizotinib which reduces the budget impact to the NHS.
    - This also assumes that not only do all patients receive an ALK-test, but the testing turn-around times are efficient; if there are delays in results being sent to the treating oncologist, an ALK-positive patient may be started on chemotherapy in an attempt to halt disease progression without further delay.
- The cost of adverse events management is not included; this is higher for pemetrexed than it is for crizotinib.
- Monitoring costs were not included. It is expected that as crizotinib significantly delays disease progression longer than pemetrexed, as well as improving on treatment HRQoL by a greater magnitude, the monitoring and management of crizotinib patients should be less costly than patients on chemotherapy.

This budget impact only provides the estimate with the list price of crizotinib, and without the PAS.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

Crizotinib for the first-line treatment of anaplastic lymphoma kinase-positive, advanced non-small-cell lung cancer

[ID865]

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

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

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

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

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The 'Specification for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

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

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

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

The patient access scheme has been submitted for crizotinib (Xalkori®) in respect of its indication for the treatment of previously untreated, anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

3.2 Please outline the rationale for developing the patient access scheme.

The patient access scheme aims to provide access to patients for a first-in class innovative targeted therapy, by improving the cost-effectiveness of crizotinib for use within it licensed indication.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The patient access scheme is a simple discount, which is conditional on the level of discount offered remaining confidential and not being published in NICE guidance. It is proposed that NHS Trust procurement entities which have entered into a contract with Pfizer that contains appropriate confidentiality provisions will purchase crizotinib at a discount applied at the point of purchase.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

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

This scheme applies to the whole licensed population, upon ID865 receiving positive recommendation.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example,

degree of response, response by a certain time point, number of injections? If so:

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

The scheme is not dependent upon any criteria and is simply applied as a discount.

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

The scheme will apply to all NHS patients for whom crizotinib is indicated and where the NHS Trusts (and relevant Commissioners requiring knowledge of the scheme for budget planning or other purposes) have received a notification letter of the scheme.

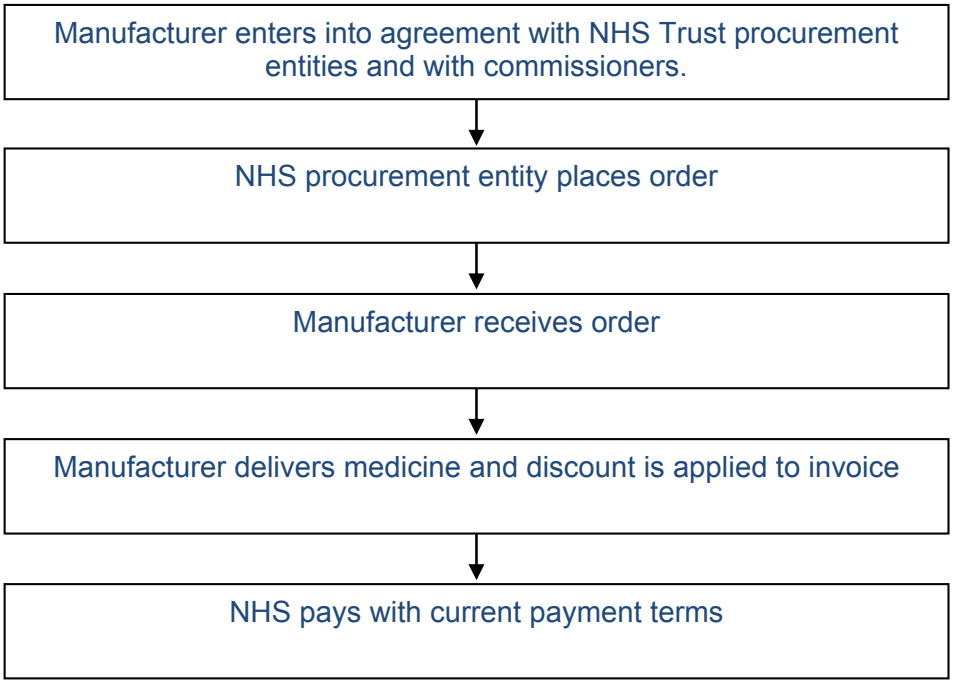
3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The discount will be applied at the point of invoice. The net price for crizotinib, offered through the proposed scheme, will be *[Academic / commercial in confidence information removed]* % below the UK NHS list price for each pack of crizotinib. Once set and following positive guidance from NICE, this net price will be fixed in relation to this scheme, regardless of any subsequent changes to UK NHS list price.

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

The discount will be applied at the point of invoice.

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



3.10 Please provide details of the duration of the scheme.

The proposed patient access scheme will remain in place so long as NICE positive guidance exists for crizotinib, and subject to Department of Health agreement.

It will be conditional upon:

(1) NICE positive guidance for crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene;

(2) NHS Trusts (and relevant Commissioners requiring knowledge of the scheme for budget planning or other purposes) receiving a notification letter of the scheme, although these organisations are not required to sign an additional agreement to receive the benefit of the scheme.

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

There are no equity or equality issues relating to the scheme taking into account current legislation.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and

physicians and patient information documents. Please include copies in the appendices.

Not applicable.

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

Not applicable.

4 Cost effectiveness

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

Not applicable.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been applied by reducing the current NHS list price of crizotinib. The functionality for changing this operates through a cell marked "PAS discount applied" on the "Controls" sheet where the percentage discount can be entered.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The PAS is a simple discount and therefore does not impact the clinical effectiveness data used in the evidence synthesis or in the economic model. The clinical input data used in the model as well as the clinical output data that is produced by the model remains the same with or without the PAS.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The PAS is a simple discount and does not carry additional implementation costs compared to crizotinib without a PAS.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

The PAS is a simple discount and does not carry additional any additional treatment-related costs with the scheme implemented compared to crizotinib without a PAS.

Summary results

Base-case analysis

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

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

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

Table 1. Base-case cost-effectiveness results – crizotinib at list price

	Crizotinib	Pemetrexed plus cisplatin/carboplatin
First-line intervention cost (£)	£65,266	£8,077
Other costs (£)	£14,618	£13,403
Total costs (£)	£79,884	£21,480
Difference in total costs (£)	£58,404	
LYG	2.42	1.49
LYG difference	0.93	
QALYs	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
QALY difference	*[Academic / commercial in confidence information removed]*	
ICER (£)	*[Academic / commercial in confidence information removed]*	

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 2. Base-case cost-effectiveness results – with the confidential PAS

	Crizotinib	Pemetrexed plus cisplatin/carboplatin
First-line intervention cost (£)	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Other costs (£)	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Total costs (£)	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Difference in total costs (£)	*[Academic / commercial in confidence information removed]*	
LYG	2.42	1.49
LYG difference	0.93	
QALYs	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
QALY difference	*[Academic / commercial in confidence information removed]*	
ICER (£)	£46,304	

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

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

Table 3. Base-case incremental results – crizotinib at list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/ carboplatin	£21,480	1.49	*[Academic / commercial in confidence information removed]*				
Crizotinib	£79,884	2.42	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	0.93	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 4. Base-case incremental results – crizotinib with the confidential PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/ carboplatin	*[Academic / commercial in confidence*	1.49	*[Academic / commercial in confidence*				

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

	information removed]		*information removed]*				
Crizotinib	*[Academic / commercial in confidence information removed]*	2.42	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	0.93	*[Academic / commercial in confidence information removed]*	£46,304

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

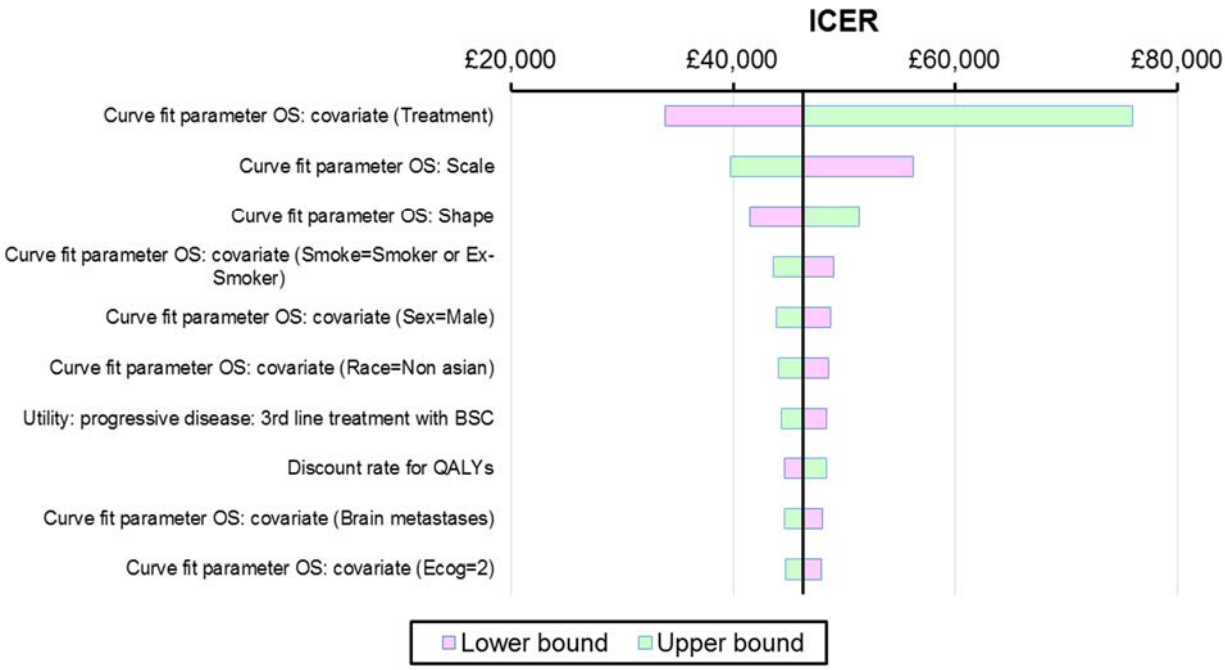
Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The tornado diagram showing the key drivers of cost-effectiveness in the comparison of crizotinib and pemetrexed plus cisplatin/carboplatin when crizotinib is offered with the PAS is presented in Figure 1**Error! Reference source not found.**. It can be seen that eight of the top ten key drivers in the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact. It is unsurprising that this parameter is the most influential as this parameter drives the incremental difference in OS between the two treatment arms, and therefore affects the overall QALYs and costs attributed to each treatment arm.

In addition to the covariates attributed to the calculation of overall survival, other model drivers are the utility applied to 3rd line treatment with BSC and the discount rate for QALYs, as seen in the tornado diagrams. As a crizotinib patients have a longer post progression survival period, then inevitably spent longer in the BSC (third line) stage than chemotherapy patients; the utility gain in this state therefore impacts the ICER, although observing the tornado diagram shows this impact is minor.

Figure 1: Tornado diagram of the ten most influential parameters: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib with the confidential PAS



Abbreviation: BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year.

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

The incremental results from the probabilistic analyses are presented in

Table 5 when crizotinib is provided with the confidential PAS. The probabilistic ICER indicates that at a willingness to pay threshold of £50,000 per QALY, crizotinib is a highly cost-effective treatment option when it is provided with the confidential PAS; the probabilistic base case ICER is £45,495 per QALY. These results are very similar to the deterministic base case result (£46,304). This similarity in results provides confidence that the most plausible estimate of the ICER is below £50,000 per QALY threshold.

Table 5. Probabilistic mean pairwise cost-effectiveness analysis results – crizotinib with confidential PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/carboplatin	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*			
Crizotinib	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,495

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Figure 2 shows the scatter plot of incremental costs and QALYs for crizotinib vs. pemetrexed plus cisplatin/carboplatin from 5,000 probabilistic simulations when crizotinib is provided with the PAS. This indicates that crizotinib consistently results in higher costs and higher QALYs compared with pemetrexed plus cisplatin/carboplatin.

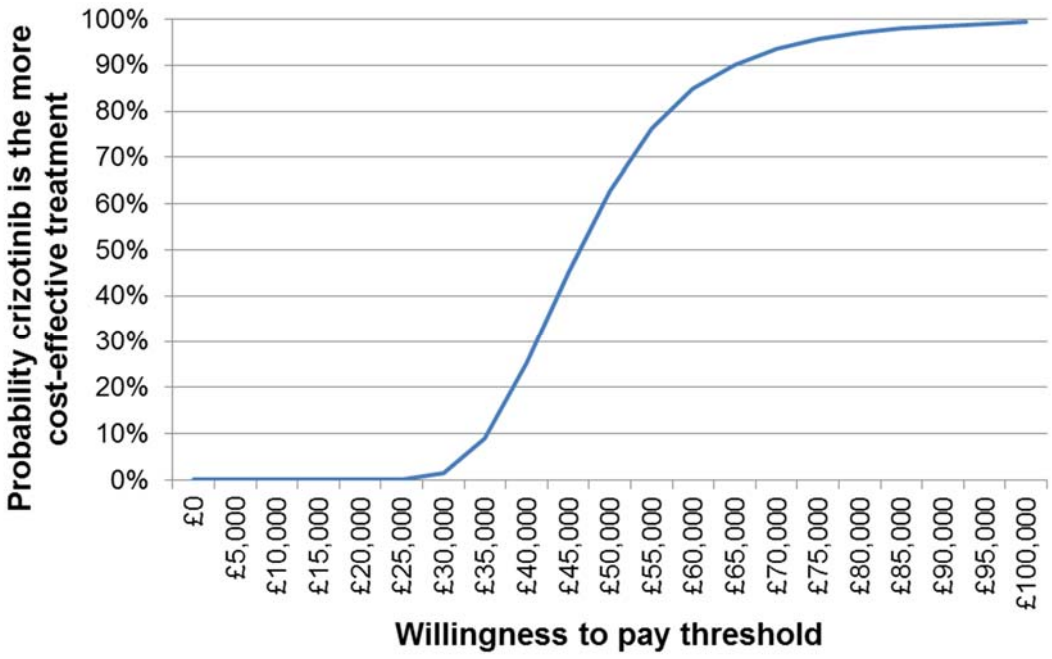
Figure 2: Cost-effectiveness plane: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib with confidential PAS

[Academic / commercial in confidence information removed]

Abbreviation: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 3 shows the cost-effectiveness acceptability curve for crizotinib versus pemetrexed plus cisplatin/carboplatin on the incremental net monetary benefit (NMB) at a range of willingness to pay thresholds up to a maximum of £100,000 per QALY when crizotinib is provided with the PAS. This demonstrates that at a willingness to pay threshold of £50,000 per QALY gained, crizotinib is considered cost-effective compared with pemetrexed on more than 60% of occasions when it is provided with the PAS.

Figure 3: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus cisplatin/carboplatin - crizotinib with confidential PAS



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

A number of parameters and assumptions that have been varied in probabilistic sensitivity analyses (5,000 simulations) are outlined in Table 6. Crizotinib remains cost-effective with the PAS at a threshold of £50,000/QALY across the majority of these extensive sensitivity analyses.

Alternative crossover adjustment methods were explored but these had a small effect on the ICER. The other two-stage models beyond the model used in the base case increased the ICER to a maximum of £47,130 with the confidential PAS. Selecting different combinations of survival curves in the model did not have a large impact on the ICER at either list or PAS price.

Allowing the patient characteristics to be those of the PROFILE 1014 trial lowers the ICER to £40,451 with the confidential PAS. Therefore we are confident that the cost-effectiveness estimate that we have produced is conservative and represents the upper bound of the likely ICER.

Table 6. Summary table of probabilistic sensitivity "scenario" analyses undertaken – crizotinib with confidential PAS

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
1	**Excluding wastage for pemetrexed plus cisplatin/carboplatin**	Include wastage	Exclude wastage	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,868
2	**Excluding ALK-testing costs**	Include	Exclude	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£42,985
3	**Alternative crossover adjustment: TSB**	TSA	TSB	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£47,130
4	**Alternative crossover adjustment: TSC**		TSC	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£44,837
5	**Alternative crossover adjustment: RPSFT-Wilcoxon**		RPSFT-Wilcoxon	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£47,394
6	**Alternative crossover adjustment: RPSFT-Log-rank**		RPSFT-Log-rank	*[Academic / commercial in confidence information*	*[Academic / commercial in confidence information*	£51,274

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
				removed]	*removed]*	
7	**Patient characteristics as per PROFILE 1014**	Real-world data	PROFILE 1014	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£40,451
8	**Alternative survival models: (PFS=Gamma, OS=Gompertz)**	PFS=Gamma, OS= Weibull	PFS=Gamma, OS=Gompertz	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£41,948
9	**Alternative survival models: (PFS=Weibull, OS=Weibull)**		PFS=Weibull, OS=Weibull	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,682
10	**Alternative survival models: (PFS=Weibull, OS= Gompertz)**		PFS=Weibull, OS= Gompertz	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£42,354
11	**Alternative survival models: (PFS= Gompertz, OS=Weibull)**		PFS= Gompertz, OS=Weibull	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,951
12	**Alternative survival models: (PFS= Gompertz, OS= Gompertz)**		PFS= Gompertz, OS= Gompertz	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*	£42,458

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
				information removed]	*information removed]*	
13	**Sustained utility not applied between progression from 1L to 2L and from 2L to 3L**	Yes - Applied to TBP and following progression	Yes - But only applied to TBP	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£44,975
14	**Alternative split of cisplatin (25%) and carboplatin (75%) to reflect perceived clinical practice**	46.15%	75.00%	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,455
15	**4 cycles of chemotherapy to represent clinical practice**	6	4	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£50,413
16	**Applying a one-off cost for crizotinib administration**	No cost	One-off	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,692
17	**Including utility decrements due to AEs**	No	Yes	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,118
18	**Time horizon: 1 year**	15	1	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*	£89,488

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
				information removed]	*information removed]*	
19	**Time horizon: 5 years**		5	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£51,927
20	**Time horizon: 10 years**		10	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,181
21	**Time horizon: 20 years**		20	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,423
22	**Squamous population (crizotinib vs. pemetrexed)**	Non-squamous population	Squamous population	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£154,092

Abbreviations: 1L: first-line; 2L: second-line; 3L: third-line; AEs: adverse events; ALK: Anaplastic lymphoma kinase; OS: overall survival; PFS: progression-free survival; RPSFT: Rank Preserved Structural Failure Time; TSA: two-stage method A; TSB: two-stage method B; TSC: two-stage method C.

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

Not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Results are as set out in Tables 1-6.

The impact of the PAS on the ICER is that the PAS makes crizotinib a cost-effective treatment option for patients with treatment naïve ALK-positive NSCLC and represents value for money to the NHS. A detailed description of the assumptions can be found in the main body of the submission; from these, we believe the results presented are a conservative upper bound estimate of the ICER. The clinical effectiveness of crizotinib in the model that pertains to the ICER versus the UK standard of care has been validated through clinical expert opinion as plausible.

- The base case deterministic ICER is £46,304/QALY with the PAS.
- The base case probabilistic ICER is £45,495/QALY with the PAS.
- The ICERs are based upon direct head-to-head evidence for crizotinib versus the comparator.
- Probabilistic sensitivity analysis indicated that at a willingness to pay threshold of £50,000 per QALY gained crizotinib is considered highly cost-effective compared with pemetrexed on more than 60% of occasions when it is provided with the PAS.
- 21 sensitivity “scenario” analyses were explored where model assumptions were changed. Crizotinib remains cost-effective with the PAS despite alternative statistical survival approaches being considered.
- The modelled clinical outcomes pertaining to the ICERs are plausible and were validated.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

The documents supplied to the Department of Health as part of the PAS can be provided upon approval of the scheme.

5.2 Appendix B: Details of outcome-based schemes

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

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

Not applicable.

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

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

Not applicable.

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

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

Not applicable.

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

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

Not applicable.

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

Not applicable.

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

Not applicable.

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.2.8 Please present the cost-effectiveness results as follows.

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

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

Not applicable.

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

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis

ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Crizotinib for the first-line treatment of anaplastic lymphoma kinase-positive, advanced non-small-cell lung cancer [ID865]

Company evidence submission

ADDENDUM TO THE SUBMISSION:

UPDATED RESULTS OF THE ECONOMIC EVALUATION (Sections 5.5.6 to 5.8)

03 March 2016

ID865

File name	Version	Contains confidential information	Date
ID865 Crizotinib 1L Company evidence submission [ACIC] noPAS (27Jan16)	1	Yes	27th January 2016
ID865 Addendum - Crizotinib 1L Company evidence submission [ACIC] noPAS (03Mar16)	2	Yes	3rd March 2016
ID865 Addendum - Crizotinib 1L Company evidence submission [ACIC] noPAS (03Mar16 _ Amended redacting 18Mar16)	2.1	Yes	18th March 2016
ID865 Addendum - Crizotinib 1L Company evidence submission [ACIC] noPAS_RECATED_18 May 16	2.2	No	18 May 2016

5 Cost-effectiveness

Due to the change in the base case of the cost-effectiveness model following corrections highlighted in the response to clarification questions, a new set of results is provided in this document to replace Sections 5.5.6 through 5.8, and Appendix 23.

- The base case deterministic ICER has increased from *[academic / commercial in confidence information removed]* in the original submission to *[academic / commercial in confidence information removed]* (at list price), an increase of £2,539.

- The base case probabilistic ICER has increased from *[academic / commercial in confidence information removed]* in the original submission to *[academic / commercial in confidence information removed]* (at list price), an increase of £1,720.

Crizotinib remains cost-effective at the £50,000/QALY threshold when offered with the PAS (Addendum to PAS results provided separately).

Base case results

- In the base case analysis, crizotinib was associated with a deterministic ICER of *[academic / commercial in confidence information removed]* at list price, and a probabilistic ICER of *[academic / commercial in confidence information removed]*. Crizotinib was cost-effective with the PAS (results in a separate document) versus pemetrexed plus cisplatin/carboplatin.
- One-way sensitivity analyses indicated that the key drivers of the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact.

Sensitivity analyses

- The mean ICER from the probabilistic analysis was similar to that in the base case analysis; at a willingness to pay threshold of £50,000 per QALY gained crizotinib with the PAS was associated with a high probability of cost-effectiveness.
- In addition to probabilistically running the base case, 21 sensitivity analyses were explored where model assumptions were changed. Crizotinib remains cost-effective with the PAS despite alternative statistical survival approaches being considered. The modelled estimates for survival were credible as they were both externally validated and also in-line with existing literature.
- The modelled clinical outcomes are plausible and were validated. The model suggests a post-progression survival advantage with crizotinib, showing that the benefits of crizotinib extend beyond progression. This benefit can be explained by the greater tumour shrinkage associated with crizotinib whilst on treatment, improving the health status of patients from baseline.
- Crizotinib is an efficacious first-line treatment for adult patients with previously untreated ALK-positive, advanced NSCLC and results in improved outcomes compared with treatment with pemetrexed plus cisplatin/carboplatin, the main comparator in the submission.
- Conservative assumptions have been used and the uncertainty around the ICER has been rigorously investigated. The cost-effectiveness results are credible, robust and plausible; this treatment represents value for money to the NHS

5.5.6 Health-state unit costs and resource use

The details of the health state costs are described in Table 1. 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

Clinical experts confirmed that resource utilisation is expected to be the same for patients receiving first-line and second-line treatment for NSCLC. Resource utilisation assumptions were derived from TA296, which used values from TA162 and TA258.[5, 81, 155] 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 Evidence Review Groups (ERGs) and appraisal committees on three previous occasions and, although not all specifically focusing on patients with an ALK mutation, are applicable for second-line NSCLC patients receiving treatment with an oral agent.

The unit costs for all resource items, other than drugs, were updated to most recently available values (2014-2015).

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 & Bardsley (2014).[156] 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 £7,318 (see Table 2).

Table 1: 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	TA296	£158.54	NHS reference costs 2014-15 Outpatient Attendances Data - medical oncology (370) [154]
	GP visit	10% of patients per month		£50.00	Curtis (2014) Clinic consultation lasting 17.2 minutes without qualification costs [157]
	Cancer nurse	20% of patients receive 1 per month		£66.42	NHS reference costs 2014-15Nurse cancer relate adult face-to-face (N10AF) [154]
	Complete Blood Count	0.75 per month		£3.01	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS05) [154]
	Biochemistry	0.75 per month		£1.19	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS04) [154]
	CT scan	30% patients receive 0.75 per month		£132.18	NHS reference costs 2014-15Direct Access: Pathology Services (RA13Z) [154]
	Chest X-ray	0.75 per month		£30.23	NHS reference costs 2014-15Direct Access Plain Film (DAPF) [154]
Total cost per month (first- and second-line treatment)				**£192.75**	

Health State	Resources Required	Frequency	Reference (frequency)	Unit cost	Reference
Patients in progressed disease health state receiving third-line treatment	Oncologist Visit	1 visit	TA296	£158.54	NHS reference costs 2014-15Outpatient Attendances Data - medical oncology (370) [154]
	GP visits	28% patients (1 visit)		£50.00	Curtis (2014) Clinic consultation lasting 17.2 minutes without qualification costs **[REF**38] [157]
	Cancer nurse	10% patients (1 visit)		£66.42	NHS reference costs 2014-15Nurse cancer relate adult face-to-face (N10AF) [154]
	Complete Blood Count	All patients, 1 per month		£3.01	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS05) [154]
	Biochemistry	All patients, 1 per month		£1.19	NHS reference costs 2014-15Direct Access: Pathology Services (DAPS04) [154]
	CT scan	5% of patients, 0.75 per month		£132.18	NHS reference costs 2014-15Direct Access: Pathology Services (RA13Z) [154]
	X-ray	30% of patients, 0.75 per month		£30.23	NHS reference costs 2014-15Direct Access Plain Film (DAPF) [154]
Total cost per month, Progressed Disease				**£195.13**	

Abbreviation: CT: computed tomography; GP: general practitioner; NHS: National Health Service

.

Table 2: Cost of palliative care

Cost	Unit cost (confidence interval)	Reference
District nurse	£278 (£226, £335)	Georghiou and Bardsley (2014) [156]
Nursing and residential care	£1,000 (£814, £1,205)	
Hospice care – inpatient	£550 (£448, £663)	
Hospice care – final 3 months of life	£4,500 (£3,661, £5,424)	
Marie Curie nursing service	£550 (£448, £663)	
Total cost	*£6,878, then inflated to 2014/15 in line with PSSRU [157]* **£7,318 (£5,901, £8,742)**	

5.5.7 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 either treatment arm in PROFILE 1014 were considered for incorporation into the model, as 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 either treatment arm of PROFILE 1014 were elevated transaminases, neutropenia, anaemia, leukopenia and thrombocytopenia.

For adverse events occurring with crizotinib, clinical expert opinion presented in TA296 indicated that neither elevated transaminases or neutropenia caused by crizotinib treatment would require pharmacological intervention, as 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.[158]

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.[83] There were no incidences of anaemia or thrombocytopenia caused by crizotinib treatment. Consequently, there is no cost associated with treatment of adverse events due to crizotinib treatment as the adverse events considered in the model are managed with dose reduction/interruption. To be conservative, we have not altered 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 chemotherapy treatment have been costed to be consistent with the costings used in previous NICE technology appraisals, 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 3. The costs associated with treating adverse events are described in Table 4.

Table 3: Proportions of patients experiencing each adverse event

Adverse event	% patients with adverse event	
	Crizotinib	Pemetrexed plus cisplatin/carboplatin
Elevated transaminases	14.04%	2.37%
Neutropenia	11.11%	15.38%
Anaemia	0.00%	8.88%
Leukopenia	1.75%	5.33%
Thrombocytopenia	0.00%	6.51%

Abbreviation: NR: not reported.
Source: Crizotinib: PROFILE 1014 [2]; pemetrexed plus cisplatin/carboplatin: PROFILE 1014 [2]

Table 4: Cost of treating adverse events due to chemotherapy with pemetrexed

Adverse event	Resource required	Reference	Unit cost	Total cost	Reference for unit cost
Anaemia	1.7 hospitalisation days	Consistent with TA296	£220.16 per day	£374.27	NHS reference costs 2014-15; Iron Deficiency Anaemia with CC Score 0-1 SA04L [154]
Thrombo-cytopenia	2.0 hospitalisation days		£375.05 per day	£750.09	NHS reference costs 2014-15; Thrombocytopenia with CC Score 0-1 SA12K [154]
Neutropenia	Managed by dose reduction		-	-	-

Abbreviation: TA: technology appraisal.

The costs associated with treating adverse events are described in Table 4 and the total cost of treating adverse events for crizotinib and each comparator treatment are summarised in Table 5, which are based on the proportion of patients experiencing each adverse event. These were applied within the model as a one-off cost during the first cycle of the model for simplicity. As discussed above, adverse events due to crizotinib are assumed to be managed by dose reduction/interruption and hence not to incur any cost.

Table 5: Total cost of adverse events, by treatment

Treatment	One-off total cost of treating adverse events
Crizotinib	£0.00
Pemetrexed plus cisplatin/carboplatin	£82.04

The model was tested with the adverse event costs set to £0 in the pemetrexed arm and this had minimal impact on the deterministic ICER (a change of only £130 with the PAS).

5.5.8 Miscellaneous unit costs and resource use

5.5.8.1 Treatment received following disease progression

Following progression of disease all patients were expected to receive second-line treatment with docetaxel, based on expert clinical opinion which stated that this is the most reflective of clinical practice. 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.[158] Following treatment with docetaxel all patients were assumed to receive best supportive care (consisting of monitoring only) until death. The unit cost and administration cost of docetaxel are provided in Table 6 and Table 7.

Table 6: Unit costs of treatment following progression

Treatment	Unit	Unit cost	Reference	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Docetaxel	20 mg (1 ml Vial)	£4.55	eMit [152]	75 mg/m^2 (21 days)	£21.49 with wastage £19.44 without wastage
	80 mg (4 ml Vial)	£12.39			
	140 mg (7 ml Vial)	£20.95			
	160 mg (16 ml Vial)	£44.84			

Abbreviation: eMit: electronic market information tool.

Table 7: Administration costs for treatment following progression, per chemotherapy cycle

Treatment	Setting	Cost code	Description	Unit cost
Docetaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£325.94

Source: NHS reference costs 2014-15 [154]

5.5.8.2 ALK-testing

In the base case the expected cost per patient to identify one ALK-positive patient from a cohort of all patients with NSCLC is applied to the crizotinib treatment arm, as crizotinib is only licensed for use in ALK-positive patients. This is the cost of one test multiplied by the number of patients needed to be tested to identify one ALK-positive patient. Only acquisition costs of the tests were considered, as the NHS already has the infrastructure in place to perform and analyse such tests.

The model assumes that the testing strategy will be to test with IHC first and then to confirm equivocal results of 1 or 2 with a FISH test, based on a recommendation that this is a "cost-effective" approach to testing in the ESMO guidelines, published in 2014.[24]

The most reliable incidence figure identified for ALK-positivity is 3.4%.[48] Therefore, 29 non-squamous patients would have to be tested to identify one ALK-positive patient (= 1 / 3.4%). Please see Section **Error! Reference source not found.** for a more detailed discussion on the incidence of ALK-positivity.

To calculate the cost per ALK-positive patient of testing for ALK-status, concordance tables were considered that show the distribution of NSCLC patients according to their IHC and FISH test results. Concordance data from high risk populations, which have a higher prevalence of ALK-positive patients than the general NSCLC population, were mapped to the expected ALK-positivity incidence of 3.4%. Two antibodies are most commonly used for ALK-testing: the Novacastra and Dako antibodies. The pooled concordance estimates from two studies for the Novacastra antibody (Table 8) were used in this analysis, as the Novacastra antibody has been shown to be slightly more accurate than the Dako antibody.

Table 8: Expected distribution of NSCLC patients according to IHC and FISH tests with Novacastra antibody – pooled data from 2 sources

IHC	FISH: ALK-positive	FISH: ALK-negative	Any FISH
0	0.00%	91.98%	91.98%
1+	0.47%	2.11%	2.59%
2+	2.26%	0.91%	3.17%
3+	2.26%	0.00%	2.26%
Any IHC	5.00%	95.00%	100.00%

Abbreviation: ALK: anaplastic lymphoma kinase; FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry.
Sources: data was pooled from 2 sources [159-161]

For the IHC validation strategies, the model divides the cost of IHC (*[academic / commercial in confidence information removed]*) by the prevalence of ALK patients (3.4%) to calculate the cost of testing a full cohort with IHC to identify one patient.[48, 162] It then adds on the cost of FISH testing for equivocal IHC cases, calculated by dividing the cost of FISH (£120) by the probability of getting a positive FISH test if there is an equivocal IHC test (37.7%, assuming that IHC 1+ and 2+ will be confirmed by FISH) and then multiplying by the prevalence of ALK-positive patients who received a FISH test (1.9%) divided by the overall prevalence of ALK (3.4%).[163] The calculation for the probability of getting a positive FISH test if there is an equivocal IHC test is as follows: Sum of the probabilities of FISH+ for IHC1+ and IHC2+ (0.47% + 2.26%; Table 8), divided by the sum of the probabilities of IHC1+ and IHC2+ (2.59% + 3.17%; Table 8).

The respective costs calculated per patient are *[academic / commercial in confidence information removed]* (Table 9). It should be noted that costs may be different when considering the price of the testing kit as purchased from the manufacturer of that test, and the overall cost to the NHS per test (overheads, laboratory costs, etc). It is assumed from the source documentation that the price of the FISH cost covers the total cost to the NHS as it is stated "prices apply to the NHS". It is more difficult to estimate what the difference between the exact cost of the testing kit and the total cost to the NHS of testing with the IHC is due to the lack of publically available data on the cost of IHC ALK-testing.

Table 9: Testing costs applied in the model

Test	Cost per test	Cost per ALK-positive patient identified
IHC 1+ and 2+ confirmed by FISH (base case)	IHC: *[academic / commercial in confidence information removed]* [162] FISH: £120 [163]	*£[academic / commercial in confidence information removed]*

Abbreviation: ALK: anaplastic lymphoma kinase; FISH: fluorescence in situ hybridization; IHC: immunohistochemistry.

5.6 Summary of base case de novo analysis inputs and assumptions

5.6.1 Summary of base case de novo analysis inputs

A full summary of model parameters is provided in **Error! Reference source not found.** in **Error! Reference source not found.**.

5.6.2 Assumptions

Table 10: Assumptions in the modelled base case

Assumptions	Assumption description	Justification
Time horizon	Lifetime (15 years)	The economic model runs for 15 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 cisplatin is 500mg	TA181 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 750mg.[83, 153] in the base case the target dose was assumed to be 500mg.	The dose of 500mg was selected in the base case as a conservative assumption as this results in the lower cost for cisplatin.
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 for pemetrexed, due to the more complex administration required for cisplatin.

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.	This is based on the median number of cycles of pemetrexed plus cisplatin/carboplatin 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.
No administration cost for crizotinib	Crizotinib is assumed to incur no administration cost in the base case.	Crizotinib is an oral therapy and does not require hospital administration. This assumption is consistent with a previous appraisal of oral therapies (TA347).[153] A one-off cost of oral administration for crizotinib during the first model cycle has been explored as a sensitivity analysis to reflect a situation where patients are given instructions on how to take the tablets by a nurse the first time they receive them. Following administrations are assumed only require the patient to collect their prescription during regular check-ups and therefore are assumed to carry no cost.
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 who treat ALK-positive NSCLC in the UK.
Adverse event costs	Adverse events were assumed not to incur a cost for crizotinib patients.	Clinical opinion in TA296 indicated that adverse events resulting from crizotinib would be managed through dose reduction, dose interruption, or “watch and wait” monitoring.[158]
Treatment beyond progression	Treatment with crizotinib beyond progression is modelled in 73% of patients for 3.1 months in the base case, so is costed for this period.	The PROFILE 1014 trial allowed treatment beyond progression with crizotinib at the investigator’s discretion. A sensitivity analysis has been included whereby crizotinib is given until progression.
Second-line treatment	It is assumed second-line treatment is docetaxel in all cases.	The clinical experts confirmed that docetaxel would be the second line treatment option in a world without crizotinib or pemetrexed in the second line. In order to compare the incremental differences between first-line treatment, it was decided to offer the same treatment to all patients in the second-line, so that factors outside the first-line setting are held constant for both arms.
ALK-testing	The cost of ALK-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 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.[24]

Real-world data	The characteristics of an ALK-positive patient in the model were taken from a retrospective cohort study of real-world patients with ALK-positive NSCLC in the USA and Canada in the base case. These difference in patient characteristics to the clinical trial considered an estimation of covariate-adjusted parametric survival models.[133]	Discussions with clinical experts in the UK around the demographic characteristics of a typical ALK-positive patient bared a strong similarity with real-world patients that have been studied in the US and Canada. Determining the effect of covariate characteristics on efficacy outcomes allowed the use of baseline patient characteristics from the US and Canadian real-world data in the model. This adjustment produced more clinically plausible extrapolations of OS in both treatment arms and more face valid results than the extrapolated PROFILE 1014 trial OS data which was immature. This adjustment increased the ICER making crizotinib less cost-effective; these results are presented in the base case to allow for a more conservative evaluation, hence reducing the uncertainty in decision making. The unadjusted characteristics taken directly from the Phase III PROFILE 1014 trial have also been modelled and are presented in a sensitivity analysis.
Proportional hazards	A common treatment effect is assumed for both PFS and OS	This assumption was assessed by inspecting the plot of log hazards by log time for OS and PFS separately. Neither plot yielded large departures from parallel lines, except in the extremes where data are limited.
PFS curve	The generalised gamma curve was selected as the base case curve for PFS.	The generalised gamma curve was selected for the base case as it had a good fit to the observed data (based on the AIC, BIC and visual inspection) and provided a plausible extrapolation; i.e. the fitted curve predicts nearly all pemetrexed plus cisplatin/carboplatin patients to have progressed by 30 months, and other curves predict longer, more unrealistic PFS times. The Weibull and Gompertz curves have been used in sensitivity analyses to explore uncertainty.
OS curve	The Weibull curve was selected as the base case curve for OS.	The Weibull curve had a good fit to the observed data (based on the AIC, BIC and visual inspection) and provided the most plausible extrapolation (and other curves predict longer, more unrealistic OS times), and this curve was therefore selected in the base case. The Gompertz curve has been used in a sensitivity analysis to explore uncertainty.
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 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 and pemetrexed plus cisplatin/carboplatin arms are taken directly from patients on treatment in the PROFILE 1014 trial, 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', however its inclusion was explored in a sensitivity analysis.

HRQoL is assumed constant over time in a given state	It was assumed that HRQoL in each disease state (progression free, progressed disease on docetaxel and progressed disease on BSC) 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.
Treatment beyond progression	Treatment with crizotinib beyond progression is modelled in 73% of patients for 3.1 months in the base case, so patients' treatment-related utility is assumed to be sustained as first-line crizotinib is much more tolerable than second-line docetaxel.	Utility is a function of both symptoms and toxicity. When disease progression occurs, it is reasonable to assume that utility falls as symptoms have worsened. However, second-line treatment (docetaxel) is far more toxic than crizotinib (reflected in its poorer EQ-5D score), so the utility of patients treating beyond progression would benefit in part from continued use of crizotinib rather than docetaxel. This 'sustained' utility is assumed to be the midpoint between crizotinib's utility in first-line and docetaxel's utility in second-line, thus reflecting the worsening symptoms from disease progression, yet maintaining benefit from lower toxicity. The sustained utility is applied for the duration of treatment beyond progression (4 cycles including wastage) for those who continue to receive treatment, after which it will be followed by a drop to the utility for second-line treatment with docetaxel.
Transitional utility	A transitional utility is applied for the first cycle following progression from first-line to second-line treatment and also from second-line to third-line treatment, to reflect the gradual change in a patient's utility. In this first cycle, a patient's utility will be at the mid-point between the utility of the two states.	This is intended to represent that, following progression between lines of treatment, it is implausible that a patients' utility will drop immediately to the level of utility associated with the next line of treatment on the first day following confirmation of progressed disease. Therefore it is logical to assume there is a short transitional period between cycles as patients' utility changes transit down. The utility in the one transitional cycle is equal to the utility for prior line of treatment, plus 50% of the difference between the utility for the current line of treatment and the utility for the prior line of treatment).

Abbreviations: 1L: first-line; 2L: second-line; AIC: Akaike information criterion; ALK: anaplastic lymphoma kinase; AUC: area under the curve; BIC: Bayesian information criterion; BSC: best supportive care; EQ-5D: EuroQoL-5 dimensions; ESMO: European Society for Medical Oncology; FISH: fluorescence *in situ* hybridisation; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; IHC: immunohistochemistry; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; TA: technology appraisal; USA: United States of America.

5.7 Base case results

5.7.1 Base case incremental cost-effectiveness analysis results

The deterministic base case results are presented in Table 11 for crizotinib at list price. Probabilistic results are provided in Section 5.8.1. These indicate that at a willingness to pay threshold of £50,000 per QALY gained, crizotinib is becomes a cost-effective treatment option when it is provided with the PAS, producing an ICER of *[academic / commercial in confidence information removed]* per QALY at list price.

Table 11: Base case results – crizotinib at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/carboplatin	£21,455	1.49	*[academic / commercial in confidence information removed]*				
Crizotinib	£79,888	2.42	*[academic / commercial in confidence information removed]*	£58,433	0.93	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

5.7.2 Clinical outcomes from the model

The clinical outcomes from the modelled base case are presented in Table 12 for crizotinib and Table 13 for pemetrexed plus platinum based chemotherapy (cisplatin/carboplatin).

The tables also present outcomes data from previously published studies. As the modelled outcomes incorporate the adjustment of patient characteristics to reflect those of real-world patients, outcomes from a crizotinib prospective real-world study (Davis *et al.* [2015]) are presented, and outcomes from a pemetrexed plus platinum prospective real-world study (FRAME) are presented.[94, 133] For further comparison, the tables also provide outcomes from the pivotal phase III trials for both crizotinib (PROFILE 1014) and pemetrexed plus platinum (JMDB; Scagliotti *et al.* [2008]).[2, 74]

A discussion of how these comparative data validate the modelled results is presented in Section **Error! Reference source not found.**.

Table 12: Clinical outcomes (in months) from the model versus published first-line studies – crizotinib

Outcome	Crizotinib		
	Model result (adjusted for real-world patients)	PROFILE 1014 phase III trial [2]	Davis *et al.* (2015) real-world data [133]
Median PFS (months)	9.9	10.9	9.6
Median OS (months)	21.7	Not reached	24
Mean OS (months)	29.0	Data not mature	NR

Table 13: Clinical outcomes (in months) from the model versus published first-line studies – pemetrexed plus platinum based chemotherapy

Outcome	Pemetrexed plus cisplatin/carboplatin			
	Model result (adjusted for real-world patients)	PROFILE 1014 phase III trial [2]	JMDB trial phase III trial [74]	FRAME real-world data [94]
Median PFS (months)	5.9	7.0	5.3	5.6
Median OS (months)	13.8	Not reached	11.8	10.6
Mean OS (months)	17.9	Data not mature	NR	NR

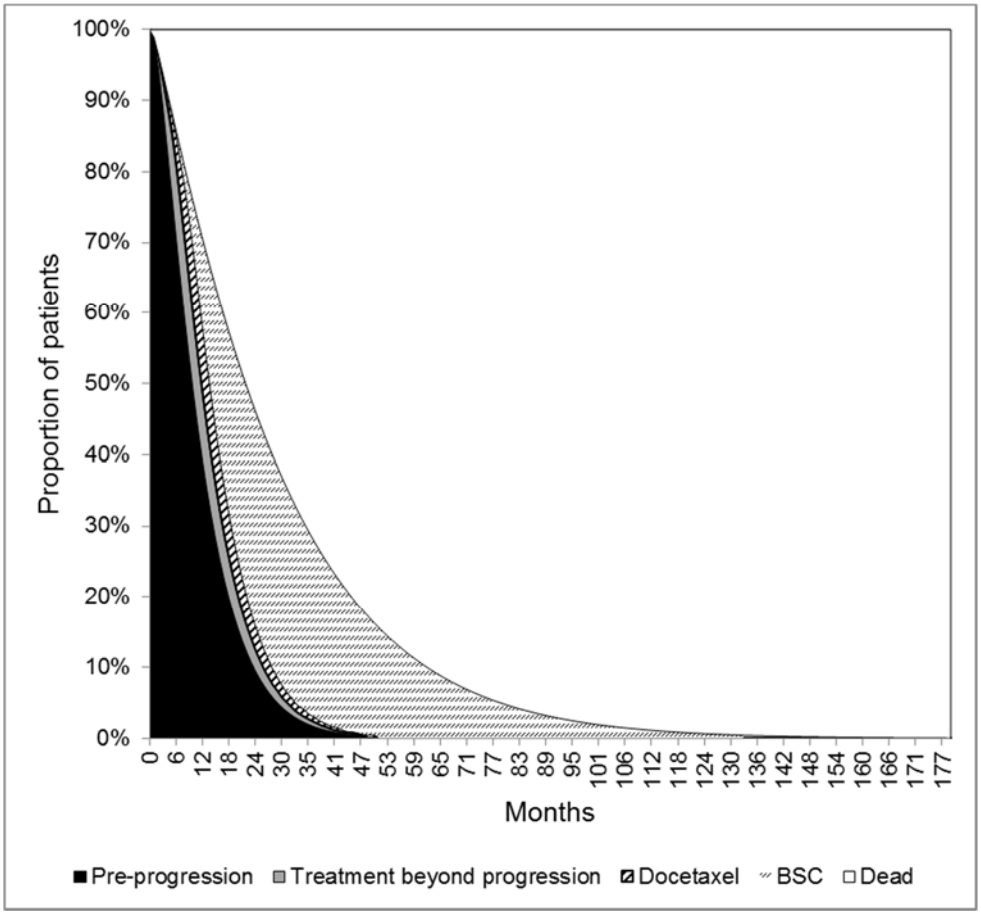
The Markov traces for crizotinib and pemetrexed plus platinum show the proportion of the cohort in each health state over time (Figure 1 and Figure 2). These highlight the time spent in the post-progression survival state in the model is higher for patients who received crizotinib compared with patients who received pemetrexed plus platinum.

This result is expected, based on the observed clinical evidence in PROFILE 1014. In the study, crizotinib demonstrates a greater tumour response and increases the degree to which the tumour shrinks relative to the pemetrexed plus platinum comparator (see Section **Error! Reference source not found.**). This improvement in tumour shrinkage is reflected through crizotinib's statistically significant improvement in symptom related HRQoL versus pemetrexed plus platinum (see Section **Error! Reference source not found.**). At the point when a crizotinib patient does

progress, the result of having an improved tumour response and superior HRQoL from their time on treatment puts a crizotinib patient in a healthier position as they enter the post-progression survival stage; this rationale was also confirmed with the clinical experts at the UK advisory board. The effect of this is that crizotinib patients entering the post-progression state are likely to experience longer post-progression survival as they begin this state in a healthier position. This extended benefit was also recognised in prior health technology appraisals for crizotinib as a second-line therapy.[5]

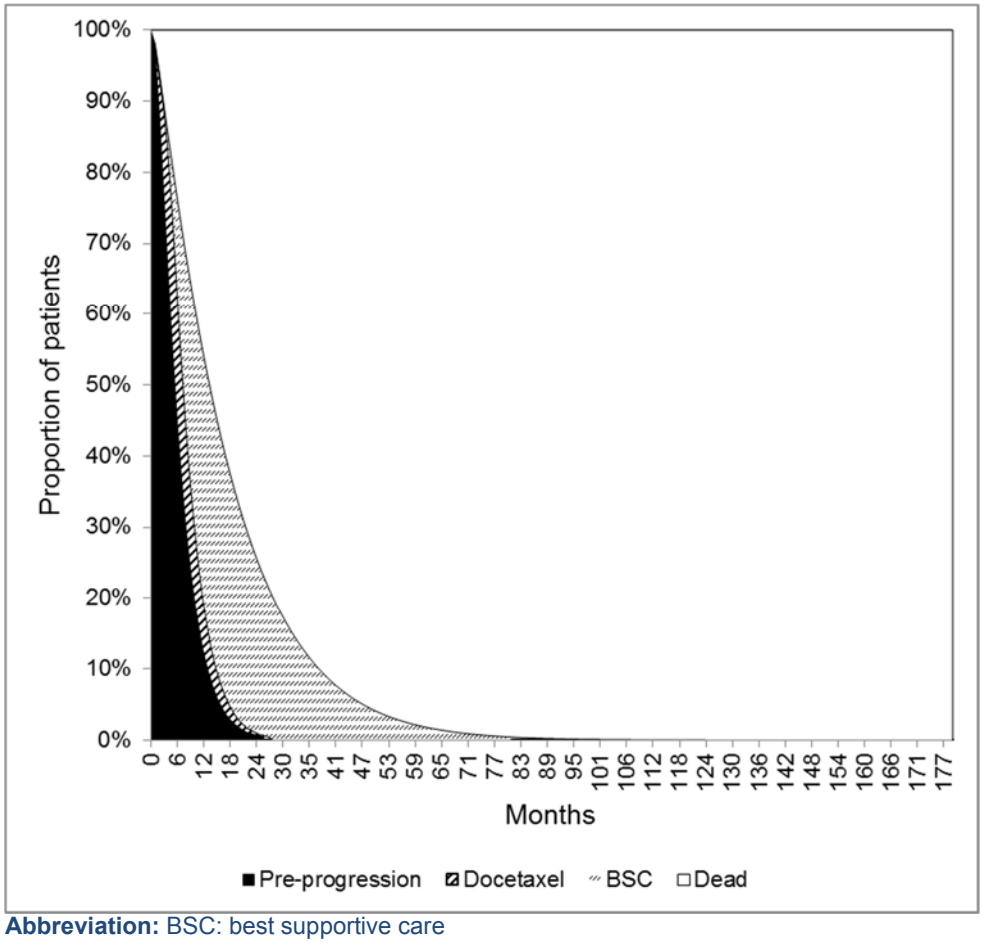
As the model results reflect crizotinib's post-progression survival benefit, the results of the cost-effectiveness evaluation can be said to be in line with not only the PFS and OS outcomes observed in clinical data, but also the tumour response and HRQoL observed outcomes.

Figure 1: Markov trace – crizotinib



Abbreviation: BSC: best supportive care

Figure 2: Markov trace – pemetrexed plus cisplatin/carboplatin



Abbreviation: BSC: best supportive care

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Disaggregated results are presented in Table 14 for the QALY gain by health state, Table 15 at list price, and Table 16 for the resource use by category of cost at list price. These demonstrate that treatment with crizotinib results in increased QALYs in pre- and post-progression states. This is likely due to the improved quality of life for crizotinib patients observed in the progression-free state, and the improved PFS and OS seen for crizotinib over pemetrexed.

Table 14: Summary of QALY gain by health state

Health state	QALY: Crizotinib arm	QALY: Pemetrexed plus cisplatin/ carboplatin arm	Increment	Absolute increment	% absolute increment
Pre-progression	*[academic / commercial*	*[academic / commercial in*	*[academic / commercial*	*[academic / commercial in*	*[academic / commercial in*
Post progression	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Total	*[academic / commercial*	*[academic / commercial in*	*[academic / commercial*	*[academic / commercial in*	*[academic / commercial in*

	in confidence information removed]	*confidence information removed]*	*in confidence information removed]*	*confidence information removed]*	*confidence information removed]*

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.
Abbreviation: QALY: quality-adjusted life year.

Table 15: Summary of costs by health state - crizotinib at list price

Health state	Cost: Crizotinib arm	Cost: Pemetrexed plus cisplatin/ carboplatin arm	Increment	Absolute increment	% absolute increment
Pre-progression	£61,086	£11,478	£49,608	£49,608	84.90%
Post progression	£18,802	£9,977	£8,825	£8,825	15.10%
Total	**£79,888**	**£21,455**	**£58,433**	**£58,433**	**100%**

* ALK-testing is performed at the initiation of treatment, and therefore has been included in the pre-progression costs for crizotinib.
* Includes the costs of treatment beyond progression for crizotinib treatment arm.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 16: Summary of predicted resource use by category of cost – crizotinib at list price

Item	Cost: Crizotinib arm	Cost: Pemetrexed plus cisplatin/ carboplatin arm	Increment	Absolute increment	% absolute increment
Drug cost*	£65,266	£8,077	£57,190	£57,190	90.56%
Administration cost*	£784	£2,849	-£2,065	£2,065	3.27%
Monitoring cost	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adverse event cost	£0	£82	-£82	£82	0.13%
Tests	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Supportive care	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Total	**£79,888**	**£21,455**	**£58,433**	**£63,152**	**100.00%**

*Includes costs associated with first- and second-line treatment.

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To determine the number of probabilistic simulations required to obtain approximately stable results from probabilistic analysis, 10,000 simulations were run (please see **Error! Reference source not found.** for the probabilistic sensitivity analysis diagnostics). Following this, it was observed that in fact 5,000 was a suitable number for obtaining reliable results as the total costs and QALYs estimated from the two runs are very similar (but will never be identical as different random numbers are used). This test was performed several times. The total costs and QALYs for crizotinib and pemetrexed plus cisplatin/carboplatin obtained from each simulation were recorded and averaged over an increasing number of simulations; this was repeated 5 times.

The incremental results from the probabilistic analyses are presented in Table 17 for crizotinib at list price. The probabilistic ICERs indicate that at a willingness to pay threshold of £50,000 per QALY, crizotinib is a cost-effective treatment option when it is provided with the confidential PAS. These results are very similar to the deterministic base case results with both the PAS and at list price *[academic / commercial in confidence information removed]*. This similarity in results provides confidence that the most plausible estimate of the ICER is below £50,000 per QALY threshold.

Table 17: Probabilistic mean pairwise cost-effectiveness analysis results – crizotinib at list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/carboplatin	£21,824	*[academic / commercial in confidence information removed]*			
Crizotinib	£82,677	*[academic / commercial in confidence information removed]*	£60,853	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Figure 3 shows the scatter plot of incremental costs and QALYs for crizotinib vs. pemetrexed plus cisplatin/carboplatin from 5,000 probabilistic simulations when crizotinib is provided at list price. Crizotinib consistently results in higher costs and higher QALYs compared with pemetrexed plus cisplatin/carboplatin.

Figure 3: Cost-effectiveness plane: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib at list price

[academic / commercial in confidence information removed]

Abbreviation: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 4 shows the cost-effectiveness acceptability curves for crizotinib vs. pemetrexed plus cisplatin/carboplatin on the incremental NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY when crizotinib is provided at list price.

Figure 4: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib at list price

[academic / commercial in confidence information removed]

5.8.2 Deterministic sensitivity analysis

The tornado diagram showing the key drivers of cost-effectiveness in the comparison of crizotinib and pemetrexed plus cisplatin/carboplatin is presented in Figure 5 when crizotinib is provided at list price.

Figure 5: Tornado diagram of the ten most influential parameters: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib at list price

[academic / commercial in confidence information removed]

Abbreviation: BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year.

In Figure 5 it can be seen that the majority of the top ten key drivers in the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact. It is unsurprising that this parameter is the most influential as this parameter drives the incremental difference in OS between the two treatment arms, and therefore affects the overall QALYs and costs attributed to each treatment arm.

In addition to the covariates attributed to the calculation of overall survival, other model driver are the utility applied to 3rd line treatment with BSC and the discount rate for QALYs, as seen in the tornado diagrams. As a crizotinib patients have a longer post progression survival period, then inevitably spent longer in the BSC (third line) stage than chemotherapy patients; the utility gain in this state therefore impacts the ICER, although observing the tornado diagram shows this impact is minor.

5.8.3 Probabilistic scenario and sensitivity of assumption analyses

A number of parameters and assumptions that have been varied in probabilistic sensitivity analyses (5,000 simulations) are outlined in Table 18.

The results of the analyses exploring the sensitivity of assumptions (numbers 1-21) are set out in Table 19 with the results of the scenario analysis exploring crizotinib's cost-effectiveness versus in the squamous population (number 22) set out in Table 20 for crizotinib at list price. Crizotinib remains cost-effective with the PAS at a threshold of £50,000/QALY across the majority of these extensive sensitivity analyses. Full results of the sensitivity analyses are presented in **Error! Reference source not found.**.

Alternative crossover adjustment methods were explored but these had a small effect on the ICER. The other two-stage models beyond the model used in the base case changed the ICER by a small degree. Selecting different combinations of survival curves in the model did not have a large impact on the ICER at either list or PAS price.

Allowing the patient characteristics to be those of the PROFILE 1014 trial lowers the ICER to *[academic / commercial in confidence information removed]* at list price. Therefore we are confident that the cost-effectiveness estimate that we have produced is conservative and represents the upper bound of the likely ICER.

The ICERs in Table 19 are all probabilistic calculations. In addition to these, the effect on the deterministic ICER was investigated around the cost of AE management. The cost for managing AEs was set to £0 in the comparator arm and this changed the deterministic ICER by £132, suggesting the cost of AEs do not drive the results.

Table 18: Full list of sensitivities undertaken and their respective settings

	Description	Base case setting	Sensitivity setting
1	**Excluding wastage for pemetrexed plus cisplatin/carboplatin**	Include wastage	Exclude wastage
2	**Excluding ALK-testing costs**	Include	Exclude
3	**Alternative crossover adjustment: TSB**	TSA	TSB
4	**Alternative crossover adjustment: TSC**		TSC
5	**Alternative crossover adjustment: RPSFT-Wilcoxon**		RPSFT-Wilcoxon
6	**Alternative crossover adjustment: RPSFT-Log-rank**		RPSFT-Log-rank
7	**Patient characteristics as per PROFILE 1014**	Real-world data (Davis *et al.* [2015]) [133]	PROFILE 1014
8	**Alternative survival models: (PFS=Gamma, OS=Gompertz)**	PFS=Gamma, OS= Weibull	PFS=Gamma, OS=Gompertz
9	**Alternative survival models: (PFS=Weibull, OS=Weibull)**		PFS=Weibull, OS=Weibull
10	**Alternative survival models: (PFS=Weibull, OS= Gompertz)**		PFS=Weibull, OS= Gompertz
11	**Alternative survival models: (PFS= Gompertz, OS=Weibull)**		PFS= Gompertz, OS=Weibull
12	**Alternative survival models: (PFS= Gompertz, OS= Gompertz)**		PFS= Gompertz, OS= Gompertz
13	**Sustained utility not applied between progression from 1L to 2L and from 2L to 3L**	Yes - Applied to TBP and following progression	Yes - But only applied to TBP
14	**Alternative split of cisplatin (25%) and carboplatin (75%) with pemetrexed**	46.15%	75.00%
15	**4 cycles of chemotherapy to represent clinical practice**	6	4
16	**Applying a one-off cost for crizotinib administration**	No cost	One-off
17	**Including utility decrements due to AEs**	No	Yes
18	**Time horizon: 1 year**	15	1
19	**Time horizon: 5 years**		5
20	**Time horizon: 10 years**		10
21	**Time horizon: 20 years**		20
22	**Squamous population (crizotinib vs. pemetrexed)**	Non-squamous population	Squamous population*

*This analysis extrapolates the outcomes in terms of costs and clinical outcomes of the model from the non-squamous population, and amends the incidence of ALK-positive NSCLC to reflect the lower incidence observed in the squamous population as this is the only parameter for which data were available for the squamous population.

Abbreviation: 1L: first-line; 2L: second-line; 3L: third-line; AEs: adverse events; ALK: Anaplastic lymphoma kinase; OS: overall survival; PFS: progression-free survival; RPSFT: Rank Preserved Structural Failure Time; TSA: two-stage method A; TSB: two-stage method B; TSC: two-stage method C.

Table 19: Summary table of probabilistic sensitivity analyses undertaken – crizotinib at list price

No.	Description	Incremental costs (£)	Incremental QALYs	ICER
1	**Excluding wastage**	£61,142	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
2	**Excluding ALK-testing costs**	£59,194	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
3	**Alternative crossover adjustment: TSB**	£60,674	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
4	**Alternative crossover adjustment: TSC**	£60,918	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
5	**Alternative crossover adjustment: RPSFT-Wilcoxon**	£60,998	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
6	**Alternative crossover adjustment: RPSFT-Log-rank**	£60,641	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
7	**Patient characteristics as per PROFILE 1014**	£76,427	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
8	**Alternative survival models: (PFS=Gamma, OS=Gompertz)**	£61,023	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
9	**Alternative survival models: (PFS=Weibull,**	£61,234	*[academic / commercial in*	*[academic / commercial*

	OS=Weibull)		*confidence information removed]*	*in confidence information removed]*
10	**Alternative survival models: (PFS=Weibull, OS= Gompertz)**	£61,411	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
11	**Alternative survival models: (PFS= Gompertz, OS=Weibull)**	£62,117	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
12	**Alternative survival models: (PFS= Gompertz, OS= Gompertz)**	£62,260	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
13	**Transitional utility not applied between progression to subsequent line of treatment**	£60,813	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
14	**Alternative split of cisplatin (25%) and carboplatin (75%) with pemetrexed**	£60,879	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
15	**4 cycles of pemetrexed to represent clinical practice**	£64,186	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
16	**Applying a one-off cost for first crizotinib administration**	£61,000	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
17	**Including additional utility decrements due to AEs**	£60,774	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
18	**Time horizon: 1 year**	£38,265	*[academic / commercial in confidence*	*[academic / commercial in*

			information removed]	*confidence information removed]*
19	**Time horizon: 5 years**	£59,687	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
20	**Time horizon: 10 years**	£60,715	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
21	**Time horizon: 20 years**	£60,861	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: 1L: first-line; 2L: second-line; 3L: third-line; AEs: adverse events; ALK: Anaplastic lymphoma kinase; OS: overall survival; PFS: progression-free survival; RPSFT: Rank Preserved Structural Failure Time; TSA: two-stage method A; TSB: two-stage method B; TSC: two-stage method C.

Table 20: Exploratory probabilistic scenario analyses undertaken – crizotinib at list price

No.	Description	Incremental costs (£)	Incremental QALYs	ICER
22	**Squamous population (crizotinib vs. pemetrexed)**	£131,018	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

An exploratory analysis was included for squamous patients in order to reflect the scope. The ICER for the squamous population is not cost-effective in Table 20, however these results should be considered with the number of squamous patients that would present. The ICERs represent a worst case scenario for cost where every squamous NSCLC patient is ALK-tested with the increased cost of testing that needs to be conducted to identify rarer squamous patients impacts the ICER heavily. However, in clinical practice it is expected that squamous patients would only be tested if they were identified as having typical ALK-positive characteristics (such as being young and a non-smoker for example). Henceforth, the number of squamous patients expected to be tested in practice in order to identify one squamous ALK-positive patient is much lower than every single NSCLC patient as is suggested in this scenario analysis; this would result in reduced testing costs and an improved ICER. However, this is difficult to quantify in absolute terms.

5.8.4 Summary of sensitivity analyses results

- The mean ICERs obtained from probabilistic analysis were consistent with those obtained from deterministic analyses. Crizotinib's probabilistic ICER versus the standard of care is lower than the £50,000/QALY threshold when provided with a PAS.
- One-way sensitivity analysis indicated that the key drivers of the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact.
- Crizotinib remained cost-effective across the majority of probabilistic sensitivity analyses when provided with a PAS. Allowing the patient characteristics to be those of the PROFILE 1014 trial (i.e. not adjusting for age or ECOG status at baseline) lowers the ICER and makes crizotinib more cost-effective.

7 References

Bibliography is as per the original submission

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

Crizotinib for the first-line treatment of anaplastic lymphoma kinase-positive, advanced non-small-cell lung cancer

[ID865]

ADDENDUM TO THE TEMPLATE:

UPDATED RESULTS OF THE ECONOMIC EVALUATION (Section 4)

03 March 2016 ***(redacting revised on 18 March 2016)***

4 Cost effectiveness

Due to the change in the base case of the cost-effectiveness model following corrections highlighted in the response to clarification questions, a new set of results is provided in this document to replace Section 4.

- The base case deterministic ICER with the PAS has increased from £46,304 in the original template to £47,620 (at list price), an increase of £1,316.
- The base case probabilistic ICER with the PAS has increased from £45,495 in the original template to £46,405 (at list price), an increase of £910.

Crizotinib remains cost-effective at the £50,000/QALY threshold when offered with the PAS (Addendum to list price results provided separately).

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

Not applicable.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been applied by reducing the current NHS list price of crizotinib. The functionality for changing this operates through a cell marked "PAS discount applied" on the "Controls" sheet where the percentage discount can be entered.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The PAS is a simple discount and therefore does not impact the clinical effectiveness data used in the evidence synthesis or in the economic model. The clinical input data used in the model as well as the clinical output data that is produced by the model remains the same with or without the PAS.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The PAS is a simple discount and does not carry additional implementation costs compared to crizotinib without a PAS.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

The PAS is a simple discount and does not carry additional any additional treatment-related costs with the scheme implemented compared to crizotinib without a PAS.

Summary results

Base-case analysis

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

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

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

Table 1. Base-case cost-effectiveness results – crizotinib at list price

	Crizotinib	Pemetrexed plus cisplatin/carboplatin
First-line intervention cost (£)	£65,266	£8,077
Other costs (£)	£14,622	£13,379
Total costs (£)	£79,888	£21,455
Difference in total costs (£)	£58,433	
LYG	2.42	1.49
LYG difference	0.93	
QALYs	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
QALY difference	*[Academic / commercial in confidence information removed]*	
ICER (£)	*[Academic / commercial in confidence information removed]*	

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 2. Base-case cost-effectiveness results – with the confidential PAS

	Crizotinib	Pemetrexed plus cisplatin/carboplatin
First-line intervention cost (£)	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Other costs (£)	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Total costs (£)	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
Difference in total costs (£)	*[Academic / commercial in confidence information removed]*	
LYG	2.42	1.49
LYG difference	0.93	
QALYs	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*
QALY difference	*[Academic / commercial in confidence information removed]*	
ICER (£)	£47,620	

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

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

Table 3. Base-case incremental results – crizotinib at list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/ carboplatin	£21,455	1.49	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*			
Crizotinib	£79,888	2.42	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	0.93	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 4. Base-case incremental results – crizotinib with the confidential PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pemetrexed plus cisplatin/ carboplatin	*[Academic / commercial in confidence*	1.49	*[Academic / commercial in confidence*				

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

	information removed]		*information removed]*				
Crizotinib	*[Academic / commercial in confidence information removed]*	2.42	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	0.93	*[Academic / commercial in confidence information removed]*	£47,620

Abbreviation: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

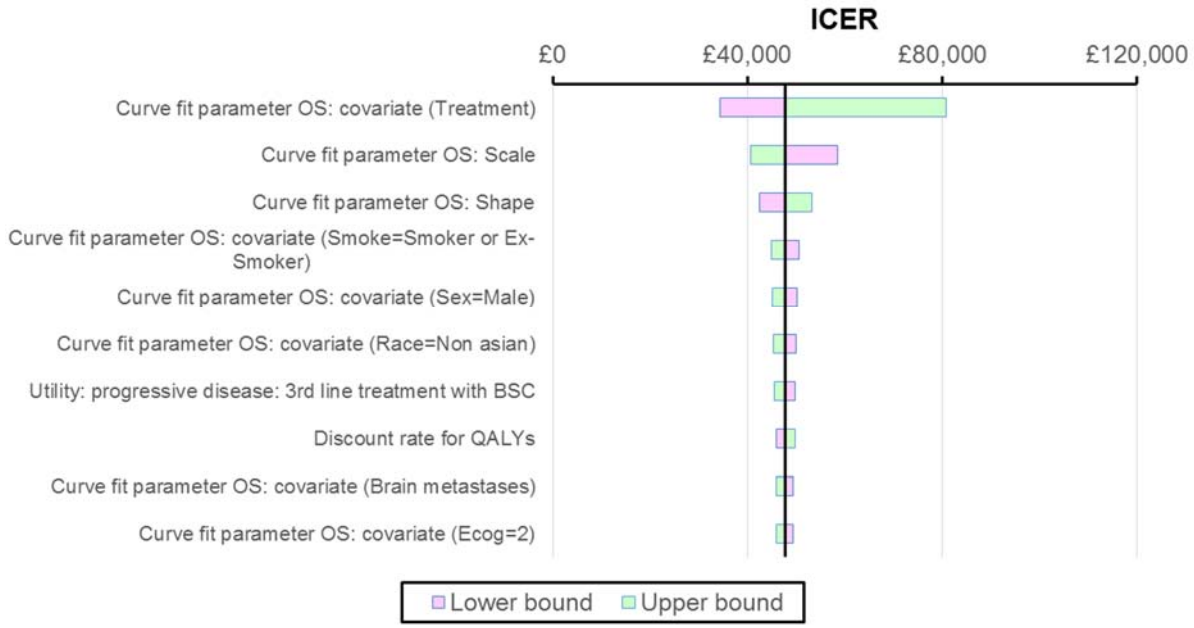
Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The tornado diagram showing the key drivers of cost-effectiveness in the comparison of crizotinib and pemetrexed plus cisplatin/carboplatin when crizotinib is offered with the PAS is presented in Figure 1**Error! Reference source not found.**. It can be seen that the majority of the top ten key drivers in the model are covariates attributed to the calculation of overall survival, with the covariate for treatment effect having the largest impact. It is unsurprising that this parameter is the most influential as this parameter drives the incremental difference in OS between the two treatment arms, and therefore affects the overall QALYs and costs attributed to each treatment arm.

In addition to the covariates attributed to the calculation of overall survival, other model drivers are the utility applied to 3rd line treatment with BSC and the discount rate for QALYs, as seen in the tornado diagrams. As a crizotinib patients have a longer post progression survival period, then inevitably spent longer in the BSC (third line) stage than chemotherapy patients; the utility gain in this state therefore impacts the ICER, although observing the tornado diagram shows this impact is minor.

Figure 1: Tornado diagram of the ten most influential parameters: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib with the confidential PAS



Abbreviation: BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year.

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

The incremental results from the probabilistic analyses are presented in

Table 5 when crizotinib is provided with the confidential PAS. The probabilistic ICER indicates that at a willingness to pay threshold of £50,000 per QALY, crizotinib is a highly cost-effective treatment option when it is provided with the confidential PAS; the probabilistic base case ICER is £46,405 per QALY. These results are very similar to the deterministic base case result (£47,620). This similarity in results provides confidence that the most plausible estimate of the ICER is below £50,000 per QALY threshold.

Table 5. Probabilistic mean pairwise cost-effectiveness analysis results – crizotinib with confidential PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)

Pemetrexed plus cisplatin/carboplatin	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	
Crizotinib	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,405

Abbreviation: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Figure 2 shows the scatter plot of incremental costs and QALYs for crizotinib vs. pemetrexed plus cisplatin/carboplatin from 5,000 probabilistic simulations when crizotinib is provided with the PAS. This indicates that crizotinib consistently results in higher costs and higher QALYs compared with pemetrexed plus cisplatin/carboplatin.

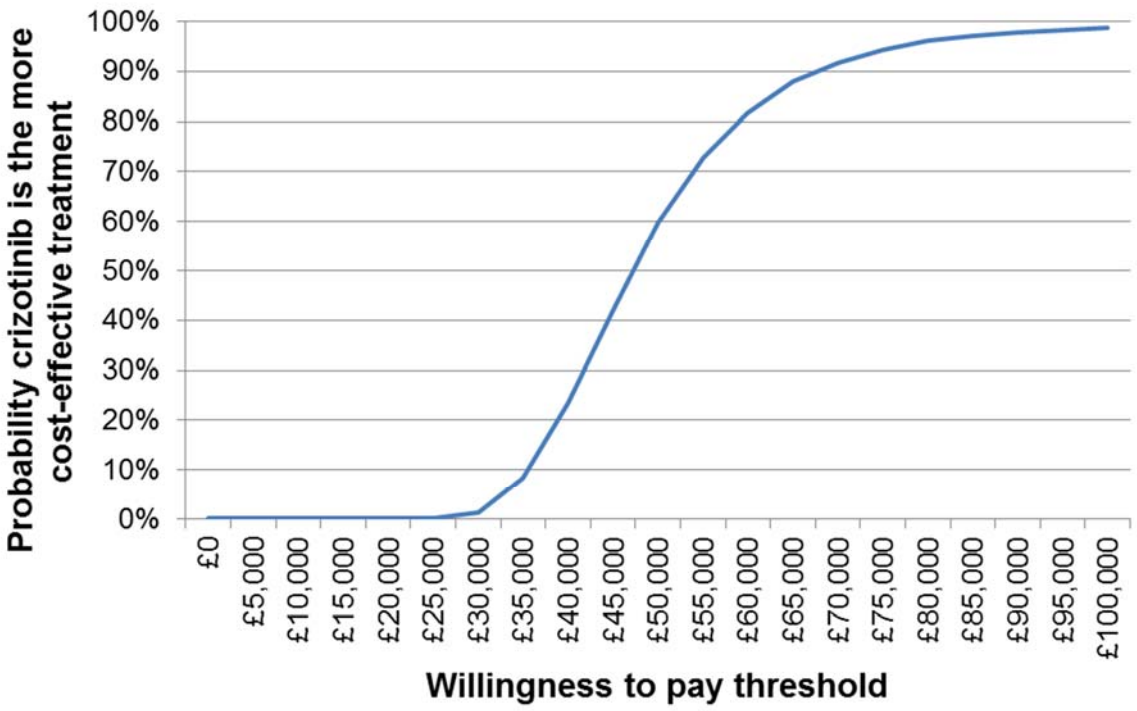
Figure 2: Cost-effectiveness plane: crizotinib versus pemetrexed plus cisplatin/carboplatin – crizotinib with confidential PAS

[Academic / commercial in confidence information removed]

Abbreviation: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 3 shows the cost-effectiveness acceptability curve for crizotinib versus pemetrexed plus cisplatin/carboplatin on the incremental net monetary benefit (NMB) at a range of willingness to pay thresholds up to a maximum of £100,000 per QALY when crizotinib is provided with the PAS. This demonstrates that at a willingness to pay threshold of £50,000 per QALY gained, crizotinib is considered cost-effective compared with pemetrexed on more than 59.7% of occasions when it is provided with the PAS.

Figure 3: Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus cisplatin/carboplatin - crizotinib with confidential PAS



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

A number of parameters and assumptions that have been varied in probabilistic sensitivity analyses (5,000 simulations) are outlined in Table 6. Crizotinib remains cost-effective with the PAS at a threshold of £50,000/QALY across the majority of these extensive sensitivity analyses.

Alternative crossover adjustment methods were explored but these had a small effect on the ICER. The other two-stage models beyond the model used in the base case increased the ICER to a maximum of £48,535 with the confidential PAS. Selecting different combinations of survival curves in the model did not have a large impact on the ICER at either list or PAS price.

Allowing the patient characteristics to be those of the PROFILE 1014 trial lowers the ICER to £41,386 with the confidential PAS. Therefore we are confident that the cost-effectiveness estimate that we have produced is conservative and represents the upper bound of the likely ICER.

Table 6. Summary table of probabilistic sensitivity "scenario" analyses undertaken – crizotinib with confidential PAS

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
1	**Excluding wastage for pemetrexed plus cisplatin/carboplatin**	Include wastage	Exclude wastage	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£47,223
2	**Excluding ALK-testing costs**	Include	Exclude	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£43,914
3	**Alternative crossover adjustment: TSB**	TSA	TSB	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£48,535
4	**Alternative crossover adjustment: TSC**		TSC	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£45,692
5	**Alternative crossover adjustment: RPSFT-Wilcoxon**		RPSFT-Wilcoxon	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£48,497
6	**Alternative crossover adjustment: RPSFT-Log-rank**		RPSFT-Log-rank	*[Academic / commercial in confidence*	*[Academic / commercial in confidence*	£52,541

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
				information removed]	*information removed]*	
7	**Patient characteristics as per PROFILE 1014**	Real-world data	PROFILE 1014	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£41,386
8	**Alternative survival models: (PFS=Gamma, OS=Gompertz)**	PFS=Gamma, OS= Weibull	PFS=Gamma, OS=Gompertz	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£43,337
9	**Alternative survival models: (PFS=Weibull, OS=Weibull)**		PFS=Weibull, OS=Weibull	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,389
10	**Alternative survival models: (PFS=Weibull, OS= Gompertz)**		PFS=Weibull, OS= Gompertz	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£43,469
11	**Alternative survival models: (PFS= Gompertz, OS=Weibull)**		PFS= Gompertz, OS=Weibull	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£47,530
12	**Alternative survival models: (PFS= Gompertz, OS= Gompertz)**		PFS= Gompertz, OS= Gompertz	*[Academic / commercial in*	*[Academic / commercial in*	£43,947

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
				confidence information removed]	*confidence information removed]*	
13	**Sustained utility not applied between progression from 1L to 2L and from 2L to 3L**	Yes - Applied to TBP and following progression	Yes - But only applied to TBP	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,622
14	**Alternative split of cisplatin (25%) and carboplatin (75%) to reflect perceived clinical practice**	46.15%	75.00%	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,451
15	**4 cycles of chemotherapy to represent clinical practice**	6	4	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£51,793
16	**Applying a one-off cost for crizotinib administration**	No cost	One-off	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,950
17	**Including utility decrements due to AEs**	No	Yes	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,468

	Description	Base case setting	Sensitivity setting	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY)
18	**Time horizon: 1 year**	15	1	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£103,837
19	**Time horizon: 5 years**		5	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£53,382
20	**Time horizon: 10 years**		10	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£47,197
21	**Time horizon: 20 years**		20	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£46,523
22	**Squamous population (crizotinib vs. pemetrexed)**	Non-squamous population	Squamous population	*[Academic / commercial in confidence information removed]*	*[Academic / commercial in confidence information removed]*	£152,012

Abbreviations: 1L: first-line; 2L: second-line; 3L: third-line; AEs: adverse events; ALK: Anaplastic lymphoma kinase; OS: overall survival; PFS: progression-free survival; RPSFT: Rank Preserved Structural Failure Time; TSA: two-stage method A; TSB: two-stage method B; TSC: two-stage method C.

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

Not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Results are as set out in Tables 1-6.

The impact of the PAS on the ICER is that the PAS makes crizotinib a cost-effective treatment option for patients with treatment naïve ALK-positive NSCLC and represents value for money to the NHS. A detailed description of the assumptions can be found in the main body of the submission; from these, we believe the results presented are a conservative upper bound estimate of the ICER. The clinical effectiveness of crizotinib in the model that pertains to the ICER versus the UK standard of care has been validated through clinical expert opinion as plausible.

- The base case deterministic ICER is £47,620 /QALY with the PAS.
- The base case probabilistic ICER is £46,405 /QALY with the PAS.
- The ICERs are based upon direct head-to-head evidence for crizotinib versus the comparator.
- Probabilistic sensitivity analysis indicated that at a willingness to pay threshold of £50,000 per QALY gained crizotinib is considered highly cost-effective compared with pemetrexed on 59.7% of occasions when it is provided with the PAS.
- 21 sensitivity “scenario” analyses were explored where model assumptions were changed. Crizotinib remains cost-effective with the PAS despite alternative statistical survival approaches being considered.
- The modelled clinical outcomes pertaining to the ICERs are plausible and were validated.

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Single Technology Appraisal (STA)

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

Dear [redacted]

The Evidence Review Group, Centre for Reviews and Dissemination/Centre for Health Economics (University of York), and the technical team at NICE have looked at the submission received on 27 January 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 **3 March 2016**.

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. Any supporting documents should be uploaded to NICE Docs/Appraisals.

If you have any queries on the technical issues raised in this letter, please contact Jasdeep Hayre, Technical Lead (Jasdeep.Hayre@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Rosie Lovett
Technical Adviser, Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Progression free survival and response rates

A1. Table 21, page 74 provides results for progression free survival (PFS). Please provide details of any model(s) and the variables used for adjustment in this analysis.

A2. Table 22, page 76: Please confirm that the figures represent the best overall tumour response.

Overall survival

A3. **Priority Question:** Table 15 page 57: The submission states that the latest data cut-off date is 30 November 2013. Page 115 states "A follow-up overall survival (OS) analysis is planned for when median OS is eventually reached." Given the length of time that has elapsed since this date:

a. Why are more recent cuts of the data not presented?

b. When can a more mature data set be expected?

c. When did follow-up of patients stop or is it still ongoing?

A4. Please provide information about the prognosis of people with advanced, non-squamous non-small-cell lung cancer (NSCLC) and the specific subgroup of people with advanced, non-squamous anaplastic lymphoma kinase positive (ALK+) NSCLC. This may be important for End of Life considerations.

A5. **Priority Question**: Please provide separate Kaplan-Meier curves (with the number of patients at risk at each time point and the total number of events over the observed period) for crizotinib patients who received pemetrexed post progression and patients that did not receive pemetrexed post progression.

A6. **Priority Question**: The rank preserving structural failure time (RPSFT) and iterative parameter estimation (IPE) methods of adjustment rely on the assumption of common treatment effect. Please provide justification for the plausibility of this assumption.

A7. **Priority Question:** Page 222, appendix 5 states that the two stage method of crossover adjustment makes the assumption that there is no time dependent confounding between the time of disease progression and the time of treatment switch. Given the wide range in the time elapsed between progression and crossover, please comment on the plausibility of this assumption.

A8. Due to the extensive crossover to the crizotinib arm, and use of crizotinib post progression in PROFILE 1014, the intention to treat (ITT) could be interpreted as a comparison of patients receiving first and second line crizotinib compared with

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patients receiving second line crizotinib. Please comment on this interpretation of the ITT analysis.

Comparators

A9. Please comment on whether pemetrexed maintenance therapy is currently used in the NHS.

Post progression treatment

A10. **Priority Question:** For PROFILE 1014, please provide further information on the post progression treatments received and the duration (such as the number of cycles) of second-line therapy. Please provide information for each treatment group separately. Please comment on the degree to which second line therapies may have influenced the observed overall survival in PROFILE 1014.

A11. **Priority Question**: Page 69 implies that [redacted] patients who were randomised to the chemotherapy group received crizotinib as follow-up treatment but had no disease progression. Please explain why these patients crossed over to crizotinib therapy instead of staying on chemotherapy? Did these patients receive any other treatments?

A12. Figure 7, page 70: Please explain the difference between the numbers reported in figure 7 for the chemotherapy group: '25 had objective PD or relapse'; '109 crossed over to crizotinib after PD' and the numbers reported in Solomon 2014 (132 independent radiologic review [IRR] documented progressive disease [PD] events).

Patient-reported outcomes and health-related quality of life

A13. Please state whether patient-reported outcome data (such as health-related quality of life) are based on the pre-progression data, i.e. that post-progression treatments are not included in the results?

A14. The median follow-up at the data cut off (30 November 2013) is reported in the submission. Please provide the range for length of follow-up.

A15. **Priority Question:** Please provide further information on the analysis of EQ-5D data – does the analysis account for differences in baseline characteristics between treatment groups?

A16. **Priority Question:** Please provide the EQ-5D utility values (mean, SD, sample size) for crizotinib and pemetrexed groups at baseline and other time points.

A17. Please comment on the difference in EQ-5D scores at baseline between the crizotinib and pemetrexed groups in PROFILE 1014.

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A18. Regarding the independent radiologic review (IRR) assessment of PD, were all patients assessed at regular intervals or were IRR assessments only done at the behest of the clinician?

Davis et al. 2015

A19. The cohort of patients reported by Davis et al. 2015 includes a larger number of older patients and a higher proportion of smokers compared with PROFILE 1014. ALK+ status could be associated with younger patients and non-smokers. Please provide data to support the generalisability of Davis et al. 2015 to the ALK+ population in England.

A20. Please provide further information about post-progression treatments in Davis et al. 2015. Did patients continue with crizotinib as in PROFILE 1014? Please provide data on the number of patients and duration of treatment for both pre-progression and post-progression crizotinib therapy.

ALK Testing

A21. **Priority Question**: Please provide evidence on whether the immunohistochemistry (IHC) test has been validated and whether it is widely used in the NHS.

A22. Other methods for testing ALK status (such as CISH, RT-PCR and next generation sequencing) are available. Are these tests used in the NHS?

A23. **Priority Question**: Is IHC testing for ALK status conducted concurrently with epidermal growth factor receptor (EGFR) testing or is IHC testing for ALK status conducted after EGFR testing in the NHS?

A24. **Priority Question**: Please provide evidence for the total time taken to complete the testing (for EGFR testing, IHC tests for ALK status and subsequent FISH tests)?

A25. Please provide information on any potential capacity issues which could arise from a larger group of individuals being eligible for ALK testing?

A26. **Priority Question**: There is some evidence that the prevalence of ALK+ status is higher in people with adenocarcinoma than in people with large-cell undifferentiated carcinoma. Please state whether a subgroup of adenocarcinoma patients was tested and subsequently treated in PROFILE 1014.

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Section B: Clarification on cost-effectiveness data

Treatments received in PROFILE 1014

B1. **Priority Question**: Please provide the mean number of cycles of pemetrexed received in PROFILE 1014.

B2. **Priority Question**: Please provide Kaplan-Meier curves for discontinuation of first line treatment (with the number of patients at risk at each time point and the total number of events over the observed period) for both crizotinib patients and pemetrexed patients.

Treatment costs

B3. **Priority Question**: Please provide individual patient data on body surface area and sex for patients from PROFILE 1014.This is to allow calculation of the mean dose of pemetrexed.

Model function and textual errors

B4. **Priority Question**: Several costs reported in the submission are different from the costs used in the executable model. Please indicate which values are correct:

a. Table 58, page 164: The cost of thrombocytopenia is reported as £758.50, however the executable model uses £750.09.

b. Table 60, page 165: The total costs of adverse events is reported as £163.20 for the pemetrexed group, however the executable model uses £82.04.

c. Table 57, page 163: The cost of end of life/supportive care is reported as £7,253, however the executable model uses £7,318.

B5. **Priority Question**: The post progression treatment option does not work in the executable model (Sheet “Model controls”). Please provide details of a potential solution and a revised executable model.

B6. **Priority Question**: The option to include a one off administrative cost for crizotinib in the executable model does not work (Sheet “Model controls”). Please confirm if this cost is included in the company’s base case analysis. Please provide details of a potential solution and a revised executable model.

B7. **Priority Question**: The base case ICER (£[redacted] per QALY gained) reported in the executable model is not the same as the one reported in the submission (table 67, page 171; £[redacted] per QALY gained). Please explain the difference between the ICERs.

B8. **Priority Question**: The ICER reported in the sensitivity analysis for ‘Patient characteristics as per PROFILE 1014’ in the executable model (£[redacted] per QALY

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gained) is not the same as the one in the submission (page 19; £[redacted] per QALY gained). Please explain the difference between the ICERs.

B9. **Priority Question**: The ERG noted a number of apparent errors in the executable model and carried out a number of fixes described below and highlighted in the (attached) executable model. Please validate and confirm that the following suggested changes are appropriate.

Sheet "Calc Tx1"

Change cells AS15:AS258 to:

=((1-TBP_prop_criz)*(Y(Row))*(p_util_sust_criz)+(OFFSET(X(Row -1),1,MIN(DOCE_duration,MAX(E(Row),1)))-Y(row)*(1-TBP_prop_criz)*p_utility_doce_pp +IFE(Row)<TBP_duration,0,(OFFSET(X(Row),1,MIN(DOCE_duration+TBP_duration,E(Row)))-OFFSET(X(Row),1,MIN(TBP_duration,E(Row)))))*TBP_prop_criz*(p_utility_doce_pp))*(cycle_length/365.25)*G(Row)

Change cells AT15:AT258 To
=(AJ(Row)*p_utility_bsc_pp+AI(Row)*(p_util_sust_doce))*(cycle_length/365.25)*$G(Row)

Change Cells BA197:258 to:

£0.00

Sheet "Calc Tx2"

Change cells AL15:AL258 to

=(AE(Row)*p_utility_bsc_pp+AD(Row)*(p_util_sust_doce))*(cycle_length/365.25)*$G(Row)

Change cells AL15:AL258 to
=((AC(Row)-Y(Row))*p_utility_doce_pp+Y(Row)*(p_util_sust_tx2))*$G(Row)*(cycle_length/365.25)

Change Cells BA190:258 to
£0.00

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Costs of testing

B10. **Priority Question**: Page 166: Please provide a breakdown of what is included in the cost of FISH testing (£120). Does this include the costs of tissue handling and processing? Please explain the difference in the cost of FISH testing used in NICE technology appraisal 296.

PFS and OS

B11. **Priority Question**: Please provide further justification of the assumption of proportional hazards in the analysis of PFS. Is this assumption clinically plausible, given that pemetrexed has a fixed cycle regimen and treatment with crizotinib continues until the absence of clinical benefit?

B12. **Priority Question**: Please provide an analysis of PFS adjusted with the baseline covariates using independent parametric functions for each treatment group and distribution (Gamma, Exponential, Weibull, Gompertz, Log Logistic and Log Normal). Please report the full set of distribution parameters estimates (as presented in Sheet: "OS_Model_Estimates" in the executable model), AIC and BIC, and plots.

B13. **Priority Question**: Please justify the assumption of proportional hazards in the analysis of OS.

B14. **Priority Question**: Please provide an analysis of OS using independent parametric functions for each treatment group for the 5 different methods of adjustment for crossover (RL, RW, TSA, TSB and TSC) for each distribution (Gamma, Exponential, Weibull, Gompertz, Log Logistic and Log Normal). Please report the full set of distribution parameters estimates (as presented in Sheet "OS_Model_Estimates" in the executable model), AIC and BIC, and plots.

B15. **Priority Question**: Please provide the IPE parametric models of OS adjusted with the baseline covariates. Please report the full set of distribution parameters estimates (as presented in Sheet "OS_Model_Estimates" in the executable model), AIC and BIC, and plots.

B16. **Priority Question**: Please provide an ITT analysis (no crossover adjustment) of the OS outcome adjusted with the baseline covariates. Please report the full set of distribution parameters estimates (as presented in Sheet: "OS_Model_Estimates" in the executable model), AIC and BIC criteria for each distribution (Gamma, Exponential, Weibull, Gompertz, Log Logistic and Log Normal), and model fit plots (curves and Kaplan-Meier).

Single Technology Appraisal (STA)

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

Dear [Insert name],

The Evidence Review Group, Centre for Reviews and Dissemination/Centre for Health Economics (University of York), and the technical team at NICE have looked at the submission received on 27 January 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 **3 March 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on 'NICE Docs/Appraisals'].

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.

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If you have any queries on the technical issues raised in this letter, please contact Jasdeep Hayre, Technical Lead (Jasdeep.Hayre@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Rosie Lovett
Technical Adviser, Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Progression free survival and response rates

A1. Table 21, page 74 provides results for progression free survival (PFS). Please provide details of any model(s) and the variables used for adjustment in this analysis.

Response: The PFS hazard ratio for crizotinib versus chemotherapy was calculated using a Cox proportional hazards model (see B11 for an explanation on the proportional hazards assumption) stratified by ECOG performance status (PS), race group, and brain metastases. The one-sided p-value is from the log-rank test stratified by ECOG PS, race group, and brain metastases.

A2. Table 22, page 76: Please confirm that the figures represent the best overall tumour response.

Response: The figures representing best overall response are for complete response, partial response, stable disease, objective response rate, progressive disease, and "patients who could not be evaluated".

Disease control rate (DCR), time to response (TTR), and duration of response (DR) were each defined by specific time criteria (see below), and therefore cannot – by definition – only include best overall tumour response.

Definitions for DCR, TTR and DR

- DCR at 12 weeks was defined as the percentage of patients with CR, PR, or stable disease at 12 weeks according to RECIST Version 1.1, as determined by IRR, relative to the FA population.
- TTR was defined as the time from randomisation to first documentation of objective tumour response (CR or PR), as determined by IRR. TTR was summarized in the subgroup of responders (CR and PR) from the FA population.
- DR was defined as the time from the first documentation of objective tumour response (CR or PR), as determined by IRR, to the first documentation of objective tumour progression or to death due to any cause, whichever occurred first. DR was summarized for the subgroup of responders (CR and PR) in the FA population using the Kaplan-Meier method and was displayed graphically.

Overall survival

A3. **Priority Question:** Table 15 page 57: The submission states that the latest data cut-off date is 30 November 2013. Page 115 states "A follow-up overall survival (OS) analysis is planned for when median OS is eventually reached." Given the length of time that has elapsed since this date:

    a. Why are more recent cuts of the data not presented?

Response: At the time of the data cut-off, when the pre-specified events for PFS had been reached, only 26% of OS events had occurred. The number of OS events in PROFILE 1014 was assessed again in *[academic / commercial in confidence information removed]* of the pre-specified number of events had occurred. As median OS had not been reached, the trial protocol was

formally amended to continue the collection of survival follow-up information for up to *[academic / commercial in confidence information removed]* after the randomisation of the last patient *[academic / commercial in confidence information removed]* in order to enhance the likelihood to obtain an estimate of the median OS for each treatment arm. As such, the next planned analyses of the trial are planned for *[academic / commercial in confidence information removed]*.

b. When can a more mature data set be expected?

Response: A review of the number of OS events that have occurred in PROFILE 1014 is next planned for *[academic / commercial in confidence information removed]*. If at that time median survival has been reached, an analysis will be conducted. Updated OS analyses will be provided with the final clinical study report *[academic / commercial in confidence information removed]*. The earliest date that we could submit new analyses to NICE would be *[academic / commercial in confidence information removed]*

c. When did follow-up of patients stop or is it still ongoing?

Response: We can confirm that follow-up of patients is still ongoing. The PROFILE 1014 protocol was amended following review of the data in *[academic / commercial in confidence information removed]* such that the collection of survival follow-up information would continue for up to *[academic / commercial in confidence information removed]* after the randomisation of the last patient.

A4. Please provide information about the prognosis of people with advanced, non-squamous non-small-cell lung cancer (NSCLC) and the specific subgroup of people with advanced, non-squamous anaplastic lymphoma kinase positive (ALK+) NSCLC. This may be important for End of Life considerations.

Response: Information on the expected survival of patients is presented in Table 10 of the submission (page 41), and is summarised in Table 1 below. These tables present the median OS for patients with advanced NSCLC treated with first-line platinum based therapy.

Based on historical estimates, median OS for patients in the general NSCLC population ranges from 10.6-11.8 months (Moro-Sibilot *et al*. 2015; Scagliotti *et al.* 2008). These estimates are similar to the modelled median OS estimate for the chemotherapy arm in PROFILE 1014 which was approximately 14 months. One published study (Shaw *et al*. 2011) has reported that median OS in patients with ALK positive NSCLC may reach up to 20 months in crizotinib naïve patients; however only 36/118 of these patients were crizotinib naïve, and of these only *[academic / commercial in confidence information removed]* received first-line standard of care (pemetrexed + platinum based therapy*).[data on file]* OS data in this study are not reported separately for these subgroups and so the results are largely confounded. We have included this study for completeness however it does not fully represent survival duration for ALK-positve patients treated on standard of care in the absence of crizotinib treatment.

Taken together the OS estimates presented here demonstrate that the life expectancy criterion of the end-of-life consideration is met for crizotinib in first-line.

Table 1. Estimates of overall survival in patients receiving current standard of care

Source	Description	Median OS, months
Scagliotti *et al.* (2008) [74]	Pemetrexed-cisplatin (n=513) Non-squamous NSCLC population	11.8 (95% CI, 10.4 to 13.2)
Shaw *et al.* (2011) [30]	ALK-positive, crizotinib-naïve, >1 line of therapy (n=36)	20 (95% CI, 13 to 26)
Moro-Sibilot *et al.* (2015) [94]	Pemetrexed-platinum (n=553) Non-squamous NSCLC population	10.6 (95% CI, 9.4 to 12.0)
UK clinical expert opinion	Expected life expectancy of patients with ALK-positive, advanced NSCLC treated with first-line chemotherapy	~15

Note: referenced texts are number in accordance with the main submission template's bibliography

A5. **Priority Question**: Please provide separate Kaplan-Meier curves (with the number of patients at risk at each time point and the total number of events over the observed period) for crizotinib patients who received pemetrexed post progression and patients that did not receive pemetrexed post progression.

Response: We are unable to provide these data as this analysis has not been carried out on the PROFILE 1014 data. At the time of data cut-off, only 45/172 patients assigned to the crizotinib arm had received follow-on systemic therapy (see response to A10 below) of these 21/172 patients (12%) had received platinum-based therapy post-progression. Due to these relatively small numbers, it's unlikely that at data cut-off, the OS estimates for the crizotinib arm were driven by follow-on therapies. It's also important to note that patients were not randomised to the type of post-progression therapy they received therefore an analysis of these patients would be biased and highly uncertain. Based on these reasons we are unable to provide these requested analyses.

A6. **Priority Question**: The rank preserving structural failure time (RPSFT) and iterative parameter estimation (IPE) methods of adjustment rely on the assumption of common treatment effect. Please provide justification for the plausibility of this assumption.

Response: The underlying method of the RPSFTM and the IPE is a structural version of the accelerated failure time (AFT) model with time dependent covariates, as introduced by Cox and Oakes (1984). The AFT model structure necessitates the assumption of "constant treatment effect" – that is, the treatment effect of the experimental treatment (crizotinib) received by patients who crossover must be the same as the treatment effect of crizotinib received by patients initially randomised to crizotinib.

Fundamentally, this structural assumption, a recognised limitation of the model, is untestable. Furthermore, there is no evidence to suggest this assumption doesn't hold. The RPSFTM is a widely accepted method to estimate survival time in the presence of crossover, and

has been used in a number of oncology clinical trials across different agents and indications. However, a range of survival models were considered in our submission and in addition to the RPSFT and the IPE, the two-stage model (which does not rely on this assumption) produced similar results.

In oncology clinical trials, treatment switches to subsequent systemic anti-cancer therapies are likely to occur and reflect appropriate treatment pathways given the initial treatment and, in general, one would not wish to adjust for these follow-up treatment changes in the OS analysis. As such, the aim of the RPSFTM method is to compare the effectiveness of crizotinib versus chemotherapy on OS, after adjusting for crossover, in the presence of follow-up systemic anti-cancer treatments. In order to achieve this aim, the additional assumption needs to be made that the effect of follow-up systemic anti-cancer treatments on OS is the same for both treatment arms.

As specific methods have specific methodological limitations, we would suggest focussing on the range of the results produced across the different model and draw conclusions from the consistent results estimated. This focuses on the range of the results rather than one specific model which are reflective of the decision made in the economic evaluation's base case to select the mid-point of HR range to best represent all the models results.

A7. **Priority Question:** Page 222, appendix 5 states that the two stage method of crossover adjustment makes the assumption that there is no time dependent confounding between the time of disease progression and the time of treatment switch. Given the wide range in the time elapsed between progression and crossover, please comment on the plausibility of this assumption.

Response: Although there is a wide range in the time elapsed between progression and crossover (*[academic / commercial in confidence information removed]*), the distribution is highly positively skewed; 75% of patients have crossed over by 7 weeks. In order to try and correct for any bias, analyses have been conducted which attempt to account for differences in the prognosis of switchers and non-switchers by covariate adjustment of post progression survival. For each of the covariate adjusted analyses, hazard ratios generated using counterfactual survival times derived from the two stage method were consistent. Furthermore, hazard ratios generated using the two-stage method are consistent with those of the RPSFT model and demonstrate a strong, consistent estimate of clinical benefit across the different crossover adjustment methods (submission Table 23, page 82).

A8. Due to the extensive crossover to the crizotinib arm, and use of crizotinib post progression in PROFILE 1014, the intention to treat (ITT) could be interpreted as a comparison of patients receiving first and second line crizotinib compared with patients receiving second line crizotinib. Please comment on this interpretation of the ITT analysis.

Response: Firstly, it is important to note that in clinical practice, treatment beyond progression (worded in the question as "*patients receiving first and second line crizotinib*") is not considered an additional treatment line; this is considered an extension of first-line treatment. Similarly, in the intervention arm, not all patients received treatment beyond progression (73% of patients). Those who received treatment beyond progression did so for a median for 3.1 months. This is not

equivalent to the expected treatment duration of receiving crizotinib as a second-line therapy, which is a median of 7.2 months (PROFILE 1007).

Secondly, caution should be given to any interpretation of the ITT analysis as a comparison of patients receiving first crizotinib versus patients receiving second line crizotinib. There are a number of reasons why such a strict interpretation of this analysis is not appropriate.

- Not all patients randomized to crizotinib experienced disease progression and not all of these patients received crizotinib beyond progression. PROFILE 1014 is neither randomised, stratified, nor powered to detect the treatment effect of second-line treatment when only an unrandomised subgroup of patients (70%) go on to receive second-line crizotinib.
- For the reasons above, crossover adjusted analyses of the ITT population is the recommended approach to examine OS. Analyses that maintain the randomised feature of the design for valid statistical comparison and interpretation have been performed using the RPSFTM, IPE and 2-stage methods. Results from all sensitivity analyses were consistent (hazard ratios ranging from *[academic / commercial in confidence information removed]* to 0.674) suggesting that the primary OS analysis, unadjusted for crossover, underestimated the treatment benefit of crizotinib on OS.
- In addition to the issues in a crossover confounded comparison of OS, using a first-line trial to provide estimates of the efficacy of a second-line treatment creates difficulties with the consideration of other comparative endpoints, as these data are collected only to the point of progression on first-line treatment and therefore by definition come from only a subgroup of the ITT population.
- In a real world clinical setting many patients treated with chemotherapy in first-line have poor outcomes and are not eligible for second-line treatment. In the UK, clinical expert opinion suggests that is lower than 50%, compared to the 70% of the chemotherapy control arm in the trial who received crizotinib as a second-line therapy. As such, the ITT analysis is not an accurate reflection of the real world cohort that would present for second-line treatment in UK clinical practice.
- Crizotinib is currently not standard of care in Wales in patients with relapsed ALK-positive NSCLC as it has not been approved by NICE. The outcome of the NICE re-appraisal of crizotinib as a second-line therapy is currently undetermined, so second-line crizotinib cannot be considered a guaranteed part of the pathway in England for the purpose of this decision.

In summary, treatment beyond progression with crizotinib is not classed as a second-line treatment, but as an extension of first-line treatment. A strict interpretation of the ITT population as a comparison of patients receiving crizotinib in the first-line versus crizotinib in the second-line is not appropriate. Additionally, consideration of any pathway with crizotinib as the second-line treatment in England and Wales is not appropriate for the purpose of appraising crizotinib in the first-line.

Comparators

A9. Please comment on whether pemetrexed maintenance therapy is currently used in the NHS.

Response: It is important to note that pemetrexed maintenance therapy is not a named comparator in the final scope for this appraisal. The inclusion of this treatment regimen was discussed during the scoping workshop and it was agreed by clinicians that it was not an appropriate comparator. More importantly, pemetrexed maintenance therapy has not been available via the CDF since September 2015 so does not represent standard of care. During the time period that this was funded via the CDF, UK clinical experts estimated that only a small proportion (approximately 15%) of non-squamous NSCLC patients would have received maintenance therapy following their treatment with pemetrexed plus cisplatin.

Post progression treatment

A10. **Priority Question:** For PROFILE 1014, please provide further information on the post progression treatments received and the duration (such as the number of cycles) of second-line therapy. Please provide information for each treatment group separately. Please comment on the degree to which second line therapies may have influenced the observed overall survival in PROFILE 1014.

Response: The summary of follow-up systemic therapies by arm of the full analysis population is reported in the table below. Information on follow-on treatment duration was not collected; however the number of treatment regimens started (by arm) has been reported.

At the time of data cut-off, only 26% of the overall survival events had occurred, therefore median survival had not been reached. The crossover adjusted median OS for patients treated with chemotherapy from the economic model was approximately 14 months which is in line with historical and UK expert estimates (see Table 1 above). Of the 171 patients in the chemotherapy arm, a significant proportion (*[academic / commercial in confidence information removed]*) received follow-on systemic therapy; of these, the majority (*[academic / commercial in confidence information removed]*) received crizotinib. The use of crizotinib as a second-line therapy in this group is assumed to have greatly influenced the observed overall survival and as a result the observed unadjusted OS in this group is higher than historical estimates for advanced NSCLC. It is for this reason that we have undertaken a number of statistical modelling approaches to adjust for cross-over so that the OS treatment effect can be compared between crizotinib and pemetrexed.

By contrast, in the crizotinib arm, only *[academic / commercial in confidence information removed]* patients had received follow-on systemic therapy, and the range of therapies received was variable and broadly reflected the international focus of this trial. It is therefore unlikely that the survival benefit for this smaller group of patients afforded by any second-line treatment would have significantly influenced the observed OS in the crizotinib arm. Please see Table 2 below for more information on the 2nd line treatments received by arm within the PROFILE 1014 trial.

Table 2. Follow-on systemic therapies in PROFILE 1014

	Crizotinib, n (%)	**Chemotherapy, n (%)**
Number (%) of subjects with systemic therapy at follow-up	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Total number of regimens started		
1 regimen	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
2 regimens	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
≥ 3 regimens	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Systemic follow-up therapies		
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
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[academic / commercial in confidence information removed]	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

A11. **Priority Question**: Page 69 implies that *[academic / commercial in confidence information removed]* patients who were randomised to the chemotherapy group received crizotinib as follow-up treatment but had no disease progression. Please explain why these patients crossed over to crizotinib therapy instead of staying on chemotherapy? Did these patients receive any other treatments?

Response: We would like to confirm that *[academic / commercial in confidence information removed]* patients had progressive disease confirmed by independent radiologic review (IRR). The main reasons provided in the study report for these patients receiving crizotinib outside of the study protocol related either to the patient's condition at the time of the progression which did not meet the protocol crossover eligibility requirements, or the patient did not want to continue participation in the crossover part of the study.

The remaining four patients from the eleven crossed over without progressive disease confirmed by IRR. In *[academic / commercial in confidence information removed]* patients health deterioration prompted disease progression as judged by the investigator's assessment (but not confirmed by IRR) and the remaining patient discontinued chemotherapy because of adverse events and crossover was not requested by the investigator.

Further case-by-case information can be provided on these patients should it be required, however as these eleven patients received crizotinib outside of the protocol, no efficacy data are available and these patients have not been considered within the efficacy results for Crizotinib.

A12. Figure 7, page 70: Please explain the difference between the numbers reported in figure 7 for the chemotherapy group: '25 had objective PD or relapse'; '109 crossed over to crizotinib

after PD' and the numbers reported in Solomon 2014 (132 independent radiologic review [IRR] documented progressive disease [PD] events).

Response: We can confirm that Figure 7, on page 70 of our submission is based on the data presented in the Solomon 2014 supplementary materials (figure S1; page 12).

The number of progression events (n=132) confirmed by IRR in the chemotherapy arm as reported in Solomon 2014 is correct. In Figure 7 the patient numbers have been analysed and are reported by various categories therefore it's not possible to identify the total number of patients with a progressive event from this figure.

Patient-reported outcomes and health-related quality of life

A13. Please state whether patient-reported outcome data (such as health-related quality of life) are based on the pre-progression data, i.e. that post-progression treatments are not included in the results?

Response: The health-related quality of life data included in our submission are based on pre-progression data, as per the definition of the PRO-evaluable population (see Table 18, page 65 of the submission) (i.e., all patients from the full analysis population who completed a baseline assessment [last PRO assessment prior to randomisation day] and at least 1 post-baseline PRO assessment prior to crossover or end of randomised study treatment.)

For those patients who crossed over from chemotherapy to receive crizotinib, all data up to and including the day prior to the first dose of crizotinib treatment were included. The PRO evaluable population was the primary population for the analysis of change from baseline scores and TTD in patient-reported pain in chest, dyspnoea, or cough.

A14. The median follow-up at the data cut off (30 November 2013) is reported in the submission. Please provide the range for length of follow-up.

Response: At data cut-off, median follow-up for the survival outcome was 17.4 months for patients randomised to crizotinib [range: 12.1 to 23.7 months], and 16.7 months for those patients randomised to chemotherapy [range: 12.2 to 23.4 months].

A15. **Priority Question:** Please provide further information on the analysis of EQ-5D data – does the analysis account for differences in baseline characteristics between treatment groups?

Response: Yes, the analysis does account for differences in baseline characteristics.

To compare actual scores and change from baseline scores between treatment arms, repeated measures mixed-effects modelling was carried out for EQ-5D VAS using 2-sided tests. Each model had an intercept term, a linear time trend term, a term for treatment arm, a baseline covariate, and a term for treatment-by-time interaction. Repeated measures over time were accounted by unstructured covariance structure. If the model could not converge with the unstructured covariance structure, a spatial covariance structure was considered and, if that did not converge, an autoregressive heterogeneous, autoregressive, or compound symmetry variance/covariance matrix

was applied (in that order). All parameter estimates were obtained using restricted maximum likelihood estimation.

The intercept and slope terms for time were random effects with an assumed unstructured variance/covariance matrix. In addition, each observation was assumed to be measured with error and the error terms were independent of each other. A sandwich estimator was used to estimate the variance of the fixed effects terms. All parameter estimates were obtained using restricted maximum likelihood estimation and all testing was 2-sided. For the EQ-5D health state profiles, the proportions of patients that reported having “no”, “some”, or “extreme” problems at each time point were reported for each of the 5 dimensions in addition to the EQ-5D health utility index scores.

Further details can be found in the PROFILE 1014 CSR, page 105

A16. Priority Question: Please provide the EQ-5D utility values (mean, SD, sample size) for crizotinib and pemetrexed groups at baseline and other time points.

Response: Please see the tables below which have been taken from the PROFILE 1014 CSR Table 14.5.2.3.8.1 (page 4139). Note that these data are not controlled for baseline; the values used in the cost-effectiveness model are controlled for baseline, as per the response to A15.

Table 14.5.2.3.8.1
Crizotinib Protocol A8081014 - (Date of Data Snapshot: 07MAR2014 and Date of Cutoff 30NOV2013) Summary of EQ-5D Health Index Score by Arm - Full Analysis

EQ-5D Index(utility score)

	Crizotinib (N=172)						Chemotherapy (N=171)					
Time Point	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**
BASELINE*	*[academic / commercial in confidence information removed]*											
CYCLE2/DAY1												
CYCLE3/DAY1												
CYCLE4/DAY1												
CYCLE5/DAY1												
CYCLE6/DAY1												
CYCLE7/DAY1												
CYCLE8/DAY1												
CYCLE9/DAY1												
CYCLE10/DAY1												
CYCLE11/DAY1												
CYCLE12/DAY1												
CYCLE13/DAY1												
CYCLE14/DAY1												
CYCLE15/DAY1												
CYCLE16/DAY1												
CYCLE17/DAY1												
CYCLE18/DAY1												
CYCLE19/DAY1												
CYCLE20/DAY1												
CYCLE21/DAY1												

Note: *Baseline is defined as Cycle 1 Day 1. EOT 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.

Table 14.5.2.3.8.1
Crizotinib Protocol A8081014 - (Date of Data Snapshot: 07MAR2014 and Date of Cutoff 30NOV2013) Summary of EQ-5D Health Index Score by Arm - Full Analysis

EQ-5D Index(utility score)

	Crizotinib (N=172)						Chemotherapy (N=171)					
Time Point	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**
CYCLE22/DAY1	*[academic / commercial in confidence information removed]*											
CYCLE23/DAY1												
CYCLE24/DAY1												
CYCLE25/DAY1												
CYCLE26/DAY1												
CYCLE27/DAY1												
CYCLE28/DAY1												
CYCLE29/DAY1												
CYCLE30/DAY1												
CYCLE31/DAY1												
CYCLE32/DAY1												
CYCLE33/DAY1												
CYCLE34/DAY1												
CYCLE35/DAY1												
CYCLE36/DAY1												
CYCLE37/DAY1												
CYCLE38/DAY1												
CYCLE39/DAY1												
CYCLE40/DAY1												
CYCLE41/DAY1												
CYCLE42/DAY1												

Note: *Baseline is defined as Cycle 1 Day 1. EOT 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.

Table 14.5.2.3.8.1

Crizotinib Protocol A8081014 - (Date of Data Snapshot: 07MAR2014 and Date of Cutoff 30NOV2013) Summary of EQ-5D Health Index Score by Arm - Full Analysis

EQ-5D Index(utility score)

	Crizotinib (N=172)						Chemotherapy (N=171)					
Time Point	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**
CYCLE43/DAY1												
CYCLE44/DAY1												
CYCLE45/DAY1												
CYCLE46/DAY1												
CYCLE47/DAY1												
CYCLE48/DAY1												
CYCLE49/DAY1												
CYCLE50/DAY1												
EOT												

[academic / commercial in confidence information removed]

Note: *Baseline is defined as Cycle 1 Day 1. EOT 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.

A17. Please comment on the difference in EQ-5D scores at baseline between the crizotinib and pemetrexed groups in PROFILE 1014.

Response: The difference in baseline mean EQ-5D was minimal; *[academic / commercial in confidence information removed]*in the crizotinib arm and *[academic / commercial in confidence information removed]*in the pemetrexed arm (CSR Table 14.5.2.3.8.1; page 4139).

In PROFILE 1014, patients were randomised in a 1:1 ratio to receive crizotinib or chemotherapy. Randomisation was stratified by ECOG performance status (0-1 vs. 2), race Asian versus Non-Asian and presence of brain metastases (presence or absence). Patients could not be randomised based on baseline EQ-5D scores as these measurements are only taken once a patient has been included in the study. As mentioned above (question A15), the analysis for EQ-5D that compared against treatment arms included a baseline covariate that adjusted for differences in baseline EQ-5D scores.

A18. Regarding the independent radiologic review (IRR) assessment of PD, were all patients assessed at regular intervals or were IRR assessments only done at the behest of the clinician?

Response: Tumours were assessed at regular intervals, i.e. every 6 weeks from the date of randomisation until radiographic PD had been documented by IRR (clinical study report; pg. 84). All scans were then sent to an independent radiology laboratory for a blinded RECIST review. Patients who completed 6 cycles of chemotherapy and/or discontinued treatment prior to RECIST-defined PD were to continue with tumour assessments per the protocol until PD was documented by IRR or additional anticancer therapy was initiated; this included patients who had discontinued study treatment for reasons other than PD but remained in the study.

<u>Davis et al. 2015</u>

A19. The cohort of patients reported by Davis et al. 2015 includes a larger number of older patients and a higher proportion of smokers compared with PROFILE 1014. ALK+ status could be associated with younger patients and non-smokers. Please provide data to support the generalisability of Davis et al. 2015 to the ALK+ population in England.

Response: The patients included in PROFILE 1014 trial are considered to be largely representative of the ALK-positive patient population in the UK; however clinical expert advice noted that a non-trial population may be slightly less healthy and 5- to 10-years older than that seen in a clinical trial. The clinical experts also confirmed the generalisability of the cohort included in Davis et al. 2015 to the ALK+ population in England.

The table below presents patient clinical characteristics from an ongoing retrospective cohort study in the UK that is assessing the treatment patterns and outcomes of patients with ALK-positive advanced NSCLC treated with crizotinib in regular clinical practice (Pfizer data on file). Patient characteristics from the UK study are similar to those in Davis et al. 2015 in the

overall population therefore supporting the generalisability of Davis et al. 2015 to UK clinical practice.

Table 3. Demographic and clinical characteristics

	Davis et al. 2015 (North America) (n = 212) Overall population		United Kingdom (n = 127)	
Age (years) at crizotinib initiation				
Mean [SD]	59.1	9.5%	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Median	60		*[academic / commercial in confidence information removed]*	
Range (min, max)	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Distribution, n (%)	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
18 - 35	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
36 - 45	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
45 - 55	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
55 - 65	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>65	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sex, n (%)				
Male	146	68.9%	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Female	66	31.1%	*[academic /*	*[academic /*

			commercial in confidence information removed]	*commercial in confidence information removed]*
Ethnicity, n (%)				
White/caucasian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
African/black	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Asian or pacific islander	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Other	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Unknown	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

A20. Please provide further information about post-progression treatments in Davis et al. 2015. Did patients continue with crizotinib as in PROFILE 1014? Please provide data on the number of patients and duration of treatment for both pre-progression and post-progression crizotinib therapy.

Response: In Davis et al. 2015 the median duration of treatment with crizotinib in the overall population was 8.7 months compared to a median PFS of 9.5 months. When considering treatment lines separately, the median duration of treatment in first line was 9 months (median PFS 9.6 months) and in second-line was 8.5 months (median PFS was 9 months).

These data suggest that patients were not treated beyond progression in any lines of therapy.

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ALK Testing

A21. **Priority Question**: Please provide evidence on whether the immunohistochemistry (IHC) test has been validated and whether it is widely used in the NHS.

Response: IHC has been validated as a test to determine the ALK status of a patient's NSCLC. Studies have indicated that IHC is sensitive and specific for determining ALK status, and is a viable alternative to ALK FISH (McLeer-Florin, 2012; Yi, 2011). Roche's IHC test (VENTANA ALK CDx Assay) has FDA approval as a companion diagnostic for crizotinib and has also received CE marketing for use in Europe.

IHC is also used widely in the NHS. Pfizer data on file encompassing data from 19 NHS Trusts in England showed that that approximately *[academic / commercial in confidence information removed]* IHC tests for ALK have been carried out between the years 2013-2015 in patients with NSCLC.

On 17th Feb 2016 NHSE Monitor published the *2016/17 National Tariff Payment System: A consultation notice*. This described the intentions of NHSE to commission ALK testing from April 2016 and have ALK testing incorporated in the National Tariff by 2019. This would support ALK testing as a routine diagnostic in NHSE.

Reference: Monitor. 2016/17 National Tariff Payment System: A consultation notic. 2016. *NHS England*. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/499594/2016-17_national_tariff_statutory_consultation.pdf Accessed 26/02/16

A22. Other methods for testing ALK status (such as CISH, RT-PCR and next generation sequencing) are available. Are these tests used in the NHS?

Response: CISH, RT-PCR and NGS are used very rarely and in a select few labs, usually for academic purposes. IHC and FISH represent the significant majority of these tests used in the NHS.

A23. **Priority Question**: Is IHC testing for ALK status conducted concurrently with epidermal growth factor receptor (EGFR) testing or is IHC testing for ALK status conducted after EGFR testing in the NHS?

Response: We understand that in the majority of NHS Trusts, testing for ALK is performed concurrently with EGFR testing upon initial diagnosis of NSCLC (often referred to as "upfront testing"). Only a few trusts may wait until after EGFR testing is done to test for ALK status.

A24. **Priority Question**: Please provide evidence for the total time taken to complete the testing (for EGFR testing, IHC tests for ALK status and subsequent FISH tests)?

Response: The average time is approximately 2 weeks from time of the initial test to the treating oncologist receiving test results. However, the total time taken will vary depending on the testing centre.

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A25. Please provide information on any potential capacity issues which could arise from a larger group of individuals being eligible for ALK testing?

Response: Most testing for ALK is currently done upfront (*i.e.* on those patients who have been newly diagnosed with non-squamous NSCLC), therefore we do not anticipate that numbers would increase significantly beyond what is currently conducted.

A26. **Priority Question**: There is some evidence that the prevalence of ALK+ status is higher in people with adenocarcinoma than in people with large-cell undifferentiated carcinoma. Please state whether a subgroup of adenocarcinoma patients was tested and subsequently treated in PROFILE 1014.

Response: The inclusion criterion specific to tumour subtype in PROFILE 1014 was “non-squamous” NSCLC, which includes adenocarcinomas and large cell carcinomas. In PROFILE 1014, 94% of patients presented with adenocarcinoma therefore we would suggest that the overall results are representative of this population and no need for further stratification of results.

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Section B: Clarification on cost-effectiveness data

Treatments received in PROFILE 1014

B1. **Priority Question**: Please provide the mean number of cycles of pemetrexed received in PROFILE 1014.

The mean duration of study treatment from PROFILE 1014 is provided in Table 4 for all treatments.

Table 4: Mean duration of study treatment

Treatment	Duration (mean [SD])*	Duration in cycles (calculated)
Crizotinib	52.0 [35.2] weeks	12.13 cycles = 13 cycles
Pemetrexed	15.7 [5.8] weeks	3.67 cycles = 4 cycles

Reference: PROFILE 1014 CSR Table 40 (page 184).

Please note the following caveats if mean values are being considered within a sensitivity analysis in the model:

- The mean number of crizotinib cycles in Table 4 includes treating beyond progression.
- As crizotinib's PFS is equal to the median number of treatment cycles (prior to including treatment beyond progression), using mean values to calculate cost will conflict with the median values used for PFS. However, as not all patients had progressed at the time of the data cut-off, the mean PFS is not available.
    - Median PFS for crizotinib is 10.9 months in the PROFILE 1014 trial
    - Median PFS for pemetrexed is 7.0 months in the PROFILE 1014 trial

It should be noted that editing the duration of treatment in the model to use the above means rather than median substantially lowers the ICER, making crizotinib more cost-effective. Hence, the submitted base case contains the more conservative estimate of crizotinib's cost-effectiveness.

B2. **Priority Question**: Please provide Kaplan-Meier curves for discontinuation of first line treatment (with the number of patients at risk at each time point and the total number of events over the observed period) for both crizotinib patients and pemetrexed patients.

The Kaplan-Meier curves for total time on treatment are provided in

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Figure 1 for all treatments. The Kaplan-Meier curves for total time on treatment for pemetrexed, cisplatin and carboplatin (excluding crizotinib) are provided in Figure 2.

Figure 1: Kaplan-Meier curves – all treatments

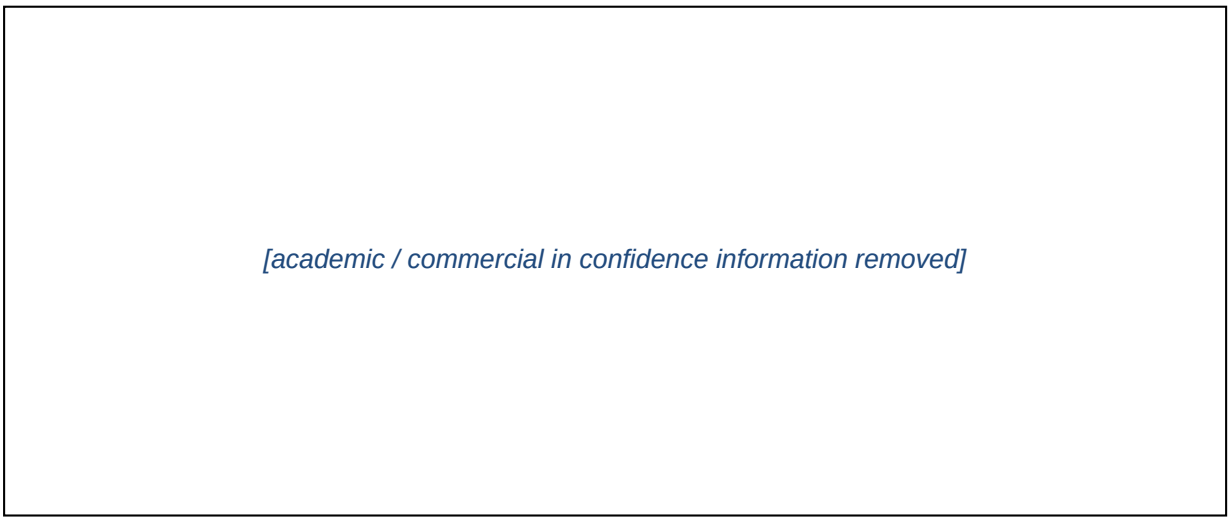
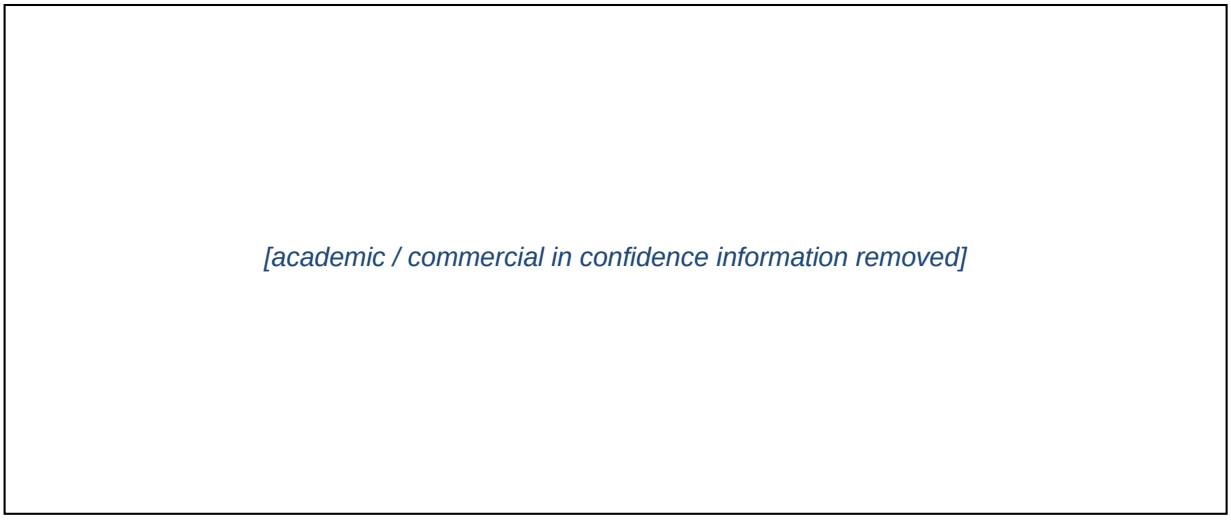


Figure 2: Kaplan-Meier curves – pemetrexed, cisplatin and carboplatin



Treatment costs

B3. **Priority Question**: Please provide individual patient data on body surface area and sex for patients from PROFILE 1014.This is to allow calculation of the mean dose of pemetrexed.

Mean dose (mg/m^2/week) is available in the CSR (Table 42):

- Mean pemetrexed dose is 152.9 mg/m^2/week (SD 18.4).

Mean BSA is available in the CSR (Table 14.1.1.3.1.2a):

- Mean BSA for males was 1.9m^2 (SD 0.18, range 1.5-2.4)

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- Mean BSA for females was 1.6m^2 (SD 0.18, range 1.3-2.2)
- Mean BSA was 1.7m^2 (SD 0.21, range 1.3-2.4)

In the basecase model we have used a mean BSA of 1.73m^2 calculated using the equation BSA (m2) = SQRT([Height(cm) x Weight(kg)]/ 3600).

Reducing the cost of comparator therapies that rely on a BSA dose (e.g. pemetrexed, cisplatin) in a scenario analysis that assumes all patients have a BSA of 1.6m^2 only increases the ICER by £1,405 per QALY with the PAS. Crizotinib remains cost-effective in this scenario.

Model function and textual errors

B4. **Priority Question**: Several costs reported in the submission are different from the costs used in the executable model. Please indicate which values are correct:

a. Table 58, page 164: The cost of thrombocytopenia is reported as £758.50, however the executable model uses £750.09.

b. Table 60, page 165: The total costs of adverse events is reported as £163.20 for the pemetrexed group, however the executable model uses £82.04.

c. Table 57, page 163: The cost of end of life/supportive care is reported as £7,253, however the executable model uses £7,318.

We can confirm that the values included in the executable model are the correct values and are now included in an accompanying Addendum document which summarises the new base case results.

The values stated in the submission text were typos for questions B4a, B4b and B4c respectively.

B5. **Priority Question**: The post progression treatment option does not work in the executable model (Sheet “Model controls”). Please provide details of a potential solution and a revised executable model.

We have reviewed the executable mode; and note that there was an error in the visual basic code which prevented this post progression option from working correctly. We have corrected this error and will send you the revised model.

B6. **Priority Question**: The option to include a one off administrative cost for crizotinib in the executable model does not work (Sheet “Model controls”). Please confirm if this cost is included in the company’s base case analysis. Please provide details of a potential solution and a revised executable model.

Please note that a revision to the executable model is not needed. To assign a one-off administrative cost in addition to changing cell J139 on the "Model controls" sheet, cell C38 on the "Tx admin cost" sheet should also be set to "Deliver exclusively Oral Chemotherapy" rather than "No cost".

A sensitivity analysis is presented in Tables 74 and 75 in the submission document that investigates the impact of introducing a one-off cost for crizotinib administration to reflect the time spent by the clinician explaining to the patient how to orally take the medicine. As the patient then collects repeat prescriptions, it is assumed no further healthcare resource use is required to re-discuss how to take the medicine with the patient.

The base case analysis assumes no administration cost for crizotinib, as it is an oral therapy, and therefore is not expected to incur any administration costs to the NHS, and the clinician explaining how to administer the medicine to the patient is already included in the time required for routine monitoring.

B7. **Priority Question**: The base case ICER (£*[academic / commercial in confidence information removed]*per QALY gained) reported in the executable model is not the same as the one reported in the submission (table 67, page 171; £*[academic / commercial in confidence information removed]*per QALY gained). Please explain the difference between the ICERs.

Please note that the figure in table 67, page 171 of a submission is a typo and we can confirm that the correct value is £*[academic / commercial in confidence information removed]*, as presented in the executable model.

Please note that this figure has changed slightly following amends noted in subsequent questions; a new set of results is provided in a separate addendum document, along with a revised version of the model.

B8. **Priority Question**: The ICER reported in the sensitivity analysis for 'Patient characteristics as per PROFILE 1014' in the executable model (£*[academic / commercial in confidence information removed]* per QALY gained) is not the same as the one in the submission (page 19; £*[academic / commercial in confidence information removed]*per QALY gained). Please explain the difference between the ICERs.

Please note that the figure on page 19 of our submission is a typo and the correct value is *[academic / commercial in confidence information removed]*presented in our executable model.

As discussed above in B7, this figure has changed slightly following amends, an Addendum document is provided with updated results, along with a revised version of the model.

B9. **Priority Question**: The ERG noted a number of apparent errors in the executable model and carried out a number of fixes described below and highlighted in the

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(attached) executable model. Please validate and confirm that the following suggested changes are appropriate.

Sheet “Calc Tx1”

Change cells AS15:AS258 to:

=((1-TBP_prop_criz)*(Y(Row))*(p_util_sust_criz)+(OFFSET(X(Row -1),1,MIN(DOCE_duration,MAX(E(Row),1)))-Y(row)*(1-TBP_prop_criz)*p_utility_doce_pp +IFE(Row)<TBP_duration,0,(OFFSET(X(Row),1,MIN(DOCE_duration+TBP_duration,E(Row)))-OFFSET(X(Row),1,MIN(TBP_duration,E(Row)))))*TBP_prop_criz*(p_utility_doce_pp))*(cycle_length/365.25)*G(Row)

Change cells AT15:AT258 To
=(AJ(Row)*p_utility_bsc_pp+AI(Row)*(p_util_sust_doce))*(cycle_length/365.25)*$G(Row)

Change Cells BA197:258 to:

£0.00

Sheet “Calc Tx2”

Change cells AL15:AL258 to

=(AE(Row)*p_utility_bsc_pp+AD(Row)*(p_util_sust_doce))*(cycle_length/365.25)*$G(Row)

Change cells AL15:AL258 to
=((AC(Row)-Y(Row))*p_utility_doce_pp+Y(Row)*(p_util_sust_tx2))*$G(Row)*(cycle_length/365.25)

Change Cells BA190:258 to
£0.00

We have fully reviewed our model and confirm that the changes you have proposed are appropriate and are now updated in our model accordingly. In addition to these changes, we have identified a further minor error which relates to a sensitivity analysis of changing the time horizon from 15 years (used in the basecase) to 20 years. Specifically, we have observed that the cells in Sheet “Calc Tx1” and Sheet “Calc Tx2” which sum results over the time horizon

(cells AM9:BN9 in sheet “Calc Tx1” and cells AG9:BB9 in sheet “Calc Tx2”) were not summing all the way up to 20 years.

To correct this, we have changed the formula in these cells from:

=SUMIF($C$15:$C$197,"<="&Time_horizon,(column)15:(column)197)

to

=SUMIF($C$15:$C$258,"<="&Time_horizon,(column)15:(column)258)

We can confirm that this additional minor amendment does not impact the base case results and does not alter crizotinib’s cost-effectiveness. Crizotinib remains cost-effective at a £50,000/QALY threshold when offered with the confidential PAS.

Revised results for this scenario are provided in an Addendum document with a full set of updated results.

Costs of testing

B10. **Priority Question**: Page 166: Please provide a breakdown of what is included in the cost of FISH testing (£120). Does this include the costs of tissue handling and processing? Please explain the difference in the cost of FISH testing used in NICE technology appraisal 296.

From the source data the price of this test “applies to NHS referrals”. Pfizer is not privy to the All Wales Genetic Laboratory’s costing breakdown within this figure so is unable to provide further information. This figure was selected in the mode as it was the only publically available up to date estimate of the cost of FISH testing following the completion of a literature review.

In NICE technology appraisal 296, the cost used is not up to date and is based on the unit cost of a test sourced through communication with the manufacturer of this test (Abbott Molecular).

More importantly, it should also be noted that the ICER is not sensitive to the price of FISH testing; increasing the cost of FISH by 10% increases the deterministic ICER by less than £30 (when crizotinib is offered with the PAS).

Reference: All Wales Genetic Laboratory *Non-small-cell lung cancer - EGFR and ALK mutation testing (2015). Available at: http://www.wales.nhs.uk/sites3/Documents/525/MI-MGN-EGFRInfo.pdf.*

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PFS and OS

B11. **Priority Question**: Please provide further justification of the assumption of proportional hazards in the analysis of PFS. Is this assumption clinically plausible, given that pemetrexed has a fixed cycle regimen and treatment with crizotinib continues until the absence of clinical benefit?

Treatment with crizotinib in the PROFILE 1014 trial was until RECIST defined progression, PFS. Treatment beyond progression could be considered to be treatment 'until the absence of clinical benefit' as the question states, so it is important to note that benefit from treatment can continue past PFS.

This assumption was assessed by inspecting the plot of log hazards by log time for PFS; in general, the plot did not yield a large departure from the parallel lines; therefore the assumption of a constant treatment effect was made for both analyses.

The proportional hazards assumption was discussed with a UK clinical expert with experience treating ALK-positive patients with both crizotinib and chemotherapy. The expert stated that it was clinically reasonable to assume proportional hazards and patients would be expected to follow proportionality extrapolated survival curves.

B12. **Priority Question**: Please provide an analysis of PFS adjusted with the baseline covariates using independent parametric functions for each treatment group and distribution (Gamma, Exponential, Weibull, Gompertz, Log Logistic and Log Normal). Please report the full set of distribution parameters estimates (as presented in Sheet: "OS_Model_Estimates" in the executable model), AIC and BIC, and plots.

The originally submitted models included covariates for treatment and prognostic factors. It is accepted that certain prognostic factors influence survival outcomes, in particular those that reflect the health of the patient at baseline (e.g. ECOG performance status).

Treatment as a covariate is a large driver of survival outcomes (as seen in the tornado diagrams in the main submission). However, whilst the choice of treatment influences survival, there is no identified clinical evidence to suggest it plausible that other baseline prognostic factors have differing effects on survival, depending on the treatment taken. For example, a patient's smoking status may influence their survival outcomes, but the influence of this factor is not expected to differ whether this patient has crizotinib or pemetrexed. The reason for the difference in outcomes in this patient is driven by the efficacy of the treatment.

Consequently, the clinical rationale supports the use of joint covariate modeling with common baseline covariate parameter estimates for both treatment arms. Nevertheless, we have described the three types of model including the original models, and an additional two types of models in order to answer the question.

These new models are as follows:

1. Joint model (**original models**)
    a. Includes treatment as a covariate
    b. Includes prognostic baseline characteristics as covariates, with common baseline covariate parameter estimates for both treatment arms
        - Used to adjust all patients characteristics to real world data which is more reflective of the UK ALK+ NSCLC population than the PROFILE 1014 trial
    c. Most appropriate model for base case. There is no identified clinical evidence to suggest the use of joint modelling is not applicable.
2. Stratified model including common baseline covariate parameter estimates for both treatment arms
    a. Both parameters (or two of the three for generalised gamma) instead of one parameter of the survival model (shape and scale, shape and rate, sdlog and meanlog, sigma and mu) are adjusted by a treatment effect
    b. The underlying shape is allowed to be different by treatment arm, but the impact of important prognostic factors is the same for both treatment arms
    c. Uses the whole PROFILE 1014 data set to fit the models
3. Fully stratified model
    a. Survival model parameters and baseline covariate parameters are estimated separately for each treatment arm
    b. The underlying shape and the impact of important prognostic factors are allowed to be different by treatment arm
    c. Uses two subsets of PROFILE 1014 data to fit the models for each treatment arm (smaller sample size)

1. Models including covariates for treatment and prognostic factors (submitted models)

Table 5: AIC and BIC for PFS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	1619.10	1653.63
Generalised gamma	1593.36	1635.58
Gompertz	1610.75	1649.12
Log-logistic	1603.05	1641.43
Log-normal	1607.92	1646.30
Weibull	1591.86	1630.24

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

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Figure 3: PFS parametric curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

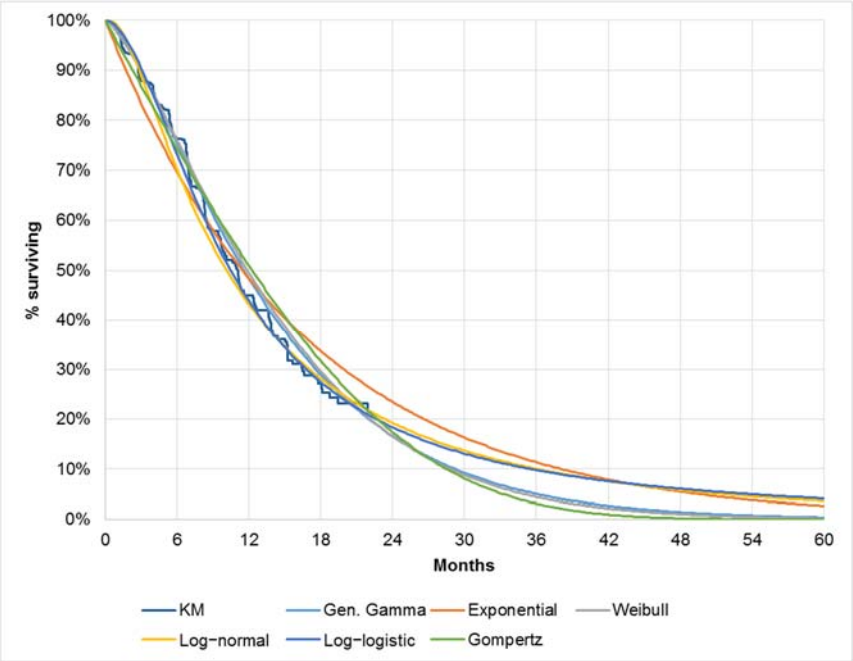
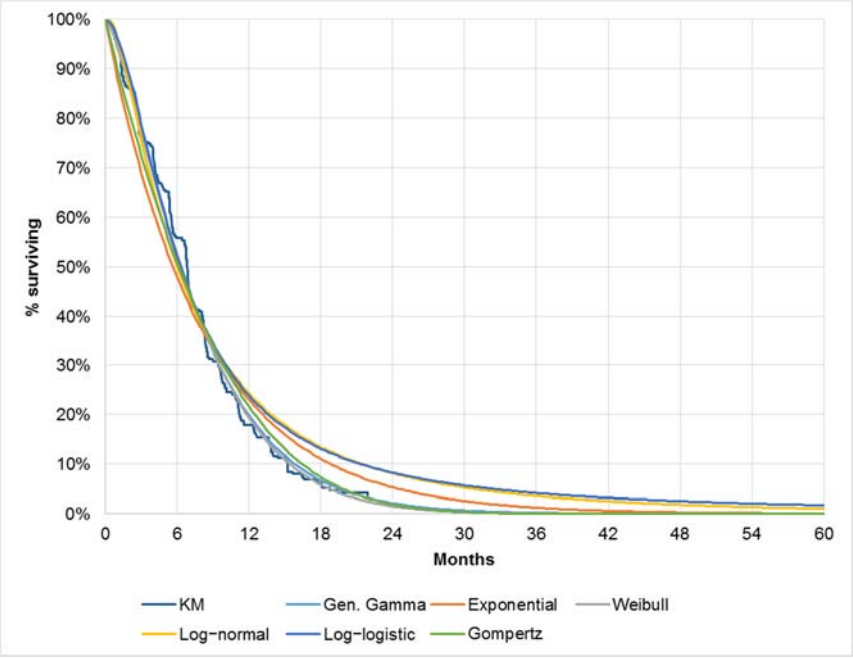


Figure 4: PFS parametric curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cis/carbo arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.
Abbreviation: KM: Kaplan-Meier; PFS: progression-free survival.

Table 6: Estimated model parameters for progression free survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	**Generalised gamma**	Log logistic
Fixed model parameters						
Q	n/a	n/a	n/a	n/a	**0.847**	n/a
Sigma	n/a	n/a	n/a	n/a	**-0.253**	n/a
Sdlog	n/a	n/a	n/a	-0.009	**n/a**	n/a
shape	n/a	0.303	0.039	n/a	**n/a**	0.587
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

The chosen base case model is indicated in bold.
Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

2. **Independent models for each treatment, with common covariates for prognostic factors)**

Table 7: AIC and BIC for PFS (models including common covariates for prognostic factors)

Model	AIC	BIC
Generalised gamma	1587.66	1633.71
Gompertz	1598.00	1640.21
Log-logistic	1595.73	1637.94
Log-normal	1600.37	1642.59
Weibull	1586.92	1629.14

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Figure 5: PFS parametric curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

[academic / commercial in confidence information removed]

Figure 6: PFS parametric curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)

[academic / commercial in confidence information removed]

For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; PFS: progression-free survival.

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Table 8: Estimated model parameters for progression free survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

3. Independent models for each treatment, with separate covariates for prognostic factors

Table 9: AIC and BIC for PFS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	766.13	791.31	864.58	889.71
Generalised gamma	762.57	794.05	834.21	865.62
Gompertz	768.12	796.45	840.47	868.75
Log-logistic	761.60	789.93	845.23	873.51
Log-normal	760.95	789.28	850.60	878.88
Weibull	764.67	793.00	832.49	860.77

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Figure 7: PFS parametric curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

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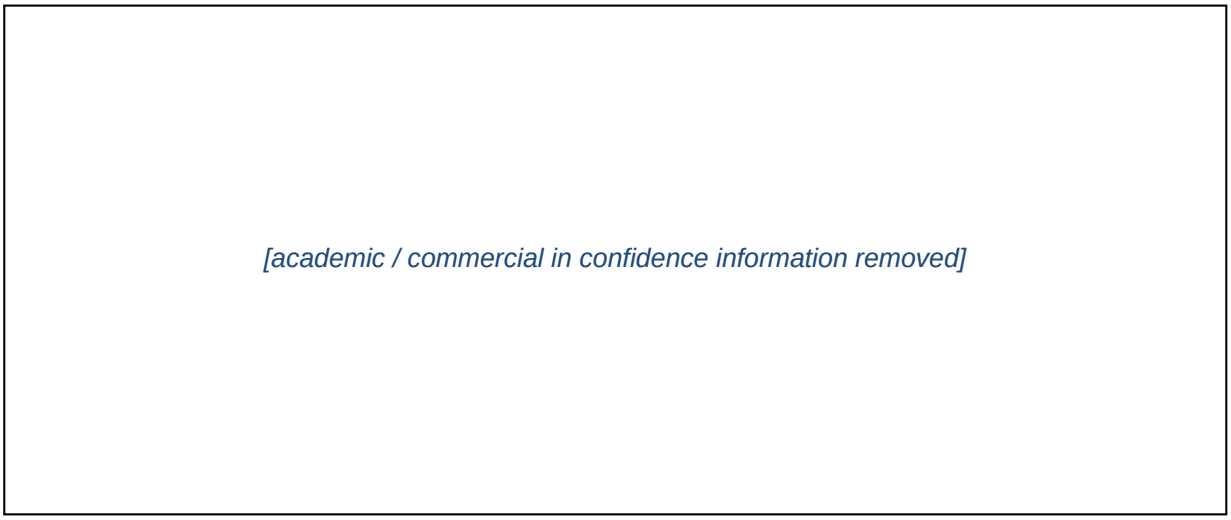
Figure 8: PFS parametric curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; PFS: progression-free survival.

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Table 10: Estimated model parameters for progression free survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

Table 11: Estimated model parameters for progression free survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*

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Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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B13. **Priority Question**: Please justify the assumption of proportional hazards in the analysis of OS.

This assumption was assessed by inspecting the plot of log hazards by log time for OS; in general, the plot did not yield a large departure from the parallel lines; therefore the assumption of a constant treatment effect was made for both analyses.

The proportional hazards assumption was discussed with a UK clinical expert with experience treating ALK-positive patients with both crizotinib and chemotherapy. The expert stated that it was clinically reasonable to assume proportional hazards, citing the only reason that a patient cohort might not follow proportionality extrapolated survival curves was because of crossover between the trial arms.

B14. **Priority Question**: Please provide an analysis of OS using independent parametric functions for each treatment group for the 5 different methods of adjustment for crossover (RL, RW, TSA, TSB and TSC) for each distribution (Gamma, Exponential, Weibull, Gompertz, Log Logistic and Log Normal). Please report the full set of distribution parameters estimates (as presented in Sheet "OS_Model_Estimates" in the executable model), AIC and BIC, and plots.

The originally submitted models included covariates for treatment and prognostic factors. It is accepted that certain prognostic factors influence survival outcomes, in particular those that reflect the health of the patient at baseline (e.g. ECOG performance status).

Treatment as a covariate is a large driver of survival outcomes (as seen in the tornado diagrams in the main submission). However, whilst the choice of treatment influences survival, there is no identified clinical evidence to suggest it plausible that other baseline prognostic factors have differing effects on survival, depending on the treatment that is used. For example, a patient's smoking status may influence their survival outcomes, but the influence of this factor is not expected to differ whether this patient has crizotinib or pemetrexed. The reason for the difference in outcomes in this patient is driven by the efficacy of the treatment.

Consequently, the clinical rationale supports the use of joint covariate modeling with common baseline covariate parameter estimates for both treatment arms. Nevertheless, we have described the three types of model including the original models, and an additional two types of models in order to answer the question.

These new models are as follows:

1. Joint model (**original models**)
    a. Includes treatment as a covariate
    b. Includes prognostic baseline characteristics as covariates, with common baseline covariate parameter estimates for both treatment arms
        - Used to adjust all patients characteristics to real world data which is more reflective of the UK ALK+ NSCLC population than the PROFILE 1014 trial

c. Most appropriate model for base case. There is no identified clinical evidence to suggest the use of joint modelling is not applicable.

2. Stratified model including common baseline covariate parameter estimates for both treatment arms
    a. Both parameters (or two of the three for generalised gamma) instead of one parameter of the survival model (shape and scale, shape and rate, sdlog and meanlog, sigma and mu) are adjusted by a treatment effect
    b. The underlying shape is allowed to be different by treatment arm, but the impact of important prognostic factors is the same for both treatment arms
    c. Uses the whole PROFILE 1014 data set to fit the models
3. Fully stratified model
    a. Survival model parameters and baseline covariate parameters are estimated separately for each treatment arm
    b. The underlying shape and the impact of important prognostic factors are allowed to be different by treatment arm
    c. Uses two subsets of PROFILE 1014 data to fit the models for each treatment arm (smaller sample size)

1. Models including covariates for treatment and prognostic factors (submitted models)

Table 12: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	831.59	866.13
Generalised gamma	833.87	876.09
Gompertz	833.55	871.93
Log-logistic	832.90	871.27
Log-normal	836.60	874.98
Weibull	832.24	870.61

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 9: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

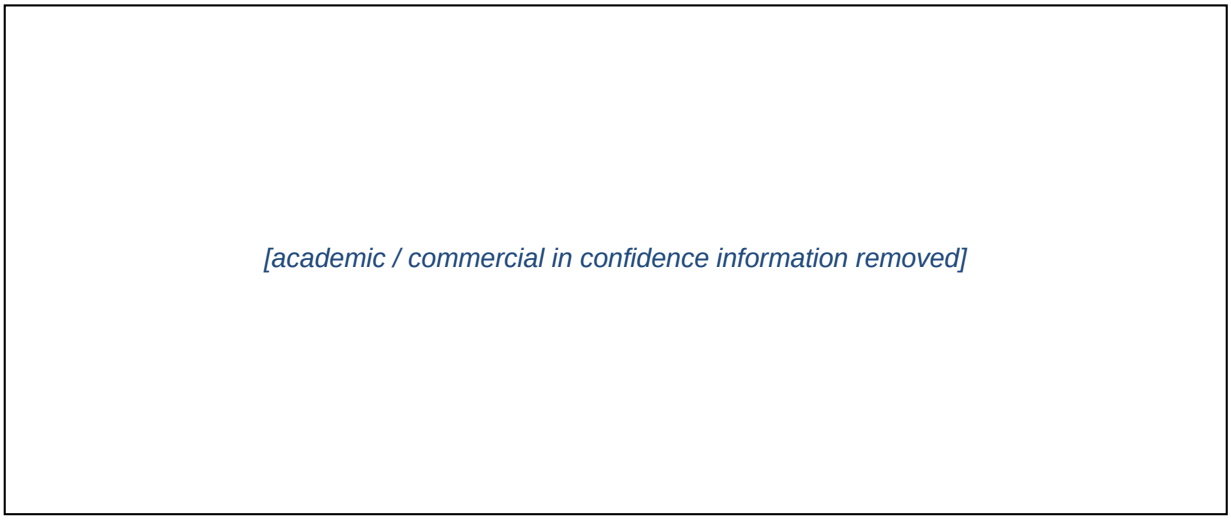
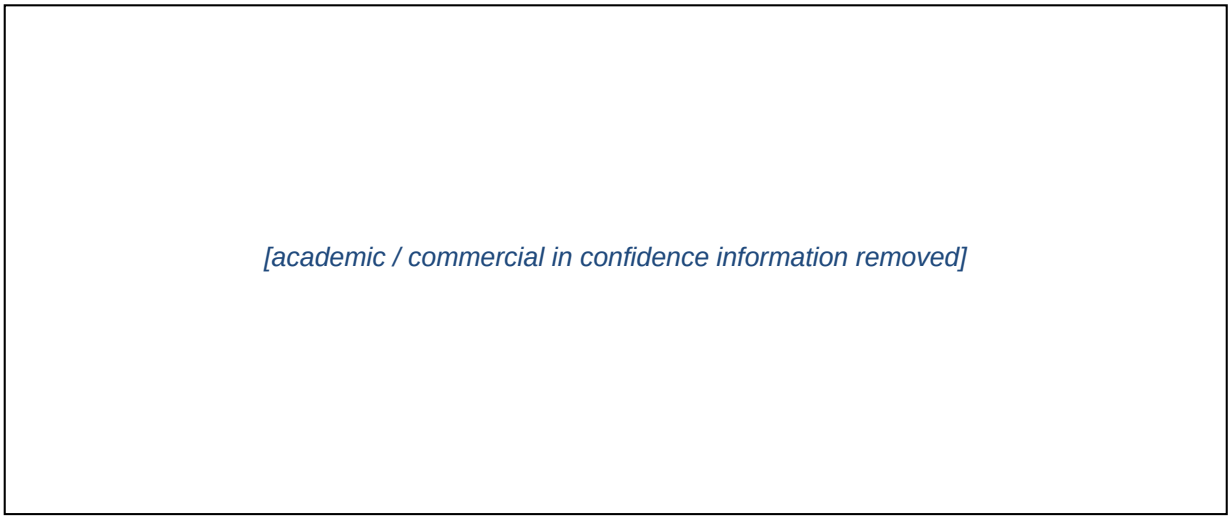


Figure 10: OS (using crossover method TSA) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 13: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

The chosen base case model is indicated in bold.

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Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

2. **Independent models for each treatment, with common covariates for prognostic factors)**

Table 14: AIC and BIC for OS (models including common covariates for prognostic factors)

Model	AIC	BIC
Generalised gamma	835.75	881.80
Gompertz	832.78	874.99
Log-logistic	834.89	877.10
Log-normal	838.57	880.78
Weibull	833.99	876.20

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 11: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

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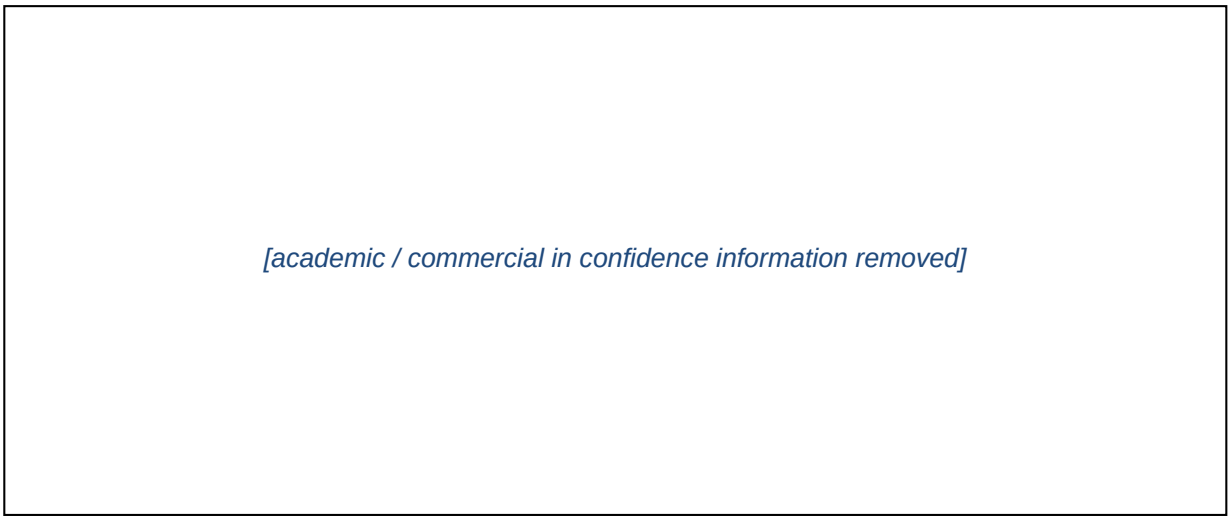
Figure 12: OS (using crossover method TSA) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 15: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

3. Independent models for each treatment, with separate covariates for prognostic factors

Table 16: AIC and BIC for OS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	433.88	459.06	406.78	431.91
Generalised gamma	433.05	464.53	409.45	440.87
Gompertz	434.12	462.44	407.57	435.84
Log-logistic	436.79	465.12	407.49	435.76
Log-normal	440.43	468.76	408.40	436.67
Weibull	433.34	461.66	408.65	436.93

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 13: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

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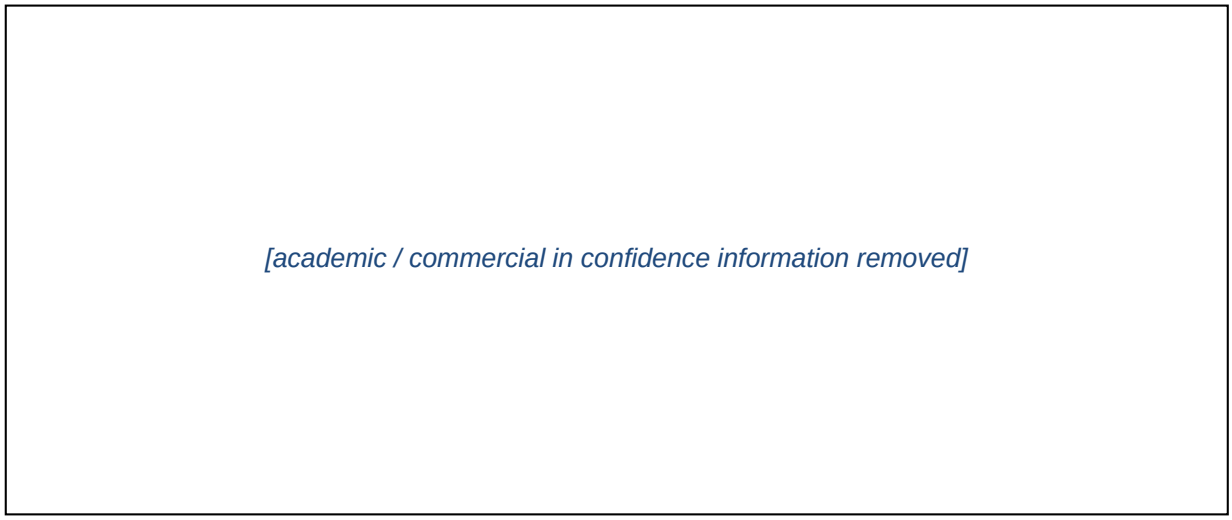
Figure 14: OS (using crossover method TSA) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 17: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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Table 18: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

4. Overall survival using crossover method TSB (question B14)

a. Models including covariates for treatment and prognostic factors (submitted models)

Table 19: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	835.21	869.75
Generalised gamma	837.50	879.72
Gompertz	837.15	875.52
Log-logistic	836.53	874.91
Log-normal	840.51	878.88
Weibull	835.81	874.19

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 15: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

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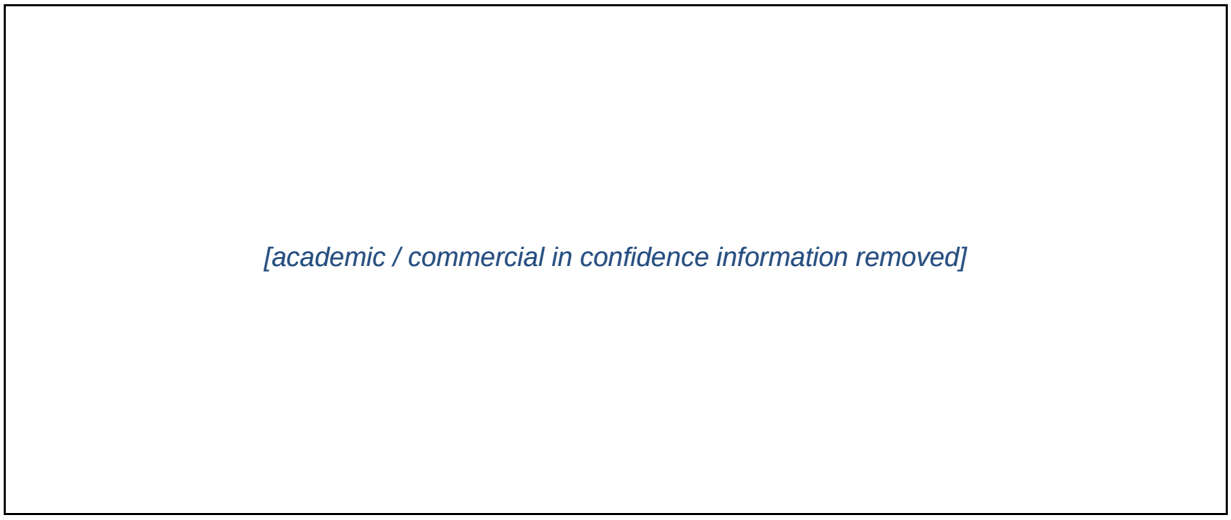
Figure 16: OS (using crossover method TSB) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 20: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

b. Independent models for each treatment, with common covariates for prognostic factors)

Table 21: AIC and BIC for OS (models including common covariates for prognostic factors)

Model	AIC	BIC
Generalised gamma	839.37	885.43
Gompertz	836.55	878.77
Log-logistic	838.53	880.74
Log-normal	842.48	884.70
Weibull	837.57	879.79

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 17: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

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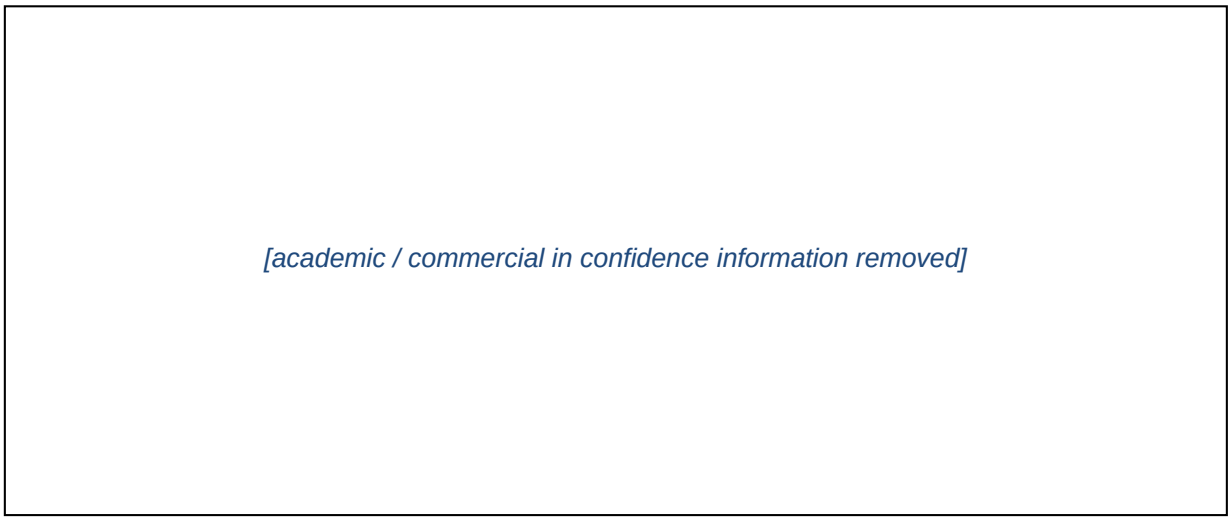
Figure 18: OS (using crossover method TSB) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 22: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

c. Independent models for each treatment, with separate covariates for prognostic factors

Table 23: AIC and BIC for OS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	433.88	459.06	410.34	435.47
Generalised gamma	433.05	464.53	413.16	444.58
Gompertz	434.12	462.44	411.29	439.56
Log-logistic	436.79	465.12	411.10	439.37
Log-normal	440.43	468.76	412.29	440.57
Weibull	433.34	461.66	412.20	440.48

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 19: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

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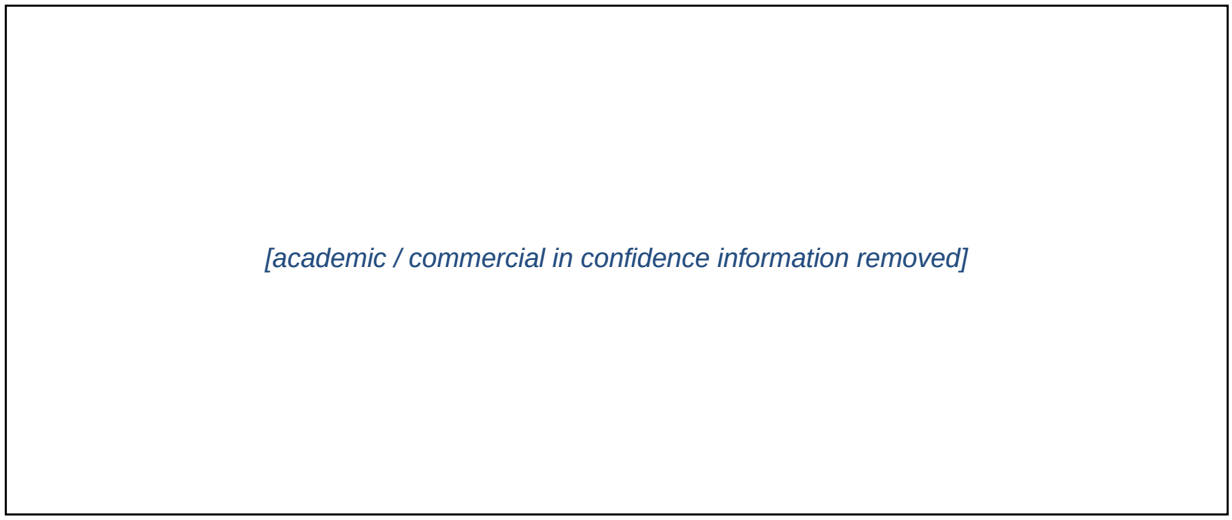
Figure 20: OS (using crossover method TSB) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 24: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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Table 25: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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5. Overall survival using crossover method TSC (question B14)

a. Models including covariates for treatment and prognostic factors (submitted models)

Table 26: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	829.96	864.50
Generalised gamma	832.23	874.44
Gompertz	831.92	870.30
Log-logistic	831.25	869.63
Log-normal	834.82	873.20
Weibull	830.62	869.00

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 21: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

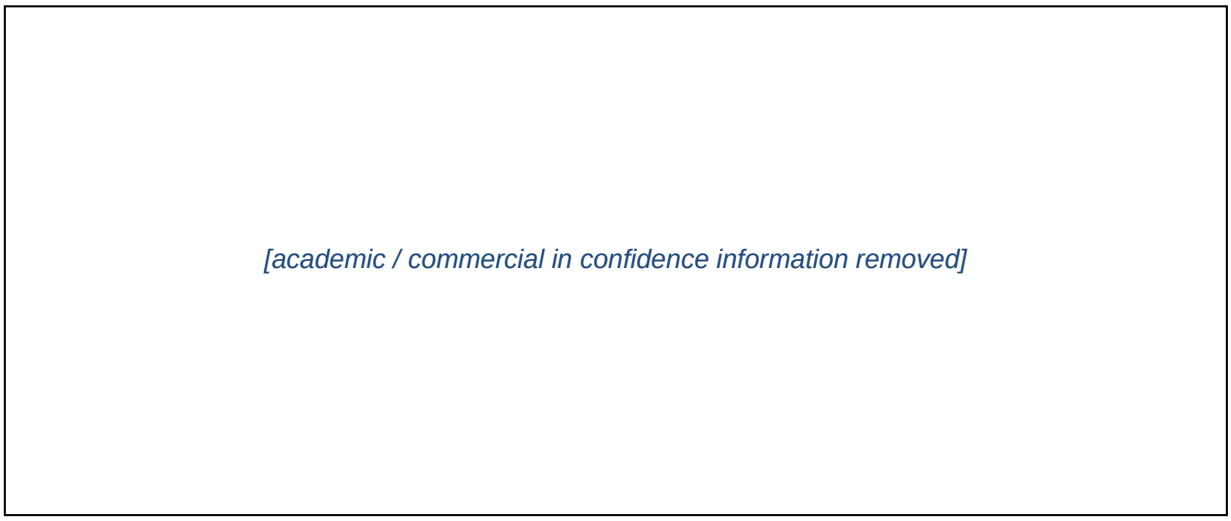
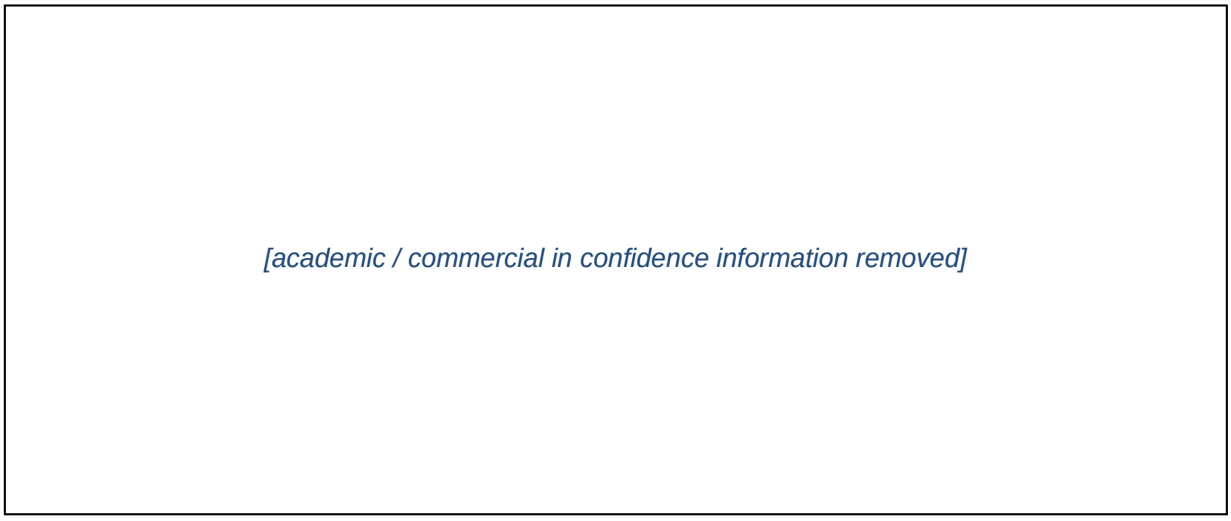


Figure 22: OS (using crossover method TSC) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.
Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 27: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

b. Independent models for each treatment, with common covariates for prognostic factors)

Table 28: AIC and BIC for OS (models including common covariates for prognostic factors)

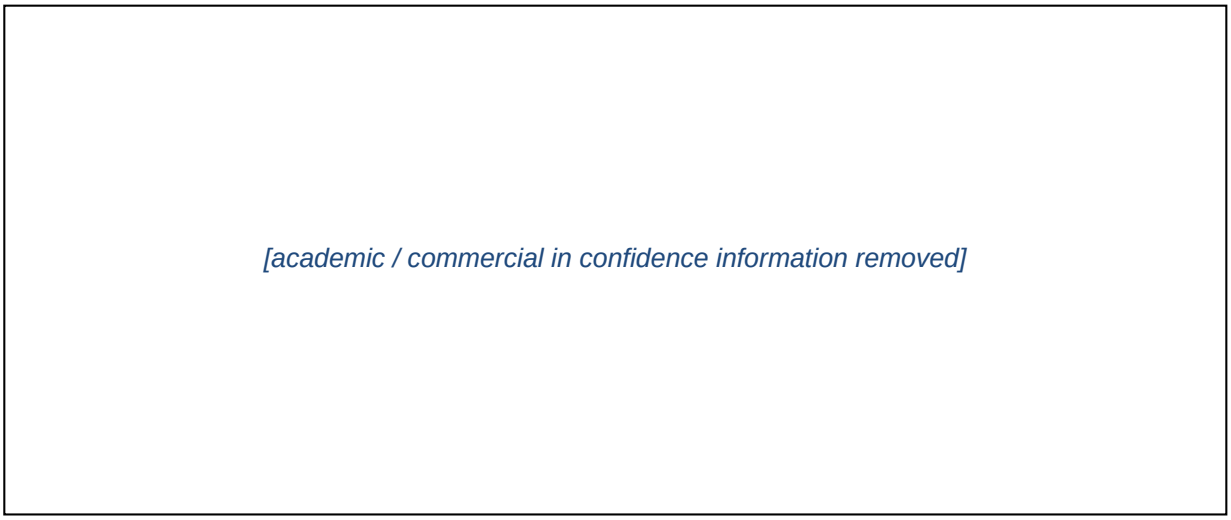
Model	AIC	BIC
Generalised gamma	834.10	880.16
Gompertz	831.05	873.26
Log-logistic	833.24	875.45
Log-normal	836.79	879.00
Weibull	832.37	874.58

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 23: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

[academic / commercial in confidence information removed]

Figure 24: OS (using crossover method TSC) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 29: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

c. Independent models for each treatment, with separate covariates for prognostic factors

Table 30: AIC and BIC for OS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	433.88	459.06	405.16	430.29
Generalised gamma	433.05	464.53	407.76	439.18
Gompertz	434.12	462.44	405.87	434.14
Log-logistic	436.79	465.12	405.85	434.12
Log-normal	440.43	468.76	406.62	434.90
Weibull	433.34	461.66	407.04	435.32

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 25: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

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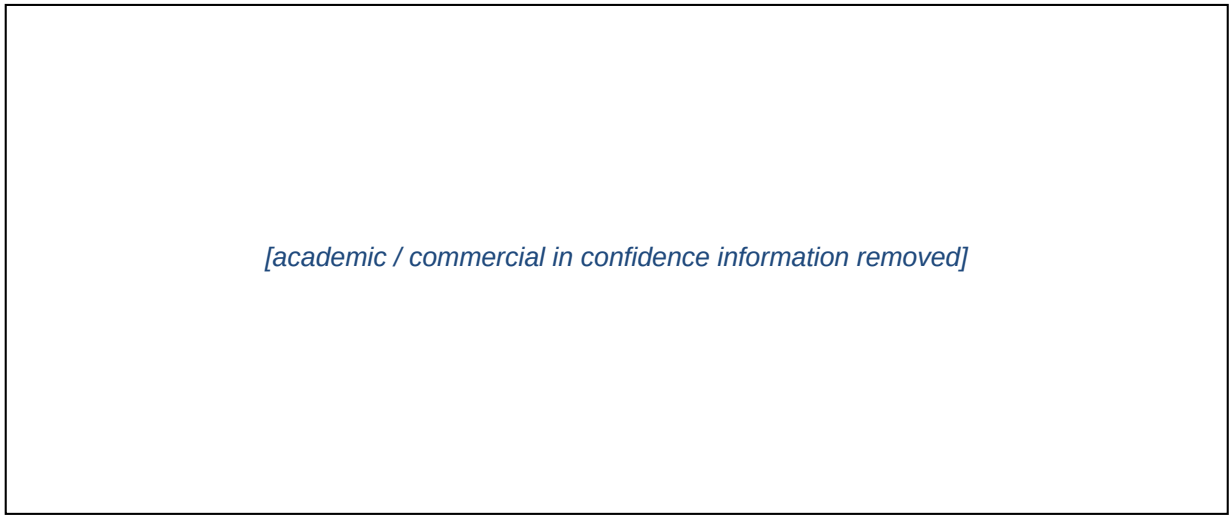
Figure 26: OS (using crossover method TSC) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 31: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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Table 32: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

6. Overall survival using the RPSFT (log rank method) crossover adjustment (question B14)

a. Models including covariates for treatment and prognostic factors (submitted models)

Table 33: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	794.05	828.59
Generalised gamma	796.45	838.67
Gompertz	795.70	834.07
Log-logistic	795.78	834.15
Log-normal	801.14	839.52
Weibull	794.49	832.87

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 27: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

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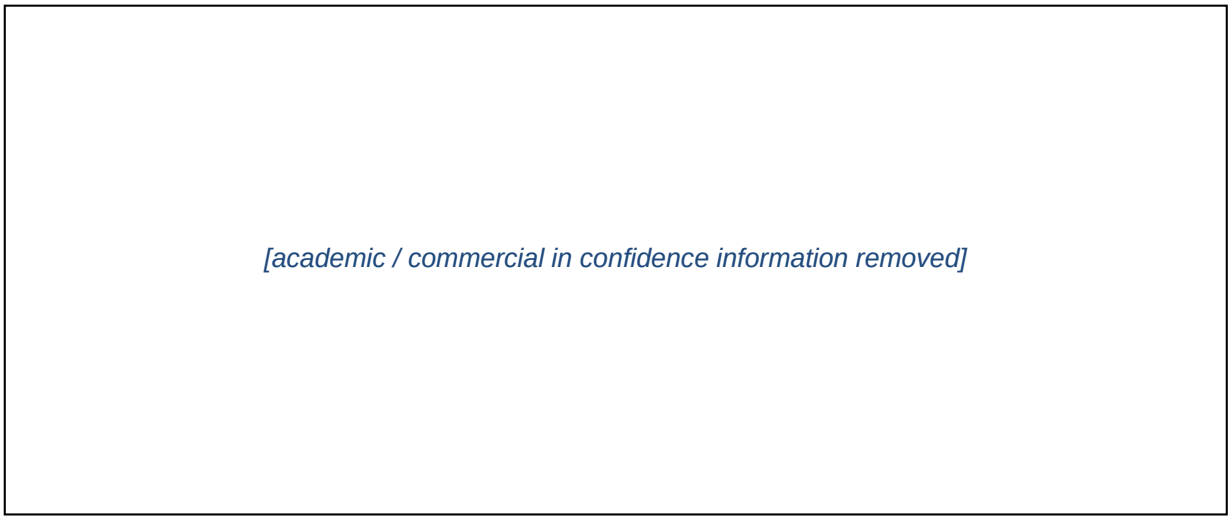
Figure 28: OS (using crossover method RPSFT – log rank method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 34: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

b. Independent models for each treatment, with common covariates for prognostic factors)

Table 35: AIC and BIC for OS (models including common covariates for prognostic factors)

Model	AIC	BIC
Generalised gamma	798.29	844.34
Gompertz	794.90	837.12
Log-logistic	797.77	839.98
Log-normal	803.13	845.34
Weibull	796.30	838.51

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 29: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

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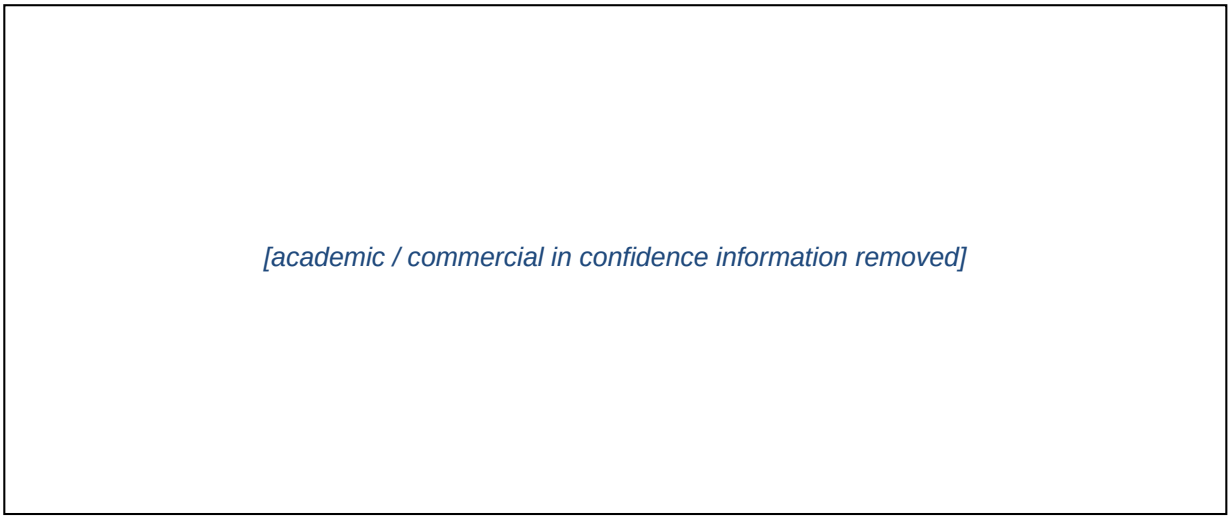
Figure 30: OS (using crossover method RPSFT – log rank method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 36: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

c. Independent models for each treatment, with separate covariates for prognostic factors

Table 37: AIC and BIC for OS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	418.95	444.13	384.16	409.30
Generalised gamma	418.36	449.83	387.71	419.13
Gompertz	418.17	446.50	385.44	413.71
Log-logistic	421.26	449.59	385.61	413.89
Log-normal	425.64	453.97	387.76	416.04
Weibull	418.10	446.43	386.02	414.29

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 31: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

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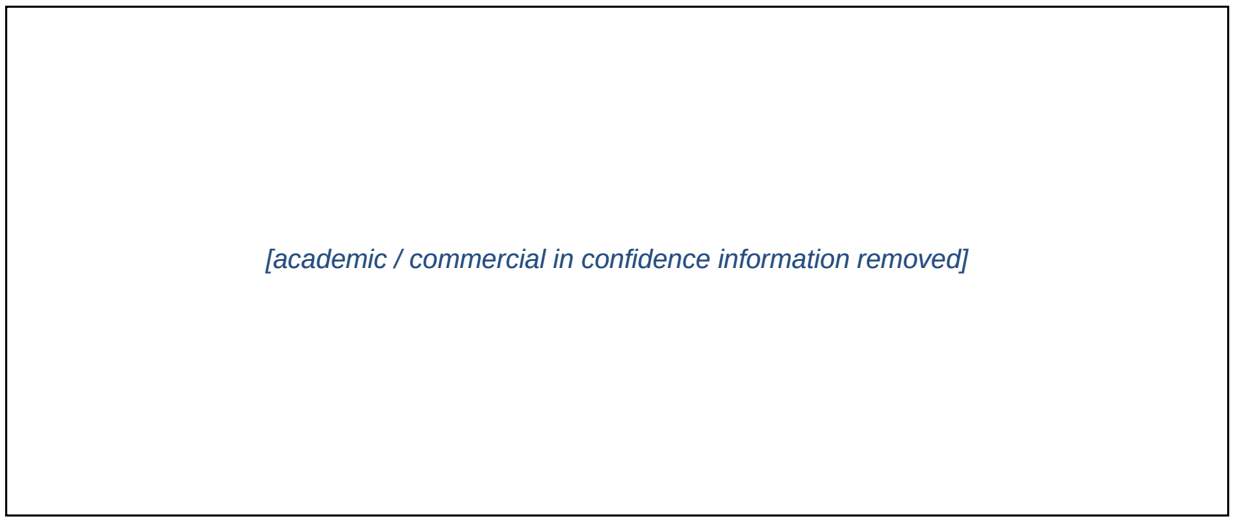
Figure 32: OS (using crossover method RPSFT – log rank method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 38: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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Table 39: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

7. Overall survival using the RPSFT (Wilcoxon method) crossover adjustment (question B14)

a. Models including covariates for treatment and prognostic factors (submitted models)

Table 40: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	780.29	814.83
Generalised gamma	782.22	824.44
Gompertz	781.34	819.72
Log-logistic	781.82	820.20
Log-normal	787.54	825.92
Weibull	780.22	818.60

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 33: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

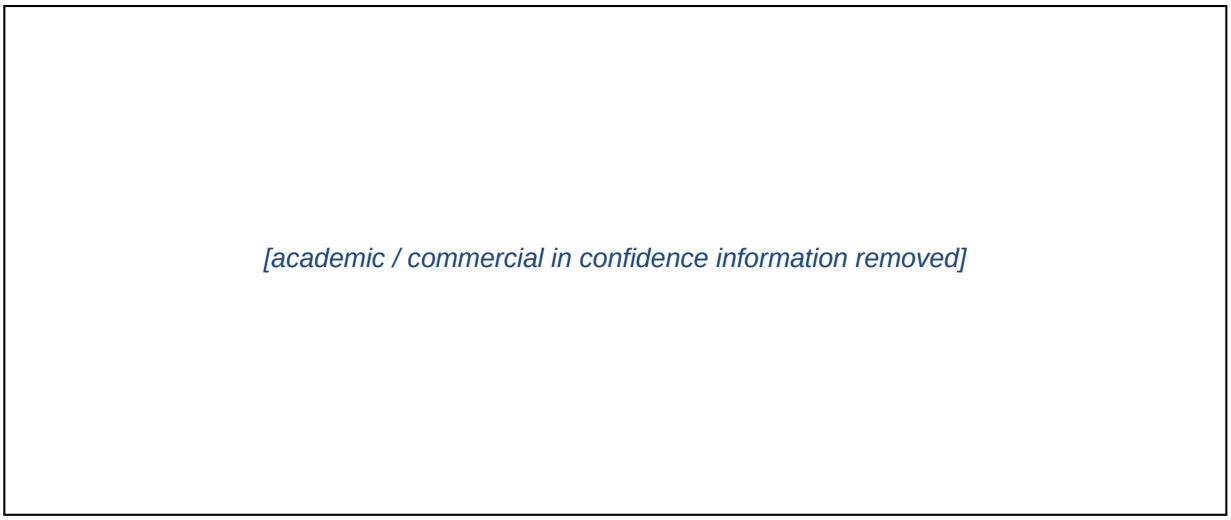
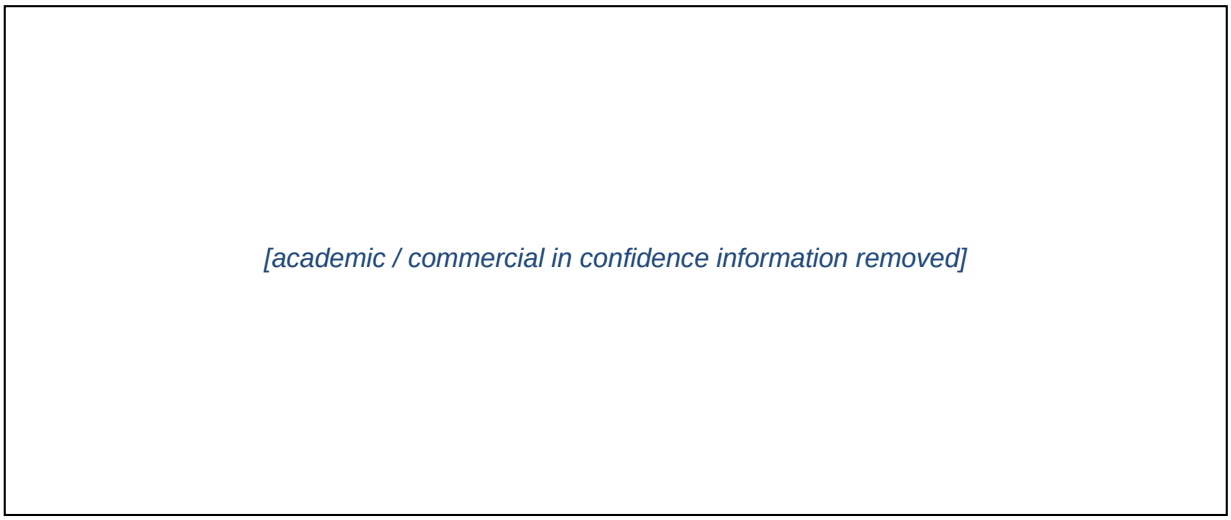


Figure 34: OS (using crossover method RPSFT – Wilcoxon method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 41: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

b. Independent models for each treatment, with common covariates for prognostic factors)

Table 42: AIC and BIC for OS (models including common covariates for prognostic factors)

Model	AIC	BIC
Generalised gamma	783.99	830.04
Gompertz	780.30	822.52
Log-logistic	783.80	826.02
Log-normal	789.53	831.75
Weibull	781.99	824.20

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 35: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

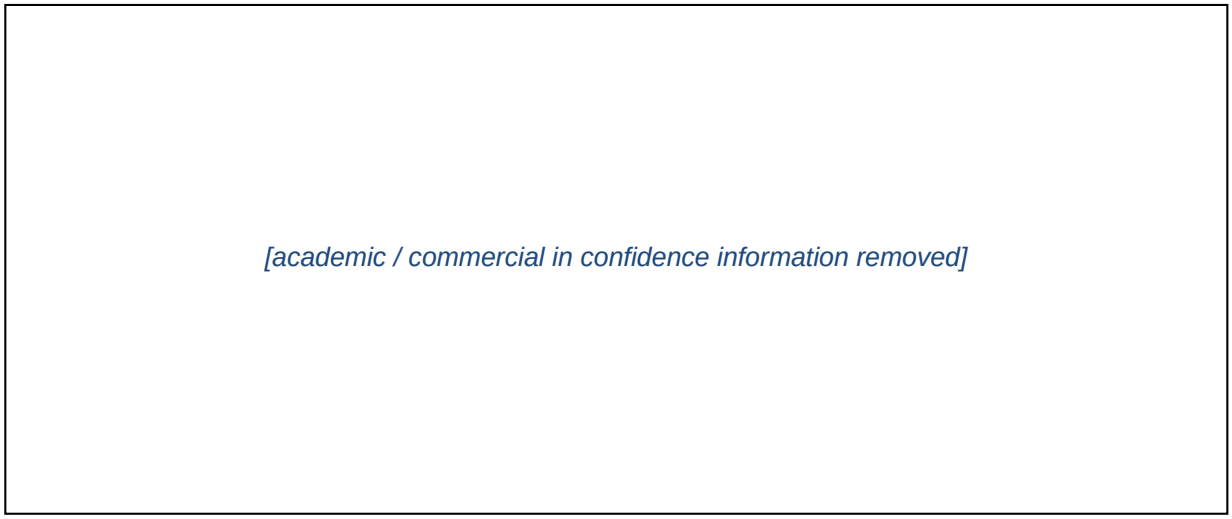
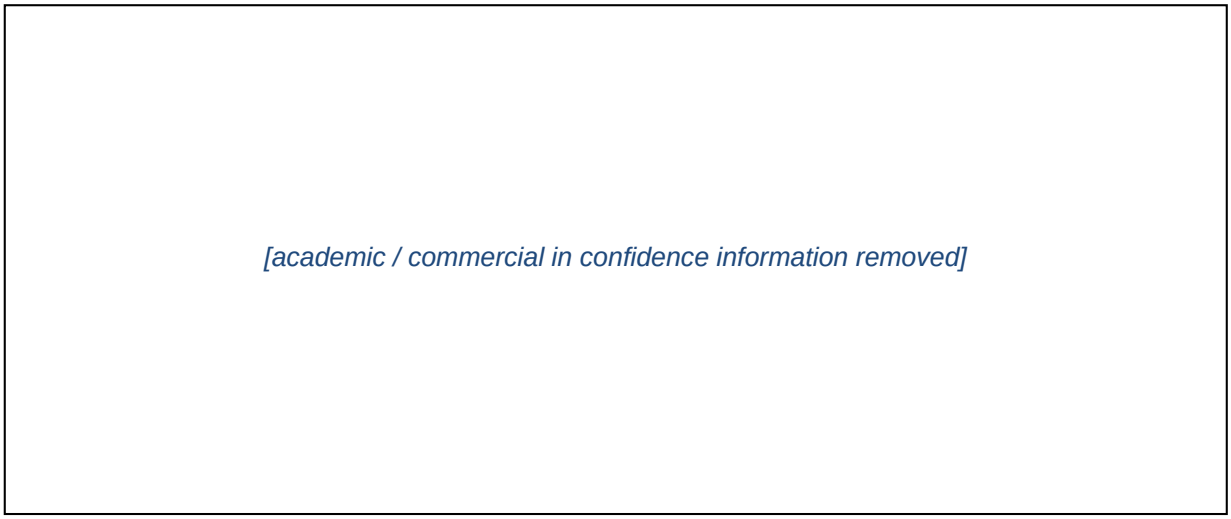


Figure 36: OS (using crossover method RPSFT – Wilcoxon method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 43: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

c. Independent models for each treatment, with separate covariates for prognostic factors

Table 44: AIC and BIC for OS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	419.45	444.63	369.80	394.94
Generalised gamma	418.03	449.50	373.32	404.74
Gompertz	417.36	445.69	371.27	399.55
Log-logistic	421.47	449.79	371.42	399.69
Log-normal	426.46	454.79	373.37	401.65
Weibull	418.05	446.38	371.54	399.81

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 37: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

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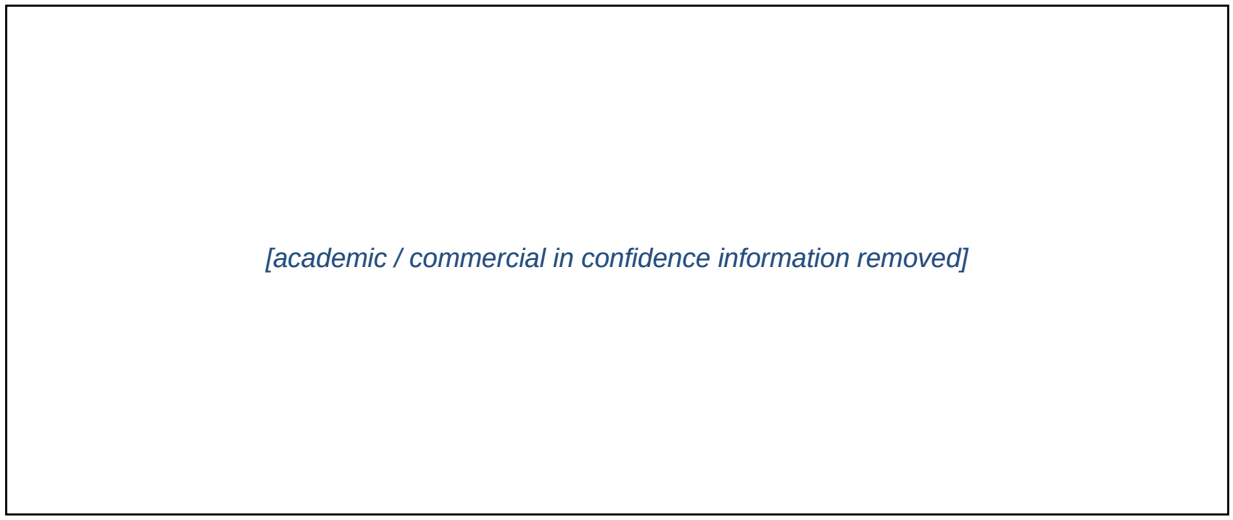
Figure 38: OS (using crossover method RPSFT – Wilcoxon method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 45: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus

Table 46: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*

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Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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B15. **Priority Question**: Please provide the IPE parametric models of OS adjusted with the baseline covariates. Please report the full set of distribution parameters estimates (as presented in Sheet "OS_Model_Estimates" in the executable model), AIC and BIC, and plots.

***** *Response to be provided on Monday 7th March* *****

B16. **Priority Question**: Please provide an ITT analysis (no crossover adjustment) of the OS outcome adjusted with the baseline covariates. Please report the full set of distribution parameters estimates (as presented in Sheet: "OS_Model_Estimates" in the executable model), AIC and BIC criteria for each distribution (Gamma, Exponential, Weibull, Gompertz, Log Logistic and Log Normal), and model fit plots (curves and Kaplan-Meier).

As per NICE Decision Support Unit (DSU) Technical Support Document (TSD) 16 and the NICE Methods Guide (2013), statistical methods have been employed to adjust for the crossover confounded ITT analysis. As the ITT is inappropriate for assessing survival benefit due to the high level of crossover, the ITT analysis was only presented in Section 4 of the submission and was not assessed in the parametric curve analyses.

Using the ITT data in any analysis of OS is severely caveated by concerns with the interpretation of the ITT as reflective of a population receiving second-line crizotinib; the difficulties around the applicability of the ITT population to clinical practice; and the uncertainty around the position of second-line crizotinib in the English and Welsh clinical pathways. Please see Question A8 in this document and Section 5.2.2 in the original submission for further details on these issues.

As these analyses are not appropriate for decision making, they should be considered with caution.

The following models are presented for the ITT, that have not been adjusted for crossover:

1. Models including covariates for treatment and prognostic factors
2. Independent models for each treatment, with common covariates for prognostic factors
3. Independent models for each treatment, with separate covariates for prognostic factors

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1. Models including covariates for treatment and prognostic factors

Table 47: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	865.58	900.12
Generalised gamma	868.45	910.67
Gompertz	867.58	905.95
Log-logistic	867.34	905.72
Log-normal	872.66	911.04
Weibull	866.64	905.01

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 39: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

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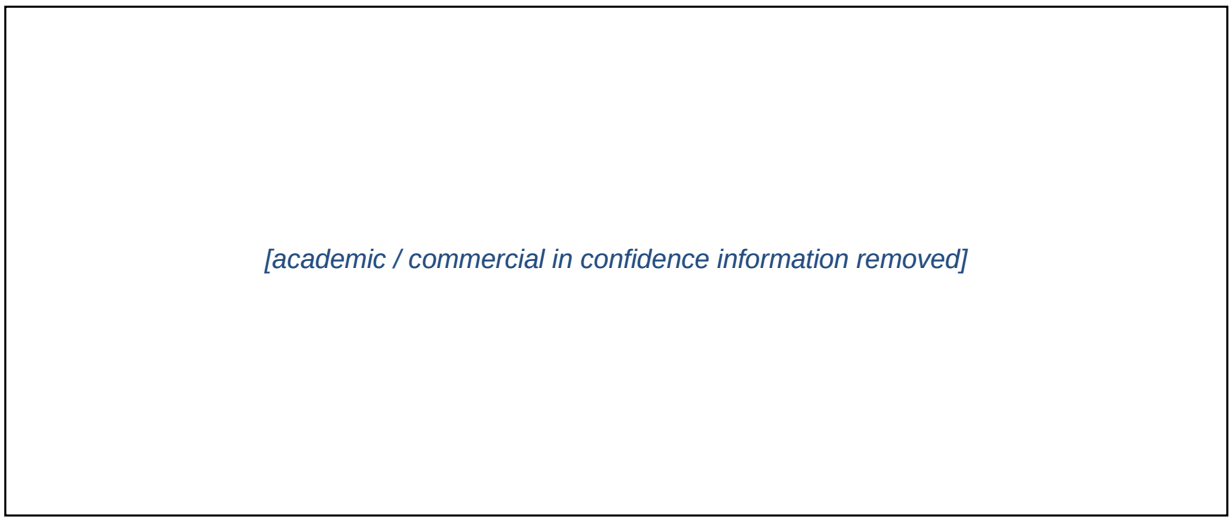
Figure 40: OS (using ITT data) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.
Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 48: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

2. **Independent models for each treatment, with common covariates for prognostic factors)**

Table 49: AIC and BIC for OS (models including common covariates for prognostic factors)

Model	AIC	BIC
Generalised gamma	870.11	916.16
Gompertz	866.95	909.16
Log-logistic	869.28	911.50
Log-normal	874.64	916.85
Weibull	868.19	910.40

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 41: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

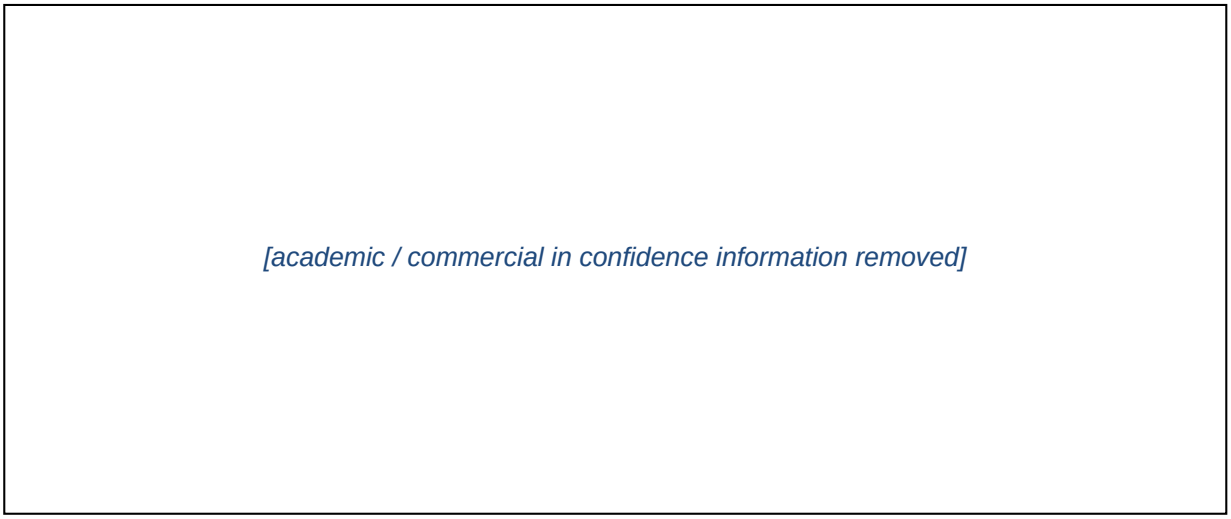
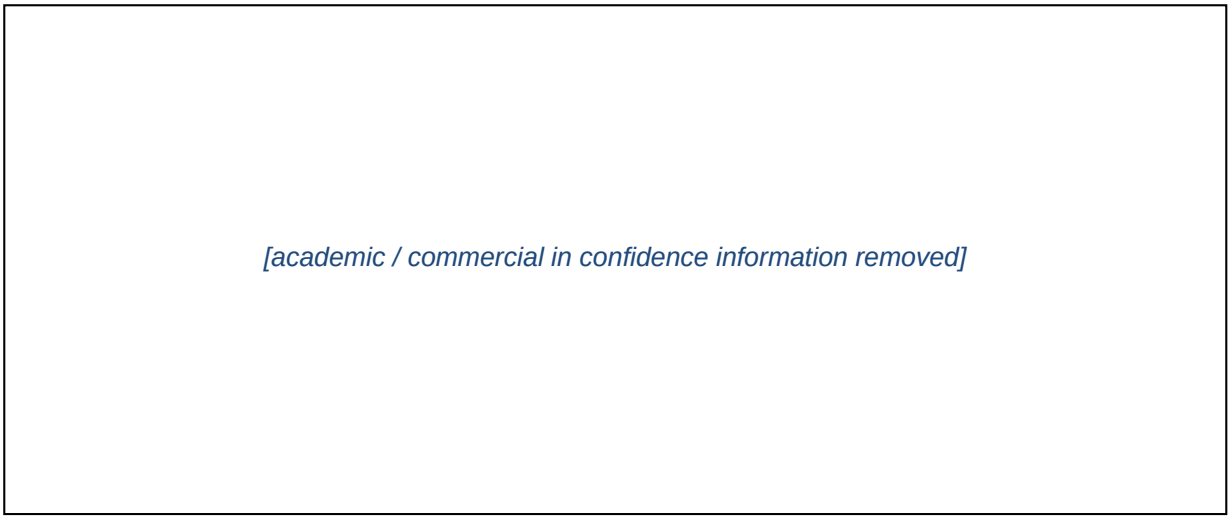


Figure 42: OS (using ITT data) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 50: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

3. Independent models for each treatment, with separate covariates for prognostic factors

Table 51: AIC and BIC for OS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	433.88	459.06	440.28	465.41
Generalised gamma	433.05	464.53	443.83	475.25
Gompertz	434.12	462.44	441.34	469.62
Log-logistic	436.79	465.12	441.44	469.72
Log-normal	440.43	468.76	444.12	472.40
Weibull	433.34	461.66	442.26	470.54

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 43: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

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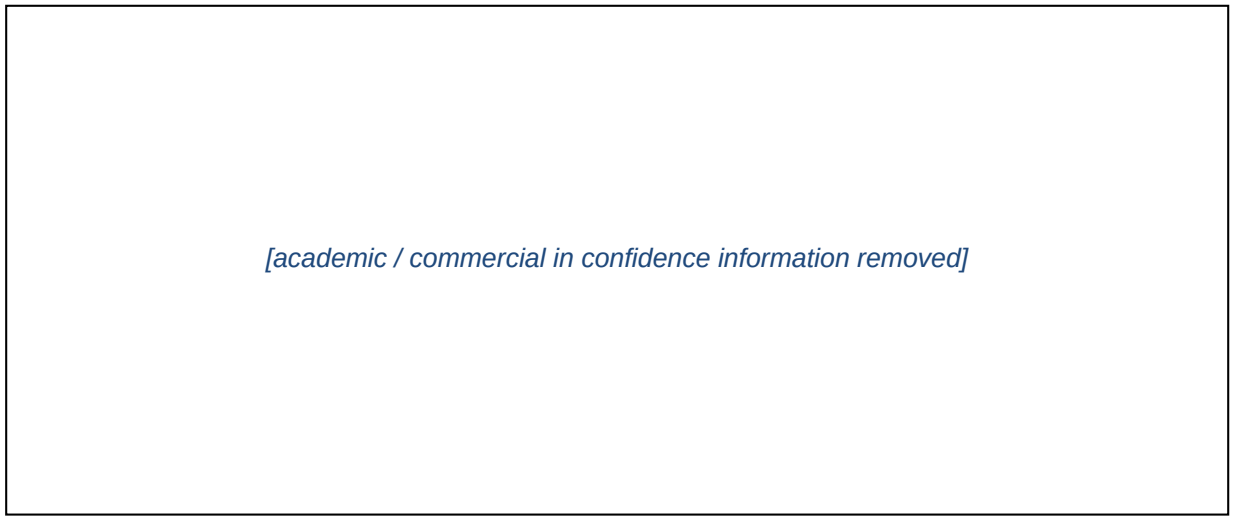
Figure 44: OS (using ITT data) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

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Table 52: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

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	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

	confidence information removed]	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*	*confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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Table 53: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*	*[academic / commercial in*

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scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

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	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

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Additional question, received from NICE on 1st March 2016: labelled 'B17' here.

B17. The CS only reports on 10 of the 20 studies include in the cost-effectiveness review. The remaining 10 studies are not even identified in the CS. We missed this at PFC's, but could we ask the company to provide a list of all 20 references included in the cost-effectiveness review?

Please see the table below for a list of the requested 10 studies and the justification for not including these in the submission. Please note that the reference lists of all systematic literature reviews were searched for relevant studies.

#	Citation	Reason for not presenting in Submission
1	Djalalov, Sandjar, et al. "Cost effectiveness of EML4-ALK fusion testing and first-line crizotinib treatment for patients with advanced ALK-positive non–small-cell lung cancer." *Journal of Clinical Oncology* 32.10 (2014): 1012-1019.	Not from a UK perspective
2	Gay-Molina, J. G., et al. "PCN73 Economic Analysis of the Use of Crizotinib, a Tyrosine Kinase ALK Inhibitor, in the Treatment of ALK Positive Non-Small Cell Lung Cancer in the Mexican Setting." *Value in Health* 15.7 (2012): A422.	Not from a UK perspective
3	Montero, Alberto J., and Gilberto Lopes. "Cost-effectiveness analysis of crizotinib in metastatic ALK plus non-small cell lung cancer (NSCLC)." J*ournal of Thoracic Oncology*. Vol. 8. 530 Walnut St, Philadelphia, pa 19106-3621 USA: Lippincott Williams & Wilkins, 2013.	Not from a UK perspective
4	Romanus, Dorothy, et al. "Cost-effectiveness of multiplexed predictive biomarker screening in non-small-cell lung cancer." *Journal of Thoracic Oncology* 10.4 (2015): 586-594.	Not from a UK perspective
5	Upadhyay, N., and N. Atreja. "Cost-Effectiveness of Eml4-Alk Gene Targeted First-Line Ceritinib Treatment Among Patients With Advanced Alk-Positive Non–Small Cell Lung Cancer." *Value in Health* 18.3 (2015): A203.	Not from a UK perspective
6	Bongers, Mathilda L., et al. "Cost Effectiveness of Treatment with New Agents in Advanced Non-Small-Cell Lung Cancer." *Pharmacoeconomics*30.1 (2012): 17-34.	Systematic Literature Review
7	Carlson, Josh J., David L. Veenstra, and Scott D. Ramsey. "Pharmacoeconomic evaluations in the treatment of non-small cell lung cancer." *Drugs* 68.8 (2008): 1105-1113.	Systematic Literature Review
8	Chouaid, Christos, et al. "Economics of treatments for non-small cell lung cancer." *Pharmacoeconomics* 27.2 (2009): 113-125.	Systematic Literature Review
9	Lange, Ansgar, et al. "A systematic review of the cost-effectiveness of targeted therapies for metastatic non-small cell lung cancer (NSCLC)."*BMC pulmonary medicine* 14.1 (2014): 1.	Systematic Literature Review
10	Zaim, Remziye, et al. "Molecular screening in advanced non-small cell lung cancer: a systematic review of cost-effectiveness	Systematic Literature Review

	analyses for first-line therapy." *Journal of Thoracic Oncology*. Vol. 8. 530 Walnut St, Philadelphia, PA 19106-3621 USA: Lippincott Williams & Wilkins, 2013.	

If wished, the Manufacturer can provide top-line data extraction for ALK-positive cost-effectiveness studies that are not from a UK perspective.

B16. **Priority Question**: Please provide the IPE parametric models of OS adjusted with the baseline covariates. Please report the full set of distribution parameters estimates (as presented in Sheet "OS_Model_Estimates" in the executable model), AIC and BIC, and plots.

Four models for the IPE were presented in the submission for crossover adjusted OS; the hazard ratios for crizotinib versus pemetrexed are presented in Table 1 below, extracted from Table 23 in the submission.

Table 1. Summary of IPE estimates of treatment effect

IPE Parametric Model	Hazard Ratio (95% CI)	1-sided p-value
Weibull	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Log-normal	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Log-Logistic	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Exponential	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

The range of IPE results are consistent with the range of hazard ratios from the other crossover adjustment models presented in the original submission. Owing to this consistency, the original base case method (Two-Stage 'A') remains the best representation of the range, in the absence of justification to use values at either extreme.

To avoid unnecessary complexity, given the consistency of the results noted above and described in the submission, parametric curves are provided for only the lower (Exponential) and upper (Log-logistic) IPE estimates.

In line with the request in clarification questions B12 and B14, models of OS using independently stratified parametric functions have been provided as part of this response, in addition to models in which the covariates are jointly stratified. However, as stated in the response to B12 and B14, the clinical rationale supports the use of joint covariate modelling for consideration in the base case.

1. Exponential IPE models

a. Models including covariates for treatment and prognostic factors

Table 2: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

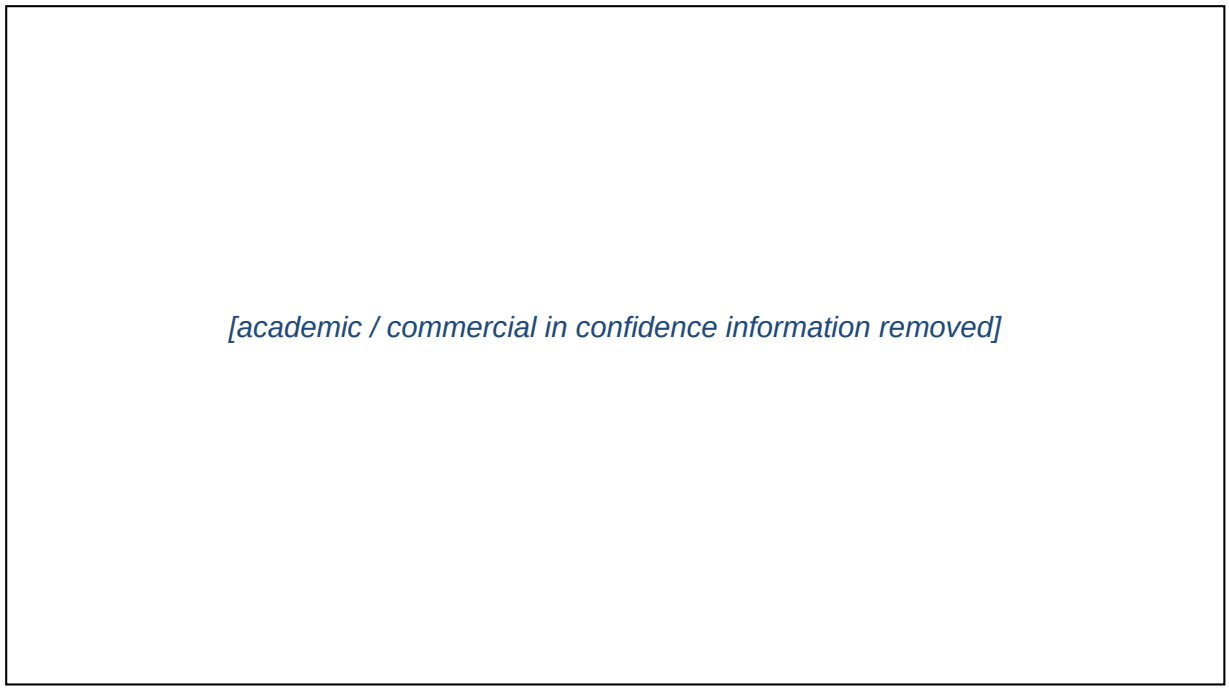
Model	AIC	BIC
Exponential	803.29	837.83
Generalised gamma	805.62	847.83
Gompertz	804.97	843.35
Log-logistic	804.88	843.25
Log-normal	810.38	848.76
Weibull	803.67	842.04

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 1: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

[academic / commercial in confidence information removed]

Figure 2: OS (using exponential IPE crossover method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.
Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 3: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*					
Sigma						
Sdlog						
shape						
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*					
scale						
meanlog						
mu						
PemCisCarb vs Crizotinib						
Non-Asian vs Asian						
>=65 vs <65 years						
Male vs Female						
Smoker vs Non- or Ex-Smoker						
ECOG 2 vs 1 or 0						
Brain metasteses: Yes vs No						
Adenocarcinoma: No vs Yes						

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

b. Independent models for each treatment, with common covariates for prognostic factors)

Table 4: AIC and BIC for OS (models including common covariates for prognostic factors)

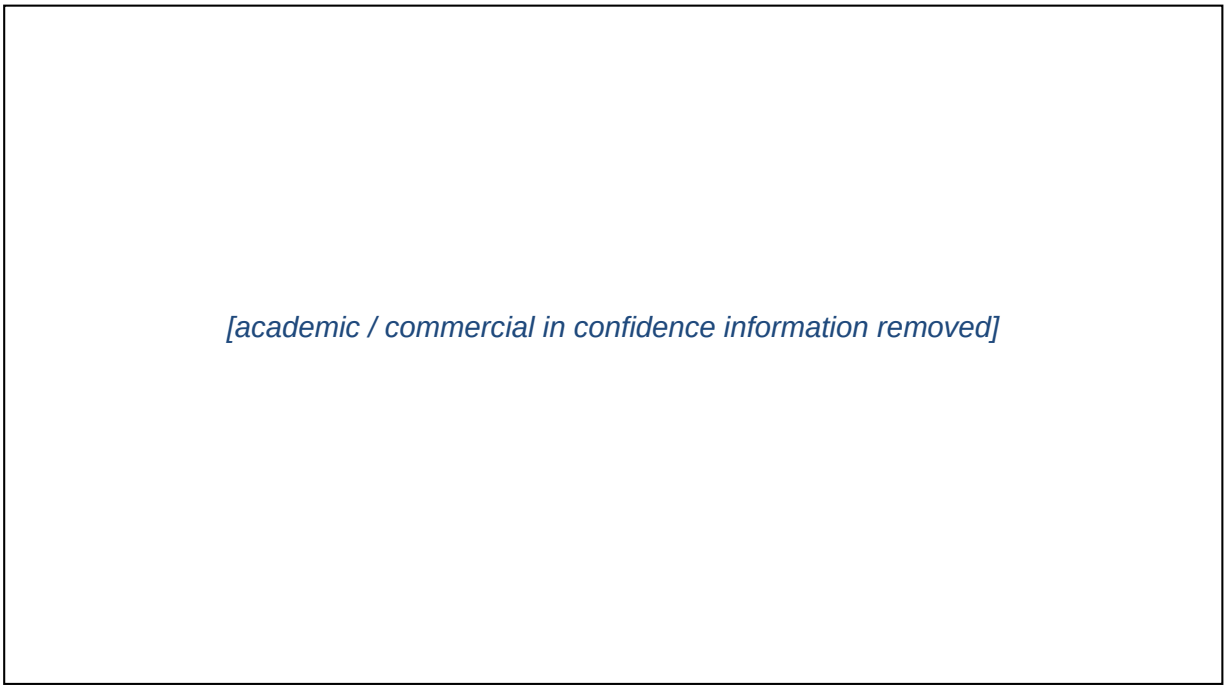
Model	AIC	BIC
Generalised gamma	807.45	853.50
Gompertz	804.45	846.67
Log-logistic	806.87	849.08
Log-normal	812.37	854.58
Weibull	805.47	847.68

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 3: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

[academic / commercial in confidence information removed]

Figure 4: OS (using exponential IPE crossover method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 5: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*

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Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

c. Independent models for each treatment, with separate covariates for prognostic factors

Table 6: AIC and BIC for OS (models including separate covariates for prognostic factors)

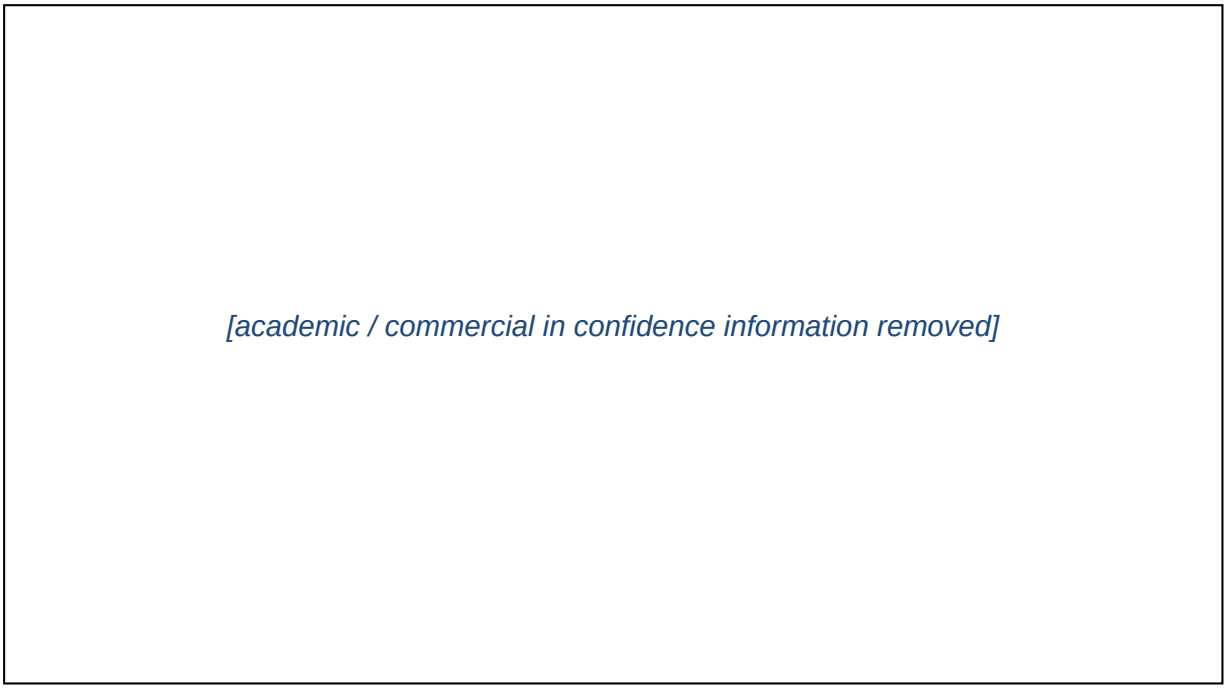
Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	418.90	444.08	393.26	418.39
Generalised gamma	418.39	449.87	396.76	428.18
Gompertz	418.25	446.58	394.65	422.93
Log-logistic	421.24	449.57	394.72	423.00
Log-normal	425.55	453.87	396.98	425.26
Weibull	418.11	446.44	395.06	423.33

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 5: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

[academic / commercial in confidence information removed]

Figure 6: OS (using exponential IPE crossover method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 7: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*

	removed]	*removed]*	*removed]*	*removed]*	*removed]*	*removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

Table 8: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

2. Log-logistic IPE models

a. Models including covariates for treatment and prognostic factors

Table 9: AIC and BIC for OS (models including covariates for treatment and prognostic factors)

Model	AIC	BIC
Exponential	690.93	725.47
Generalised gamma	693.73	735.94
Gompertz	692.67	731.05
Log-logistic	694.10	732.48
Log-normal	699.51	737.89
Weibull	691.76	730.14

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 7: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including covariates for treatment and prognostic factors)

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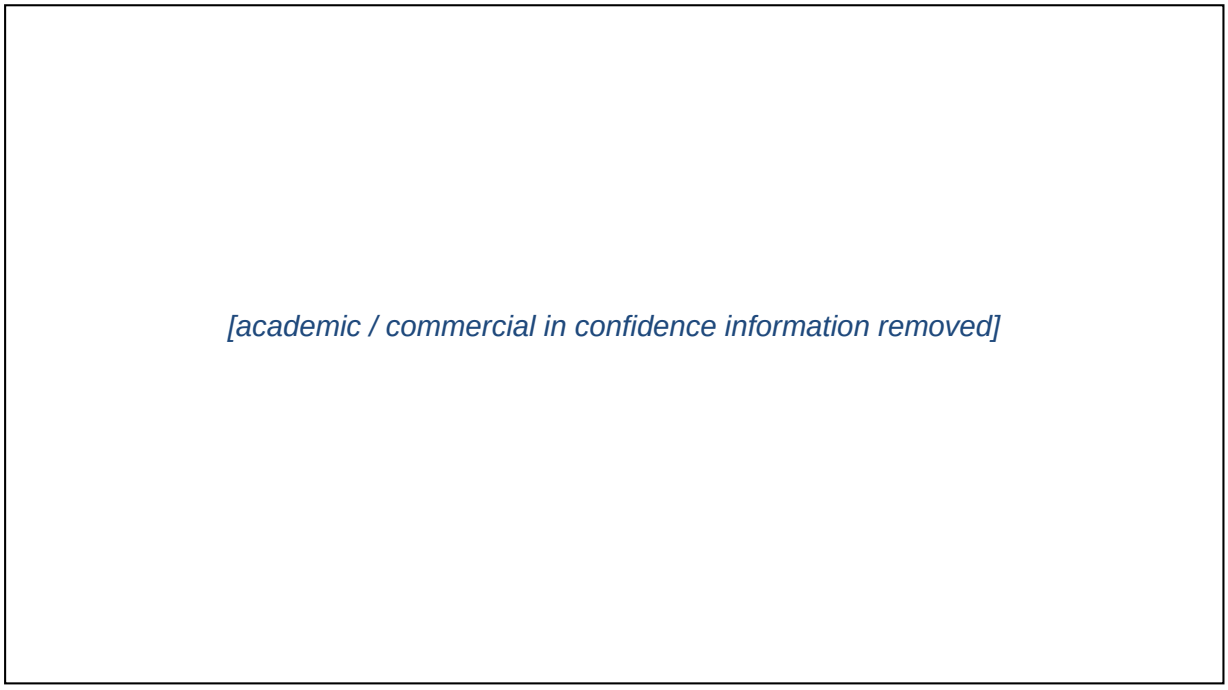
Figure 8: OS (using log-logistic IPE crossover method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including covariates for treatment and prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 10: Estimated model parameters for overall survival (models including covariates for treatment and prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*

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Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

b. Independent models for each treatment, with common covariates for prognostic factors)

Table 11: AIC and BIC for OS (models including common covariates for prognostic factors)

Model	AIC	BIC
Generalised gamma	695.47	741.52
Gompertz	691.68	733.89
Log-logistic	696.08	738.30
Log-normal	701.45	743.66
Weibull	693.55	735.76

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 9: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including common covariates for prognostic factors)

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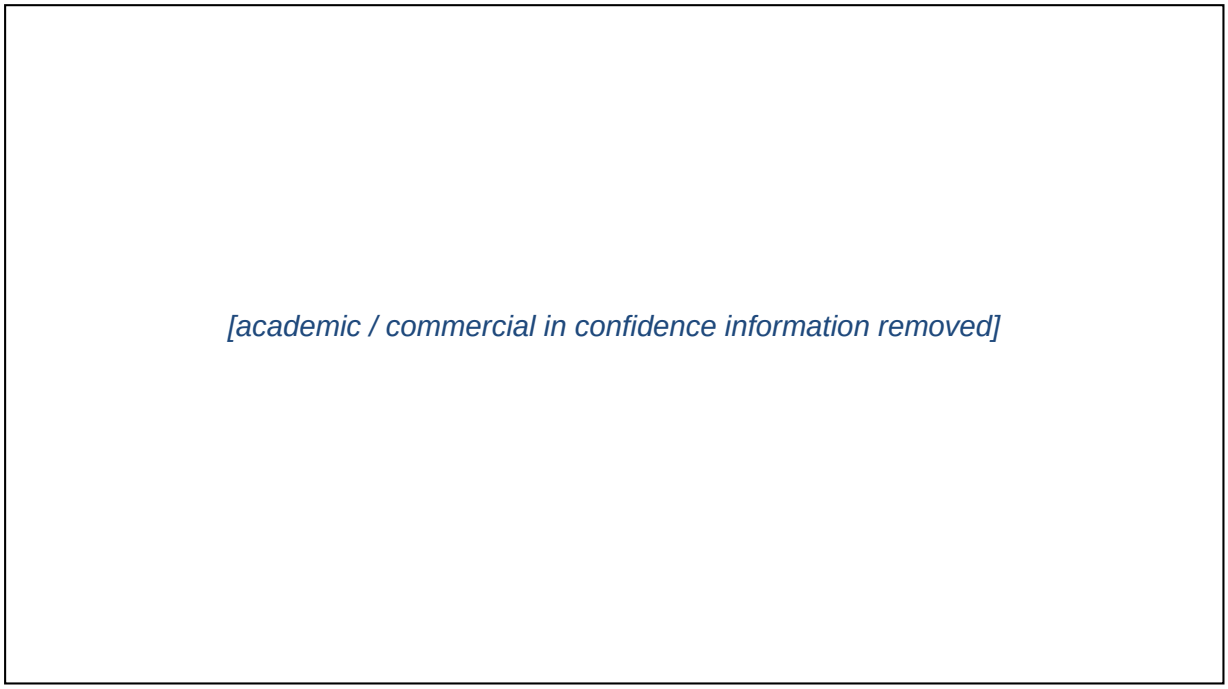
Figure 10: OS (using log-logistic IPE crossover method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including common covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 12: Estimated model parameters for overall survival (models including common covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
PemCisCarb vs Crizotinib	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*

	removed]	*removed]*	*removed]*	*removed]*	*removed]*	*removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sdlog(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
sigma(Treatment)Pem_CisCarb	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

c. Independent models for each treatment, with separate covariates for prognostic factors

Table 13: AIC and BIC for OS (models including separate covariates for prognostic factors)

Model	Crizotinib		Pemetrexed	
	AIC	BIC	AIC	BIC
Exponential	381.56	406.74	318.82	343.95
Generalised gamma	381.10	412.58	322.34	353.75
Gompertz	380.69	409.02	319.68	347.95
Log-logistic	385.06	413.39	320.66	348.94
Log-normal	390.42	418.75	321.74	350.02
Weibull	381.43	409.76	320.63	348.91

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

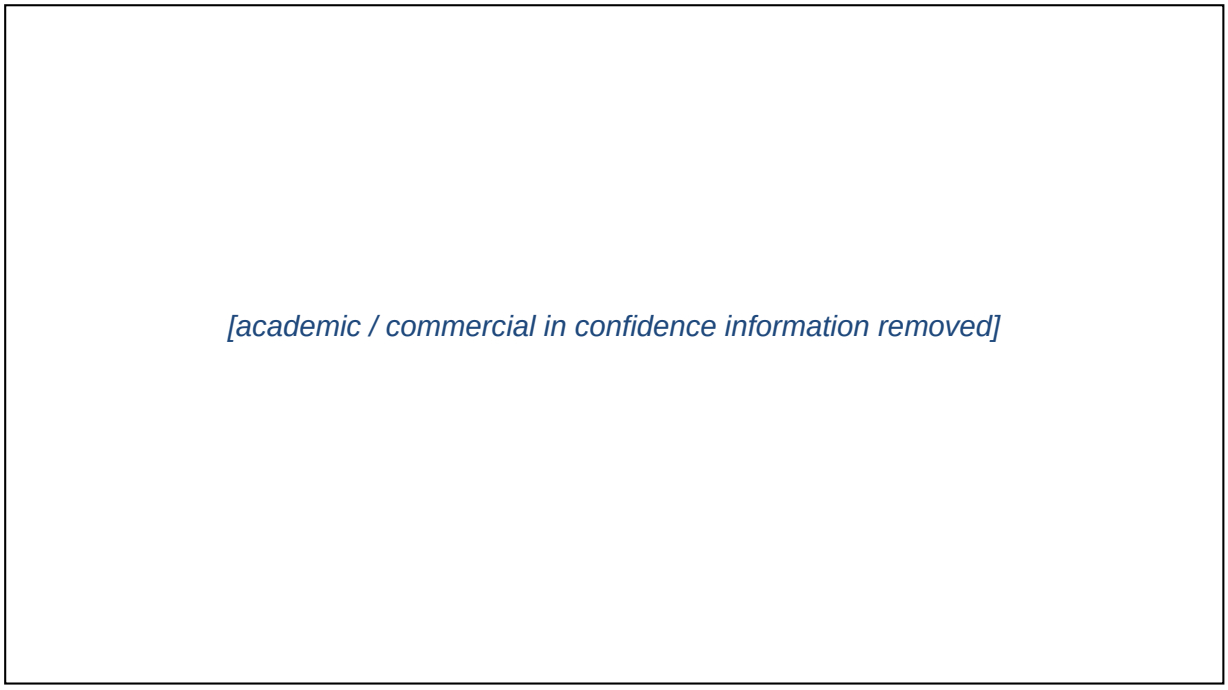
Figure 11: OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

[academic / commercial in confidence information removed]

When using the log-logistic IPE crossover adjustment method, the crizotinib generalised gamma curve fit in the model with separate covariates for prognostic factors does not provide a rationale extrapolation (the curve looks like a straight line). We believe this is likely to be caused to some degree by the smaller sample size and the small number of events caused by the subgrouping of the data into treatment arms.

The data are used to adjust for 7 covariates along with 3 parameters associated with fitting a generalised gamma model and the model may therefore not be able to reliably estimate the parameter values. A lack of convergence was also observed for this curve fit; most likely due to the immaturity of the data.

Figure 12: OS (using log-logistic IPE crossover method) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)



For both figures: 'Kaplan-Meier' plot is actually non-parametric estimates of survival predicted from covariate adjusted Cox proportional hazards models, to be able to compare covariate adjusted parametric survival estimates with covariate adjusted non-parametric survival estimates.

Abbreviation: KM: Kaplan-Meier; OS: overall survival.

Table 14: Estimated model parameters for overall survival - crizotinib (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
meanlog	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*	*[academic /*

	commercial in confidence information removed]	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*	*commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*	*[academic / commercial in confidence information*

	removed]	*removed]*	*removed]*	*removed]*	*removed]*	*removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

Table 15: Estimated model parameters for overall survival - pemetrexed plus cisplatin/carboplatin (models including separate covariates for prognostic factors)

	Exponential	Weibull	Gompertz	Log Normal	Generalised gamma	Log logistic
Fixed model parameters						
Q	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sigma	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Sdlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
shape	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Linear combination parameters						
rate	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
scale	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

meanlog	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
mu	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Non-Asian vs Asian	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
>=65 vs <65 years	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Male vs Female	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Smoker vs Non- or Ex-Smoker	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
ECOG 2 vs 1 or 0	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*
Brain metasteses: Yes vs No	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*	*[academic / commercial in confidence*

	information removed]	*information removed]*	*information removed]*	*information removed]*	*information removed]*	*information removed]*
Adenocarcinoma: No vs Yes	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*	*[academic / commercial in confidence information removed]*

Abbreviation: ECOG: Eastern Cooperative Oncology Group; n/a: not applicable; PemCisCarb: pemetrexed plus cisplatin/carboplatin; vs: versus.

Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Crizotinib for untreated, advanced, ALK positive non-small cell lung cancer [ID865]

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 and even small extensions in duration of life are of considerable significance to the individual and their family.

2. As overall outcomes for this patient population remain poor, the availability of new choices, offer 'hope' for patients

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

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

This Product

1. Oral Preparation
   Thus, reducing current first line intravenous therapy preparation and administration costs.
   Oral therapy has obvious additional benefits of importance to patients, in spending less time at hospital and in not requiring intravenous cannulation for treatment.

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

3. Improvement in survival
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available. Patients with advanced/metastatic non-squamous cell NSCLC are a group with significant unmet medical need.

4. Very targeted population.
   It is reported that ALK rearrangements are found in 3% to 5% of patients. This therapy therefore represents a targeted treatment option, providing benefit to a clearly defined small segment of non small cell lung cancer.

5. As noted above, even relatively small benefits can be disproportionately large for patients.

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

In summary

Patients with advanced and metastatic lung cancer are in a particularly devastating situation. Even with the currently recommended options, the outlook for the majority is relatively poor. It is for this reason that the availability of additional options is very important.

Crizotinib is the first therapy shown to have benefits in the first line setting, for ALK positive NSCLC patients. As such, it represents a therapy option, for a very small number of clearly defined patients.

We urge NICE, in its deliberations of this submission, to recommend the use of this therapy

[redacted]

January 2016.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

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

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

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

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

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

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

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

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

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

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

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

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

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

In real-life practice crizotinib is accepted to be a highly effective therapy for the very small cohort of patients with ALK positive advanced NSCLC. It is one of the forerunners of personalised medicine that is likely to become the dominant treatment strategy in metastatic NSCLC in years to come. As with TKI therapy for EGFR positive NSCLC, crizotinib is a highly desirable treatment compared to platinum doublet chemotherapy in terms of side effects and quality of life. I believe the vast majority of medical oncologists would like to be able to offer crizotinib as first line treatment but currently this is only within the confines of a clinical trial.

The European Society of Medical Oncology (ESMO) touch on crizotinib in their 2014 guidelines on the management of advanced NSCLC, as part of personalised medicine, but note the lack of first line comparison trial data at that stage.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

The advantages and disadvantages of the technology

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

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

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

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

- The vast majority of clinical trials in medical oncology, including targeted therapies, involve good performance status patients (PS0-1). This does not reflect the patients presenting with advanced NSCLC in real-life practice. A dilemma often faced by lung cancer physicians & MDTs is whether to pursue a tissue diagnosis in PS2-3 patients. In the era of targeted therapies there may be an argument for obtaining a tissue diagnosis to allow molecular testing in case one of the targetable mutations is identified. The evidence base does not cover this group of patients and could be an area for NICE to consider in this appraisal. Maybe there are specific scenarios that may warrant recommendations to pursue a tissue diagnosis in PS2-3 patients, eg never smokers, younger age, poor performance status due to disease rather than co-morbidities / underlying frailty. Obviously it also comes down to individual case by case consideration and informed discussions with the patients around risks (eg procedural risks, low prevalence of targetable mutations) and benefits (eg tolerable oral medication with better outcomes over chemotherapy with minimal side effects).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

- A key area for appraisal in connection with Crizotinib is quality assurance of testing centres. There are different methodologies for testing - what is the most effective and how is standardisation and quality assurance achieved? QA is vital to ensure equitable access to this drug. Some centres use immunohistochemistry as a "screening" test and FISH testing to confirm positive results. Is this the right approach? The indications for EGFR testing are the same as for ALK testing yet the mutations do not occur together. Should testing for EGFR and ALK occur in parallel or in sequence? What is most cost effective approach yet does not cause undue delay in the patient pathway? Furthermore, what are the correct indications for ALK testing? All non-squamous NSCLC? Squamous NSCLC but light or no smoking history as well?

- It is worth considering what are the requirements for adequate and reliable testing for ALK, eg proportion of viable tumour cells - >10%. In other words how the local trust should process and examine tissue samples to ensure a very high proportion of samples sent for ALK testing result in successful tests. Data from the Stratified Medicine / Matrix Trial has already confirmed there is variability in the proportion of successful tests across the UK - how can this be tackled? An expert pathologist (eg Keith Kerr -Aberdeen or John Gosney - Liverpool) should surely be part of the appraisal team and perhaps additional representation from the stratified medicine / matrix trial eg Sanjay Popat - medical oncologist & Chief Investigator.

- Crizotinib is effective against other mutations in advanced NSCLC - particularly ROS-1, should this also be included in this appraisal?

Any additional sources of evidence

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Implementation issues

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

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

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

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

Equality

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

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

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer

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

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

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

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

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

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- **SPECIALIST ADVISOR TO RCPATH FOR LUNG PATHOLOGY, I REPRESENT PATHOLOGISTS WHO WOULD DEAL WITH THE BIOPSIES FOR DIAGNOSING LUNG CANCER AND HELP WRITE NATIONAL GUIDELINES FOR DATASETS AND HANDLING OF TISSUE**

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer

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

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

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

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

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

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

The advantages and disadvantages of the technology

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer

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

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

Any additional sources of evidence

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

Implementation issues

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

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

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

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer

The main issue for pathologists in relation to treatment with this kind of drug is the possible/probable need for an associated diagnostic test that may decide whether the patient is eligible for treatment.

From what I understand of reported evidence to date, data suggest that those with greater immunostaining of the tumour for PD-L1 have a better response to this type of drug, though it is currently being called a complementary diagnostic (28-8pharmX) and not a companion diagnostic, as it is not deemed essential in terms of eligibility.

If it is not deemed a requirement, then there is little issue for pathologists. If it is deemed a requirement, then pathologists will have to be trained in interpretation and systems for validaton will need to be put in place, as well as the cost of the test (and possible rebiopsy) taken into account

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

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

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

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

Please do not exceed the 8-page limit.

About you

Your name:

Dr Martin Forster

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **NO**
- other? (please specify)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Lung cancer is the most common cancer globally and the highest cause of cancer related death. Over 80% of lung cancers are 'Non-Small-Cell Lung Cancers' (NSCLC), with approximately 3-4% of NSCLC harbouring an EML4-ALK translocation, the vast majority being lung adenocarcinoma. Testing for EGFR mutation status has become well established in lung adenocarcinomas (first line EGFR TKI therapy licensed and available as 1st line therapy) but there remains variability in ALK testing across the UK; in time of testing (at diagnosis or following progression on chemotherapy) and the type of testing performed (IHC or FISH).

Currently patients with advanced ALK-driven NSCLC who are fit enough for chemotherapy will receive platinum based combination chemotherapy as a first line of systemic treatment. A cisplatin/carboplatin combination is a well-established NICE-approved treatment with little regional variability. As ALK-driven NSCLC is usually adenocarcinoma, this combination will generally be cisplatin/carboplatin and pemetrexed (little geographical variation), for between 4-6 cycles depending on response and tolerability. Up to 25% of patients are refractory to this treatment (actually progress on treatment) but the majority gain some degree of disease stabilisation or response. However, disease control is of short duration and combination chemotherapy is associated with significant toxicity with some patients being unable to complete their planned treatment. For patients with ALK-driven disease, crizotinib offers an improvement in likelihood of response / clinical benefit, duration of response and better tolerability than combination platinum-based chemotherapy. Also, as crizotinib is an oral therapy there is less impact on day care units, with cisplatin combination treatments in particular required a long day stay. As mentioned above the vast majority of ALK driven NSCLC are adenocarcinoma and the data on squamous cell cancers are more limited, however, there are no data to my knowledge suggesting that squamous cell lung cancers with ALK translocations have less benefit from crizotinib than adenocarcinoma.

A small proportion of patients, who both remain fit after completing 4 cycles of combination cisplatin-pemetrexed chemotherapy and whose disease is controlled, may go on to receive maintenance pemetrexed until disease progression or intolerance. This is currently only available in England via the CDF and therefore there will be variable use. This access may not be sustained depending on CDF / NICE review.

For patients who are less fit (PS 2) there is variability of clinical practice, with some patients receiving combination chemotherapy (possibly with dose modification), some single agent chemotherapy and others supportive care only, depending on patient and clinician factors.

All patients will subsequently develop progressing disease. Patient fitness will influence whether they receive further therapy at this point, with many patients (>50% NSCLC) not receiving any further systemic anti-cancer therapy. Currently, those with an ALK translocation may proceed to receive crizotinib (via CDF in England) if well

enough for any therapy. Access will be variable due to CDF access only. The majority of patients will gain clinical benefit and treatment continues until progression and occasionally beyond progression. Treatment beyond progression is most relevant when there is small volume disease progression radiologically, with continuing clinical benefit, especially if progression is in limited sites where localised therapy may also be possible. As crizotinib is better tolerated than chemotherapy patients with ALK-driven disease are more likely to receive crizotinib, even if they would be of borderline fitness for chemotherapy.

Although crizotinib is an oral therapy it currently requires to be prescribed by an onocologist within a secondary / tertiary care institution. This allows appropriate governance and will remain to be the case as first line therapy.

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

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

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

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

When crizotinib is approved and available it **will replace** first line combination chemotherapy for patients with ALK-driven disease. There is strong support for this from thoracic oncologists. The clinical trial data are representative of UK patients, both in efficacy and tolerability of crizotinib, although it is noted that more patients received cisplatin based treatment within the clinical trial than would be usual practice in UK. There will need to be more consistent ALK testing to ensure implementation, with ALK testing performed at diagnosis in all NSCLC patients fit for treatment. This should be manageable but will require MDT endorsement in some centres.

As outlined above, as an oral therapy crizotinib will be easier to deliver than combination chemotherapy, although will still require clinical review and prescribing within a cancer unit. Patients will no doubt tolerate this better than chemotherapy. There may be the potential for nurse-led management in some centres.

It is likely that some patients will continue on crizotinib beyond radiological progression. As outlined above, this is most likely to be relevant in patients who have maintained clinical benefit despite small volume progression, and may involve localised therapy to progressing areas, particularly if these are intra-cerebral metastases.

Platinum combination chemotherapy (platinum-pemetrexed for most patients) will be deferred to second line treatment following clinical progression on crizotinib (until next generation ALK inhibitors have been appraised and approved for use).

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

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

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

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

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

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

The inclusion of all patients with ALK-driven NSCLC for potential crizotinib therapy should not lead to any discrimination. Currently the lack of access to crizotinib in England as a standard of care makes England a bad outlier in comparison to other countries globally.

Any additional sources of evidence

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

Nothing that I am aware of.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

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

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

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

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

Some revision of the lung cancer patient pathway will be needed, in particular the histopathological assessment. However, the use of an ALK immunohistochemistry assay should be relatively easily accommodated. FISH testing is more expensive and adds a time delay.

Staff may need some education but crizotinib has been available through the CDF for some time now and most cancer units will have experience of its use.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Please sign and return via NICE Docs/Appraisals.

I confirm that:

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

Name: Professor Andrew Nicholson

Signed: ..... 

Date: .....21/4/16.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

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

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

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

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

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

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

1. About you

Your name: Carol Davies
Name of your nominating organisation: NLCFN
Do you know if your nominating organisation has submitted a statement?

☐✓
Yes ☐ No

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

☐✓
Yes ☐ No

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

Are you:

- a patient with the condition?

☐ Yes ☐✓ No

- a carer of a patient with the condition?

☐ Yes ☐✓ No

- a patient organisation employee or volunteer?

☐✓Yes ☐ No

Do you have experience of the treatment being appraised?

☐✓
Yes ☐ No

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

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

2. Living with the condition

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

3. Current practice in treating the condition

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

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

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

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

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

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

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

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

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

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

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

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

6. Patient population

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

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

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

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

☐ Yes ☐ No

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

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

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

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

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

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

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

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

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

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

10. Key messages

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

-
-
-
-
-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Please sign and return via NICE Docs/Appraisals.

I confirm that:

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

Name: Dr Jesme Fox

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

Date: ..... 05/05/16 .....

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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Date completed 5 April 2016

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Declared competing interests of the authors

None.

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We would like to thank Dr Katy Clarke (Consultant in non-surgical oncology, Leeds Teaching Hospital), Dr Neal Navani (Consultant in respiratory medicine, University College London Hospital) and Dr Phillipe Taniere (Consultant Histopathologist, University Hospitals Birmingham NHS Foundation Trust) for their clinical advice throughout the project.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Robert Hodgson and Mousumi Biswas wrote the cost effectiveness sections of the report and conducted the economic analyses. Philip Morgan, Teumzghi Mebrahtu and Nerys Woolacott wrote the clinical effectiveness sections of the report. Melissa Harden wrote the sections on the search strategies. Nerys Woolacott and Rob Hodgson commented on drafts of the report and took overall responsibility for the clinical and cost-effectiveness effectiveness sections of the report respectively.

Note on the text

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

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List of abbreviations

AEs: Adverse Events

AIC: Akaike Information Criterion

ALK-positive: Anaplastic Lymphoma Kinase-positive

AUC: Area Under the Curve

BIC: Bayesian Information Criterion

BSA: Body Surface Area

BSC: Best Supportive Care

CDF : Cancer Drug Fund

CHMP: Committee for Human Medicinal ProductsCRD : Centre for Research and Dissemination

CS: Company's Submission

CSR: Clinical Study Report

CTCAE: Common Terminology Criteria for Adverse Events

DCR: Disease control rate

DR: Duration of Response

ECOG: Eastern Cooperative Oncology Group

EGFR: Epidermal Growth Factor Receptor

ELCC: European Lung Cancer Conference

EMA: European Medicines Agency

EML4-ALK: Echinoderm Microtubule associated protein-Like 4

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: EuroQol-5 Dimensions

ERG: Evidence Review Group

ESMO: European Society for Medical Oncology

FISH: Fluorescence in situ Hybridisation

FDA: Food and Drug Administration

HR: Hazard Ratio

HRQoL: Health-related Quality of Life

ICER: Incremental Cost Effectiveness Ratio

IHC: immunohistochemistry

IPCW: Inverse Probability of Censoring Weights

IPE: Iterative Parameter Estimation

IRR: Independent Radiologic Review

ITT: Intention to Treat

FISH: Fluorescence in Situ Hybridisation

LYG: Life Years Gained

MIMS: Monthly Index of Medical Specialities

NGS: Next Generation Sequencing

NHS: National Health Service

NICE: National Institute for Clinical Excellence

Non-RCT: Non-Randomised Controlled Trial

NSCLC: Non-Small-Cell Lung Cancer

ORR: Objective Response rate

OS: Overall Survival

PAS: Patient Access Scheme

PD: Progressed Disease

PF: Progression Free

PFS: Progression Free Survival

PRO: Patient Reported Outcome

PSA: Probabilistic Sensitivity Analysis

PSS: Personal Social Services

PSSRU: Personal Social Services Research Unit

QALYs: Quality Adjusted Life Years

QoL: Quality of Life

RCT: Randomised Controlled Trial

RTK: Receptor tyrosine kinase

RECIST: Response Evaluation Criteria in Solid Tumours

RPSFTM: Rank Preserving Structural Failure Time Model

SCLC: Small Cell Lung Cancer

SLR: Systematic Literature Review

SMC: Scottish Medicines Consortium

SmPC: Summary of Product Characteristics

STA: Single Technology Appraisal

TAs: Technical Appraisals

TSA: Two-stage Crossover Adjustment

TTD: Time to deterioration

TTP: Time to progression

TTR: Time to Response

VAS: Visual Analogue Scale

1 Summary

Crizotinib is a first-in-class, inhibitor of anaplastic lymphoma kinase (ALK) and is indicated for adults with ALK-positive advanced non-small-cell lung cancer (NSCLC).

Based on tumour histology, there are two types of lung cancers: NSCLC and small cell lung cancer (SCLC). NSCLC can be further grouped into: adenocarcinoma (approximately 40%), squamous cell carcinomas (25-30%), large cell carcinoma (10-15%) and other subtypes (e.g. adenosquamous carcinoma and sarcomatoid carcinoma). About 4% and 10% of adenocarcinoma patients are believed to have ALK gene rearrangement (ALK-positive NSCLC) and EGFR gene mutations, respectively. ALK-positive NSCLC is characterised by alterations (translocations) of ALK gene and is more commonly related with adenocarcinomas although it can occur in any of the NSCLC: estimates are 3.4% of non-squamous and 0.08% of squamous tumours, though these are uncertain and could be higher.

Prognosis for patients with advanced NSCLC is poor and although only limited information is available regarding the prognosis of ALK-positive patients specifically, estimated life expectancy is around 15 months.

1.1 Critique of the decision problem in the manufacturer's submission

The population in the NICE scope is patients with untreated, advanced ALK-positive NSCLC that included both squamous and non-squamous patients. The company's decision problem restricts this to non-squamous disease. This is acceptable as the vast majority (98.7%) of ALK-positive patients are expected to be of non-squamous tumour histology. This reflects the population of the main randomised controlled trial presented as evidence. The cost-effectiveness of crizotinib in squamous patients is considered in a scenario analysis.

The NICE scope also included the population with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate. This subgroup is not considered in the CS because expert clinical advice to the company highlighted that this sub-group accounts for less than 2% of the ALK-positive patient population. Furthermore, there is a lack of evidence for standard therapy and it is not possible to conduct an evaluation of the cost-effectiveness of crizotinib in this sub-group.

The CS statement of the decision problem adheres to the intervention specified in the NICE scope: crizotinib 200 and 250 mg capsules and is administered orally, 250mg twice daily taken continuously until disease progression or unacceptable toxicity.

The NICE's final scope identified three types of comparator based on tumour histology:

a) For non-squamous patients, pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin);
b) For people with squamous tumour histology, a third-generation drug (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin); and,
c) For people with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate, single-agent chemotherapy with a third generation drug (for example, gemcitabine or vinorelbine).

As only the first patient population is considered fully in the CS, only pemetrexed plus platinum-based therapy is included as a comparator. This is in line with the NICE scope. The CS states that cisplatin and carboplatin have the same PFS outcomes so can be considered to be equal; they are treated as a single comparator. However, based on clinical expert's advice, the ERG notes that although the two drugs have similar PFS, they differ significantly in terms of their toxicity level.

Clinical advisors to the ERG advised that 30% of patients receive cisplatin and 70% patients receive carboplatin. This can be compared with the proportion patients who received cisplatin and carboplatin in the PROFILE 1014 trial: 53% and 47% respectively, which therefore may not represent the clinical practice in the UK.

In line with the NICE scope, pemetrexed maintenance therapy is not considered as a comparator as NICE guidance was that it was not recommended. However, the ERG notes that, based on its clinical advisor's opinion, pemetrexed maintenance therapy for patients who received first line pemetrexed plus cisplatin was used when available through the Cancer Drugs Fund and would be used again if available.

The CS statement of the decision problem adheres to the outcome measures specified in the NICE scope: progression free survival, objective response rate, overall survival, adverse events and health-related quality of life outcomes.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission presented data from three clinical studies: one open label randomised controlled trial of crizotinib with pemetrexed plus a platinum based agent (cisplatin or carboplatin) in patients with advanced non-sqauamous ALK-positive NSCLC (PROFILE 1014); a single-arm trial of crizotinib in patients with both previously treated, and untreated ALK-positive stage III or IV NSCLC (PROFILE 1001); and a retrospective cohort study of patients with confirmed ALK-positive NSCLC, which involved reviewing medical charts of patients receiving crizotinib in a first-line and second-line setting in clinical practice in the US and Canada (Davis et al. 2005).

1.2.1 Progression-free survival

Results from the RCT PROFILE 1014 show that patients in the crizotinib arm had an increase in median PFS of 3.9 months compared to the pemetrexed combination chemotherapy group and a significantly reduced risk of progression or death, with a hazard ratio of 0.45 (95% CI, 0.35 to 0.60; P<0.001). There was no evidence of different effects by sub group.

1.2.2 Tumour response

Based on RCT PROFILE 1014 , the objective response rate (ORR) (complete or partial response) was 74% (95% CI 67%–81%) with crizotinib compared with 45% (95% CI 37%–53%) with chemotherapy (P<0.0001). Crizotinib also had a shorter time to response and a longer duration of response.

1.2.3 Overall survival

In the RCT PROFILE 1014 trial, the median duration of follow-up was 17.4 months (range [redacted] to [redacted]) in the crizotinib arm and 16.7 months (range [redacted] to [redacted]) in the chemotherapy arm. Median OS was not reached. Post- disease progression patients randomised to crizotinib continued with crizotinib until symptomatic benefit was lost, whilst in the pemetrexed combination chemotherapy arm 70% of patients crossed over to crizotinib treatment. The unadjusted hazard ratio for death with crizotinib was 0.821 (0.536 to 1.255). A number of methods of adjustment for crossover from chemotherapy to crizotinib were implemented and the crossover adjusted hazard ratios ranged from 0.571 to 0.674, across nine parametric models using three methods of analyses; not all were statistically significant.

1.2.4 Patient reported outcomes

Crizotinib had statistically significant benefits in terms of HRQoL measures including EORTC QLQ-C30 and the EORTC QLQ LC-13 (which is a lung cancer-specific module), and EQ-5D, which is the measure preferred by NICE.

1.2.5 Adverse effects

The adverse event profile of crizotinib presents a clinically significant, but as determined by the CHMP a manageable, burden to patients. The most frequently reported adverse events experienced on crizotinib are vision disorders (62%), nausea (57%), and diarrhoea (54%).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Whilst PROFILE 1014 was appropriately randomised and well-conducted it subject to some flaws: the open label design puts it at a high risk of bias for the primary outcome PFS, and the open label design combined with permitted treatment decisions post disease progression, put the trial at high risk of bias for overall survival.

1.3.1 Progression-free survival

PFS was the primary outcome of the trial assessed as the time from randomisation to RECIST-defined progression, as assessed by independent radiologic review (IRR) or death. This objective measure of disease progression can mitigate against the risk of bias due to the open-label nature of the trial. However, in clinical practice RECIST criteria which assess tumour size are not used to determine disease progression, instead it is determined by the worsening of symptoms, which means the results seen in the trial may not be reflected in clinical practice. Furthermore, whilst patients in the chemotherapy arm of the trial may have initiated second-line therapy earlier in PROFILE 1014 than they would likely have done in clinical practice, this was not the case in the crizotinib arm, where patients continued on crizotinib whilst there was still some symptomatic treatment benefit. This potential for imbalance would have been exacerbated by the open label nature of the trial.

Follow-up was not complete for PFS: at the time of the data cut-off cancer had progressed in 51.7% of crizotinib patients and in 77.2% of chemotherapy patients and [redacted] of patients randomised to crizotinib were continuing in the trial at the data cut off. In addition, in the analysis of PFS an assumption of proportional hazards was used: with the availability of individual patient data this was unnecessary.

1.3.2 Tumour response

The results for tumour response, being based on IRR and not subject to the problems associated with limited follow-up or post-progression treatment and are likely to be reliable.

1.3.3 Overall survival

The results for OS are highly uncertain due to the following factors:

- The immaturity of the data due to a too short follow-up period and lower than expected mortality rate.
- The high levels of cross-over from chemotherapy to crizotinib at REIST-defined disease progression
- The use of an assumption of proportional hazards in the analysis
- The imbalance of post-progression follow-up therapy.

There is also a potential issue with the very low mortality rate in the chemotherapy arm. At the time of the data cut off (pre-specified point for primary outcome, 30th November 2013) deaths had occurred in only 26% of those who underwent randomisation.

Of the 171 patients randomly assigned to chemotherapy, 120 patients (70%) subsequently received crizotinib. This high level of cross-over is likely to have had an impact on the results in an under-estimation of the effect of crizotinib. The adjusted analyses all produced lower hazard ratios than the

unadjusted analysis but all still generated wide confidence intervals and only some produce statistically significant results. Analysing such data adjusting for cross-over is now accepted best practice. However there is uncertainty about which if any of the available methods are most appropriate. Although the results from all of the cross-over adjustment methods are fairly consistent, with the mean hazard ratios calculated from the nine methods ranging from 0.571 to 0.674; falling substantially below the unadjusted value of 0.821 the confidence intervals around each of the cross-over adjusted hazard ratios are wide, with five of the nine methods producing upper confidence interval values of greater than or equal to one. Thus the results are uncertain.

The CS assumes proportional hazards for the survival data, which may not hold. The log-cumulative hazard plots show the curves diverging for OS, highlighting that the assumption of common treatment effect may be unjustified. Little clinical evidence has been presented in the CS to justify the assumption of proportional hazards, with the expert opinion presented lacking a clear clinical rationale. As well as this, the survival data presented is immature and is not near to completion, meaning survival estimates produced using proportional hazard modelling may be unreliable. Additionally, there appears to be little necessity in making use of proportional hazard modelling as patient level data are available, and only one comparator is included in the analysis, allowing for separate parametric models to be fitted which require fewer assumptions. The ERG therefore believes that fitting separate parametric models for each of the treatment arms is likely to produce more reliable estimates of OS, as well as PFS.

The present appraisal requires an evaluation of the effect of first-line therapies and therefore it is important that the outcomes generated from the trial reflect the impact of these first-line therapies only, and not follow-up treatments. However, there are imbalances in the two arms of the trial in the numbers who went onto receive follow-up therapy, and also in the therapies that patients went on to receive. Furthermore, the open label nature of the trial and the facility in the trial protocol to allow those randomised to crizotinib to remain on crizotinib after RECIST-defined disease progression has exacerbated the issue around follow-on therapies. This continuation of crizotinib until there was no symptomatic benefit, which occurred in a high proportion of patients, is not considered to be second-line therapy. In contrast, patients randomised to chemotherapy could cross-over to crizotinib at this point, and the majority did so. Thus the trial design facilitated a delay in the start of second-line therapy in the crizotinib arm compared to that in the chemotherapy arm.

Doubts regarding the generalisability of the trial results for overall survival are also raised by the low mortality rate seen in the chemotherapy arm of PROFILE 1014, which reported one year and 18 month survival estimates of 79% and [redacted] respectively. These compare with estimates of 50% and 35% for pemetrexed + cisplatin {Scagliotti, 2008 #74} and 40% and 20% for pemetrexed + carboplatin{Grønberg, 2009 #257}, albeit for broader non-squamous advanced NSCLC. This raises

the question of whether the trial results are, for unknown reasons, not generalisable to the real ALK-population, or if ALK-positive patients have a better prognosis than the broader non-squamous population.

1.3.4 Generalisability of results

There is some uncertainty about the generalisability of the trials results to the UK population. Comparison with a 'real life' cohort from US and Canada suggests the trial patients are younger and have better performance status and fewer were smokers than real-life patients. A small UK cohort was also older than the trial population. However, ALK-positive patients are believed to be younger than the broader advanced NSCLC population. Consequently, the evidence is not compelling one way or the other.

The non-RCT evidence included in the CS supports the RCT results.

1.4 Summary of cost effectiveness submitted evidence by the company

The *de novo* analysis presented by the company compared the cost-effectiveness of first-line crizotinib with first-line pemetrexed in combination with either cisplatin or carboplatin in advanced or metastatic NSCLC patient. The model used a three health state model (progression free, progression and death) referred to as a semi-Markov "area under the curve" analysis. The proportion of patients in the different health states at each cycle was calculated from parametric survival curves fitted to empirical data and OS from PROFILE 1014. A single parametric function was fitted to the Kaplan-Meier data on PFS with a covariate for treatment effect. OS was estimated by applying the crossover adjusted hazard ratio (Two stage model) to the parametric OS function calculated for crizotinib.

Quality of life data were derived from number of sources. For progression free health states data were sourced EQ-5D data collected during the PROFILE 1014 trial and converted to QALYs. Utility while on second line therapy was derived from EQ-5D data collected during the Profile 1007 trial. Utility while on third line therapy was derived from a published QoL Costs were assessed from an NHS and personal and social services perspective and incorporated acquisition, administration and monitoring costs of the alternative regimens, ALK testing, adverse events and other supportive care and terminal care costs associated with the management of progressed disease.

The company presented both deterministic and probabilistic analysis. The deterministic incremental cost-effectiveness ratio (ICER) in the base-case analysis was [redacted] per QALY and [redacted] per QALY in the probabilistic analysis. The company also presented a series of one-way sensitivity analyses and scenario analyses to assess the impact of uncertainty around key input variables and assumptions on the ICER estimates. The results of these indicated that the base-case ICER estimates

were most sensitive to: (i) the curve fit and scale parameters for OS; (ii) time horizon; (iii) NSCLC population- Squamous rather than non-squamous ; and (iv) the method of adjustment for crossover.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic model submitted by the company is considered by the ERG to meet the NICE reference case and is broadly in-line with the decision problem specified in the scope. Furthermore, the general approach taken by the company is considered to be reasonable. However, the electronic model submitted by the company was subject to a considerable number of critical calculation errors and as such the results presented in the CS should not be relied upon. The most important of the errors related to the duration of treatment beyond progression. As a consequence of these errors, the company model considerably underestimates the duration of treatment beyond progression and as such substantially underestimates total drug acquisition costs for crizotinib. The CS therefore underestimates the ICER considerably. Due to the design of the PROFILE 1014 trial the ERG was not able to fully correct for this error, but was able to implement a partial correction which removed second-line treatment from the economic model. The ERG consider their corrected model to be a reasonable approximation of the ICER for crizotinib given the input assumptions made by the company because similar second-line treatment strategies will be adopted regardless of first-line treatment given. The ERG, however, acknowledge this is not ideal. In additional to these internal validity issues the ERG also identified a number of uncertainties around assumptions made in the company model. The most significant of these concerns are outlined in brief below:

1. *Reliability of OS data and assumption of proportional hazards*

   As outline above, the clinical evidence supporting the estimated OS benefits is subject to a number of uncertainties these relate to the immaturity of the OS data; the extensive cross-over that occurred; and imbalances in the second-line treatments received once cross-over had been accounted for. The ICER generated by the economic model is particularly sensitivity to the OS estimates and the majority of the QALY benefits in the economic model are due to the extension to life expectancy estimated to occur on crizotinib. These uncertainties therefore suggest considerable uncertainty with regards to the estimated ICER. Furthermore, this uncertainty cannot be parameterised and included in any probabilistic analysis.

   Further to the above, in both the analysis of PFS and OS proportional hazards assumption is made and therefore a single parametric survival function is fitted to the data with a covariate for the treatment effect. This assumption is justified by inspecting the log-cumulative hazard plots for both PFS and OS. The ERG, however, consider there to be a number of reasons why the assumption required for proportional hazard modelling do not hold. Most significant of

these is the different duration over which treatment is received suggesting fundamental differences in the mode of action.

2. *Differential HRQoL for pre-progressed patients*
   The company model assumes differential utility rates for pre-progressed patients receiving crizotinb first-line compared with patients receiving pemetrexed combination therapy first-line. This is based on utility values observed in the PROFILE 1014 study. The ERG, however considers that PROFILE 1014 may underestimate the HRQoL of pemetrexed patients as data was only collected while they patients were on treatment. Unlike crizotinib chemotherapy is a fixed cycle regime, therefore for a period prior to progression chemotherapy patients receive no treatment. During this period patients are will experience no side effects and will enjoy relative symptom control and therefore potentially higher HRQoL. The data on HRQoL in the PROFILE 1014 study will therefore not capture this higher HRQoL experienced by patients as data was not collected post discontinuation of treatment.

3. *Costs of ALK testing*
   Costs f ALK testing were sourced from data on file for IHC testing and from the All Wales Genetics Laboratory pricing list for FISH testing in the company model. It was uncertain whether the costs used include laboratory and overhead costs. Further, the ERG identified alternative source of testing costs that were substantially higher than those identified by the company.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The evidence presented for the effectiveness of crizotinib was identified through a systematic review and derived primarily from a single well-conducted RCT which demonstrated a benefit of crizotinib in terms of PFS and OS over pemetrexed although there were high rates of crossover and the data were immature in terms of OS. The non-RCT evidence included in the CS supports the RCT results.

There is a lack of published evidence on the cost-effectiveness of crizotinib; the only studies, identified being non-UK comparisons, making generalisability of the results to the UK uncertain. The ERG therefore considers company's model to provide the most relevant evidence for the decision problem. The model structure was appropriate for the decision-problem and included a number of sensitivity analyses: the majority of the sensitivity analyses did not alter the ICER substantially.

1.6.2 Weaknesses and areas of uncertainty

Clinical

Although a benefit relative to pemetrexed combination chemotherapy in terms of PFS seems certain, the size and duration of the relative effect is still uncertain. Results from a later more complete data cut are required; these are anticipated in early 2017.

The results for OS are highly uncertain. Whilst mature data are anticipated in early 2017, adjustments for the high levels of crossover from chemotherapy to crizotinib and disease progression will still be required and results are likely to remain uncertain.

The PROFILE 1014 RCT was open label and allowed different options for post-progression treatments. Whilst differences in follow-on therapies a can be accepted, in PROFILE 1014 as discussed above the trial design facilitated a delay in the start of second-line therapy in the crizotinib arm compared to that in the chemotherapy arm, exacerbating the differences between the treatment arms. Therefore it is likely that the comparison of OS is confounded and not fully adjusted for by the adjustment for crossover methods employed.

Remaining uncertainties surrounding the evaluation of the clinical evidence are:

- The comparability of the populations in PROFILE 1014 with the UK ALK positive NSCLC population;
- The clinical characteristics and prognosis of a typical population of patients with advanced non-squamous ALK-positive NSCLC;
- The efficacy and safety of crizotinib in a population who are not eligible for chemotherapy;
- The efficacy and safety of crizotinib in who are ALK positive and patients who do not have adenocarcinoma NSCLC.

Cost-effectiveness

The major weakness of the cost-effectiveness model presented in the CS related to the modelling of duration of crizotinib treatment beyond progression. As outlined above, this mean that the model underestimated total time on crizotinib and therefore total costs associated with crizotinib treatment. Further, to these calculation errors the ERG did not consider that the manufacturer had adequately justified a number of assumptions made in the economic model. These main weakness and uncertainties in the model are as follows:

- Uncertainties regarding estimated OS benefits due the immaturity of the OS data; the extensive cross-over that occurred; and imbalances in the second-line treatments received once crossover had been accounted for.
- Assumption of proportional hazards for PFS and OS data;

- The HRQoL of patients who initiate pemetrexed combination therapy, post treatment pre-progression;
- Costs associated with ALK testing.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG's primary concern with the company's base case estimate of cost-effectiveness related to the large number of calculation errors, most particularly errors in the calculation of duration of crizotinib treatment beyond progression. Correcting for these calculation errors significantly increases the estimated ICER from [redacted] in the company's base-case to [redacted]. Note these ICER estimates do not include a PAS which is currently awaiting approval with the Department of Health.

In addition to correcting the calculation errors identified in the company model the ERG carried out series of sensitivity analyses, the result of which are summarised in the Table 1 below. The ERG also presented an alternative base-case based on a combination of a number of these scenario analyses. The ERG base-case made the following assumptions:

- Drug wastage for both crizotinib and pemetrexed was include;
- Transitional utilities were exclude for the model with the exception for crizotinib patients treated beyond progression;
- A higher utility was assigned to patients who initiating on chemotherapy who had completed treatment, but were yet to transition to progressive disease;
- An alternative split regarding the number of patients receiving cisplatin and carboplatin was assumed based a scenario analysis presented in the CS;
- Alternative higher ALK testing costs;
- Inclusion of on-going administration costs for crizotinib.

Table 1 Summary of results from additional analyses carried out by the ERG (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
Analysis	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's base-case (corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including drug wastage for both crizotinib and pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removing transitional utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including a higher utility value for chemotherapy patients post discontinuation of first-line treatment and prior to progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assuming a 25%/75% split in the use of cisplatin and carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including alternative higher ALK testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including on-going administration costs for crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ICER for the ERG base-case analysis was [redacted] per QALY not including any PAS. The ERG also carried a series of exploratory analyse using the ERG base-case in which the impact of the assumption of proportional hazards on the estimated ICER was explored. The results of the most plausible estimates of cost-effectiveness are summarized in Table 2 below. Due to the lack of any clinical or statistical justification for selecting one curve over another the ERG could not select any individual analyses as being the most plausible, but consider the analysis assuming a generalised gamma for PFS and Weibull for OS to be particularly relevant for comparative purposes as these were the distributions used in the company's base-case analysis in which proportional hazards was assumed.

Table 2 Incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model (without PAS)

	Fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		
	PFS	**OS**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model and curves selected using lowest AIC)	Log-normal – crizotinib; and gamma - pemetrexed	Gamma – crizotinib; and exponential - pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.8 Conclusions from the ERG analyses

The ERG corrections of calculation errors suggest that the ICER for crizotinib compared with pemetrexed combination therapy is [redacted] per QALY gained. The ERG's additional exploratory analyses using a range of alternative assumptions indicate that this ICER is likely to represent a lower bound. The results from the ERG base-case which can be considered as plausible as the base-case see's this ICER increase [redacted]. Further, additional exploratory analysis carried out by the ERG in which independent parametric survival curves are fitted have substantial impact on the ICER which varies between [redacted] and [redacted] per QALY in these analyses.

Finally, it should be noted that the assessment of clinical and cost-effectiveness of crizotinib presented in this report matches the NICE scope but ignores the possible future use of pemetrexed maintenance therapy as a more effective comparator than pemetrexed plus platinum therapy alone. The possibility of using crizotinib as a 2nd line treatment in ALK-positive NSCLC patients is similarly not included.

2 Background

2.1 Description of the technology under appraisal

The company submission (CS) states that crizotinib is a first-in-class, orally available, small-molecule, receptor tyrosine kinase (RTK) inhibitor with selective, dose-dependent activity against anaplastic lymphoma kinase (ALK) RTK and its oncogenic variants. Crizotinib is indicated for adults with ALK-positive advanced non-small-cell lung cancer (NSCLC).

The CS states that crizotinib was granted 'accelerated approval' in the United States of America by the FDA in August 2011 and that it is approved for use in ALK-positive NSCLC in [redacted] countries across North America, South America, Africa, Europe, Asia and Australia.

Crizotinib was launched in the UK in November 2012 for the treatment of adults with previously treated ALK-positive, advanced NSCLC (i.e. in the second-line setting). Crizotinib was granted EU marketing authorisation for use in the first-line setting on 24th November 2015.

The CS recommends that crizotinib to be administered orally, 250mg twice daily to be taken continuously until disease progression or unacceptable toxicity. Based on individual safety and tolerability, treatment may be interrupted or dose can be reduced. If dose reduction is required, crizotinib should be reduced to 200mg twice daily or 250mg once daily. The CS states that treatment of crizotinib should be initiated and supervised by a physician experienced in the use of anticancer medical products, followed by home self-administration. Based on clinical expert's opinion, the ERG agrees with CS's description of the drug's regimen which is the clinical practice in the UK.

2.2 Critique of manufacturer's description of underlying health problem

The CS included a brief description and over view of the underlying health problem – ALK-positive NSCLC. Lung cancer is a disease which is characterised by abnormal or uncontrolled growth of lung cells.[3] Based on tumour histology, there are two types of lung cancers: NSCLC and small cell lung cancer (SCLC). In 2014, there were about 33,027 reported new cases of lung cancer in England and Wales[4] and NSCLC accounts for around 85% of the total lung cancer patients. [5] Based on tumour histology, NSCLC can be further grouped into: adenocarcinoma (approximately 40%), squamous cell carcinomas (25-30%), large cell carcinoma (10-15%) and other subtypes (e.g. adenosquamous carcinoma and sarcomatoid carcinoma).[3] This means that non-squamous NSCLC (i.e. adenocarcinoma and large-cell carcinoma) would make up about 50-55% of the NSCLC patients.

2.2.1 ALK Prevalence

About 4% and 10% of adenocarcinoma patients are believed to have ALK gene rearrangement (ALK-positive NSCLC) and EGFR gene mutations, respectively. [5] The CS indicated that ALK translocation

and EGFR mutations are mutually exclusive in NSCLC. However, the ERG notes that whilst some studies showed that ALK and EGFR are mutually exclusive, [6, 7] other studies have reported that there is overlap between ALK and EGFR.[8, 9]

ALK-positive NSCLC is characterised by alterations (translocations) of ALK gene and is more commonly related with adenocarcinomas although it can occur in any of the NSCLC.[10] The CS reports estimates for ALK-positive status in 3.4% of non-squamous disease (the CS estimates there are 459 cases of advanced/metastatic non-squamous NSCLC in England and Wales per annum) but only 0.08% of squamous tumours. The Clinical Advisors to the ERG confirmed that ALK-positive status was extremely rare in squamous disease and that testing for EGFR and ALK status was not standard practice on squamous tumours.

This value of 3.4% is taken from a study conducted by the Clinical Lung Cancer Genome Project which characterised genome alterations in 1,255 clinically annotated lung tumours [11]. These findings are supported by results reported in Bang 2011[12] who summarises the findings of 14 different studies, focussing on a total number of 2,864 patients. The results of this study find an average percentage across all of the studies of 3.4% as well, with estimates varying from 1.6% to 11.7%.

The ERG searched for further studies to identify the prevalence of ALK fusion which are summarised in Table 3. The reported prevalence figures range from 3.2%-6.2%[13-19]. A systematic review and meta-analysis conducted by Zhao et al. 2015[20] also reports findings from 27 retrospective studies, some of which are included in the review by Bang 2011. The 27 studies investigated a total of 6,950 patients, and the prevalence was found to be 6.8% (472/6,950).

Table 3 ALK-positive Prevalence Studies

Study	Country	Total, N	ALK+, n (%)
Blackhall et al. 2014	EU	1,281	80 (6.2)
Kim et al. 2011	Korea	465	19 (4.2)
Kwak et al. 2010	USA/Australia/Korea	1,500	82 (5.5)
Paik et al. 2011	Korea	640	28 (4.4)
Takeuchi et al. 2008	Japan	253	11 (4.4)
Tfayli et al. 2015	Lebanon/Jordan/Iraq	125	4 (3.2)
Zheng et al. 2016	China	1,407	74 (5.3)

These findings are generally slightly higher than the value reported in the CS. However, it is difficult to assess the figures as the number with ALK fusion status is small, and many of the studies take convenience samples of patients who are more likely to be ALK-positive (e.g. adenocarcinoma patients) in order to assess the characteristics of ALK-positive patients rather than using a representative sample. Many of the studies are also based in Asia, meaning the study participants may

not be representative of patients in UK practice. This means that many of the studies may over-estimate the prevalence of ALK-positive status. The value of 3.4% reported in the CS therefore seems reasonable, however, there is uncertainty surrounding the true prevalence, with the figure potentially being higher.

2.2.2 Prognosis of ALK-positive patients

The CS appropriately summarises the burden of illness of NSCLC and the advanced forms of the disease. However, no information is presented regarding the disease burden and prognosis of ALK-positive patients relative to other non-squamous NSCLC patients other than that ALK-positive tumours have shown associations with non-smoker status and earlier age of diagnosis (REFS 4, 43 and 65 in CS). The ERG notes that this is not reflected in the 'real life' cohort [Davies et al, 2015] identified in the CS (see section 4.3).

The CS presents information of the life expectancy of patients with advanced and metastatic NSCLC (see section 3.4 of the CS). The life expectancy for patients with ALK-positive NSCLC is not known with any certainty. The CS presented four estimates of median overall survival without crizotinib. Two were of patients treated with pemetrexed + platinum but were of non-squamous but not specifically ALK-positive patients (median OS = 11.8 (95% CI 10.4, 13.2) [1] and 10.6 (95% CI 9.4 to 12.0).[21] The ERG identified a further trial in non-squamous advanced NSCLC with a relevant treatment arm (pemetrexed + carboplatin); this reported median OS of 7.8 (95% CI 5.4, 10.1). [2] It is unclear how ALK-positive patients compare with the wider non-squamous population. One estimate specific to ALK-positive patients (20 (95% CI 13, 26) was based on 36 crizotinib naïve patients but most had received previous treatments for advanced disease, i.e. they were not a first-line population. [22] The estimate given by UK clinical experts is an expected life expectancy of around 15 months. The ERG acknowledges that other sources of evidence are unavailable: ALK-positive patients have been studied only in the context of investigations of crizotinib.

2.3 Critique of manufacturer's overview of current service provision

2.3.1 First-line therapy for advanced NSCLC

The CS presented a clinical pathway for patients with advanced NSCLC which the CS stated was based on NICE clinical guidelines (see Figure 1 in CS). This figure indicates that at first-line patients who are EGRF-positive are treated with EGRF-TKIs (afatinib, erlotinib or gefitinib). Other patients with non-squamous disease can be treated with pemetrexed plus cisplatin, or a third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin). The ERG agree that this summary reflects the existing NICE guideline and TA guidance issued to date (CG 121, NICE pathway for the treatment of NSCLC and TA310, TA 258, TA192, TA181, TA190 and TA 309).

Clinical expert advice to the CS and to the ERG indicates that in current practice, for the vast majority of patients first line treatment for advanced NSCLC patients in the NHS is a pemetrexed plus platinum based combination therapy; although NICE guidance recommends only pemetrexed plus cisplatin, in UK clinical practice carboplatin is also used. The expert clinical advice to the company stated that combination therapy is split between cisplatin and carboplatin based on the patients' fitness and drug toxicity. Clinical advice to the ERG estimated that in UK clinical practice about 30% and 70% of ALK-positive NSCLC patients receive cisplatin and carboplatin, respectively, and that the selection of cisplatin or carboplatin is also influenced by whether the use of pemetrexed maintenance therapy is being considered, as it only used following the combination with cisplatin. The proportion of patients who received cisplatin and carboplatin in the PROFILE 1014 trial presented in the CS was 53% and 47%, respectively.

The CS states that pemetrexed plus platinum chemotherapy is given every 3 weeks for a maximum of 6 cycles. Based on the clinical experts' advice, the ERG notes that this is broadly the same as the clinical practice, though most patients would receive a maximum of four cycles of chemotherapy.

The CS stated that pemetrexed monotherapy as maintenance therapy is not recommended for ALK-positive NSCLC patients in the UK. This is correct in that it was not recommended by NICE in TA309. However, the ERG understands that pemetrexed maintenance therapy was available through the CDF and was used in clinical practice following induction treatment with pemetrexed + cisplatin, and would be used again if it became available in future: it is currently on the list of treatments to be reappraised by NICE.

2.3.1.1 Second-line therapy

Although this current appraisal is concerned with crizotinib in the first-line setting, the ERG includes here a consideration of the treatments provided at second-line following disease progression.

The CS mentions that current recommendations for treatment following disease progression on a first-line therapy includes docetaxel: this reflects the NICE guideline on lung cancer (CG121) TA296 [23] that states that crizotinib is not recommended as second-line therapy for patients with ALK-positive NSCLC that agrees with the CS. However, the ERG notes that crizotinib second-line therapy is available through CDF and this would mean that pemetrexed combination first-line and crizotinib second-line therapy could represent an alternative pathway. This has not been discussed in the CS.

2.3.2 ALK Testing

As crizotinib is indicated only in ALK-positive patients, for crizotinib to be a treatment option, ALK testing has to be performed. The CS states that identification of patients with ALK-positive tumours who would be eligible to receive crizotinib requires histological and molecular testing (page 26 of the

CS). The Vysis ALK Break-Apart FISH probe kit is considered the gold standard for identifying the ALK fusion gene1. Other screening methods available include: immunohistochemistry (IHC), chromogenic in situ hybridisation (CISH), reverse transcription polymerase chain reaction (RT-PCR), and next generation sequencing (NGS). The proposed testing strategy is a two-tiered approach whereby testing is carried initially with IHC and ambiguous results (IHC = 1+/+2) are then validated by FISH.[24, 25] Based on clinical experts' advice, the CS indicates that IHC and FISH are routinely used for ALK-testing of non-squamous NSCLC patients in the UK. The CS also adds that patients with squamous carcinomas can be tested if they present with other feature characteristics of ALK-positive NSCLC (e.g. being young age and non-smoker during diagnosis). The ERG also notes that although not nationwide, next generation sequencing (NGS) is also available for ALK testing that would make the cost of ALK testing less predictable in the near future.

2.3.2.1 Test Accuracy

A variety of studies have been conducted to test the sensitivity and specificity of the IHC test compared to FISH. Thunnissen et al. 2012[26] conducted a review which identified four studies comparing the results of IHC and FISH. These studies tested a combined 1,779 patients with NSCLC and found that every patient with an IHC score of 0 was found to be ALK-ve with FISH, and every patient with an IHC score of 3+ was found to be ALK-positive. A study conducted by Yi et al. 2011 yielded similar results, with IHC scores of 0 and 3+ having corresponding negative and positive FISH scores respectively.

However, a study conducted by Blackhall et al. 2014[13] tested 237 patients with both FISH and IHC and found that 2/22 who had an IHC score of 3+ were found be ALK-ve with FISH. Similar results were found in a study conducted by Wu et al. 2013[27], with 2/12 patients with an IHC score of 3+ having corresponding negative FISH scores.

On balance the ERG finds the proposed strategy of testing patients using IHC initially, followed by FISH for those with a score of 1+/2+ is reasonable. An IHC score of 0 appears to produce results which are consistent wish FISH, whereas a score of 3+ appears to largely produce results which are largely consistent, but this is not the case in every study identified by the ERG. There is therefore a chance that some patients would be incorrectly treated with crizotinib if this testing strategy is adopted, but the exact number is unknown.

2.3.2.2 Population to be screened

The CS proposes that NSCLC patients with a non-squamous histology should be the population to be screened, as well as those with a squamous histology who show the characteristics of being ALK-positive e.g. young and a non-smoker. Global guidelines differ on the population who should be eligible for screening and there appears to be little consensus[26]. Lung Cancer molecular testing

guidelines produced by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology, recommended the testing of all NSCLCs that have an adenocarcinoma component[28].

Although guidelines tend to differ, the recommendations tend to be based on tumour histology and EGFR status. Studies have shown that the number of ALK-positive patients who have a squamous histology is small (REF), however, if all squamous patients are not screened there will be a number of ALK-positive who may not be identified. However, on balance this number is likely to be minimal, making this treatment strategy reasonable.

2.3.2.3 Timing of screening

The screening method proposed in the CS is that patients are first tested with IHC, and all of those who receive an ambiguous score (IHC = 1/2) would then receive a FISH test. The FISH test is used in the PROFILE 1014 trial, and must be used in some capacity in practice in order to make the trial results generalizable. The issue however is whether a stepwise approach should be adopted where patients receive IHC before they receive a FISH test.

Stepwise testing algorithms have the advantage that they can make more efficient use of resources than simultaneous testing. However, the downside to this approach is that it can result in treatment being delayed as it can take longer to correctly identify someone as being ALK-positive. The timing of treatment is important as delays can mean that patients miss out on the benefits of treatment and may have a reduced capacity to benefit from treatment if the disease is allowed to progress. As patients can experience rapid deterioration the lung cancer molecular testing guideline recommends that testing algorithms should be completed within 10 working days [28]. There is also an additional concern that if crizotinib becomes available as a first line treatment then the demand for ALK testing may increase, and therefore there is the potential for capacity issues. In response to the questions raised by the ERG the company stated that the average testing period is approximately two weeks from the time of the initial test to the treating oncologist receiving the test results, however this will vary depending on the test centre.

3 Critique of manufacturer's definition of decision problem

3.1 Population

Based on the NICE's final scope, the target population are those patients with untreated, advanced ALK-positive NSCLC that included both squamous and non-squamous patients and the population specified in the CS matches this. However, the CS points out that the majority (98.7%) of ALK-positive patients are expected to be of non-squamous tumour histology. Furthermore the population of the trial PROFILE 1014 that the CS has presented as evidence is exclusively non-squamous ALK-positive advanced NSCLC. The supporting evidence (PROFILE 1001[29] and Davies et al 2015 [10]did not excluded squamous patients but the numbers were very small (1% and 3% respectively)(..

The estimate of the number of patients expected to be eligible first-line crizotinib treatment (459), considers only non-squamous ALK-positive NSCLC patients.

The cost-effectiveness of crizotinib in squamous patients is considered only in a scenario analysis.

Thus, the ERG considers that the population addressed in the submission is narrower than that in the NICE scope, in that it considers almost exclusively non-squamous patients. However, given the rarity of ALK-positive status in squamous patients, this is appropriate.

The NICE scope also included the population with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate. This subgroup is not considered in the CS; expert clinical advice to the company highlighted that this sub-group accounts for less than 2% of the ALK-positive patient population. The lack of evidence for standard therapy for this sub-group (see section 3.3) meant it was not possible to conduct an evaluation of the cost-effectiveness of crizotinib in this sub-group.

3.2 Intervention

The intervention drug is Xalkori that contains an active ingredient of crizotinib.[30] It is prepared as 200 and 250 mg capsules and is administered orally, as described in the CS, 250mg twice daily taken continuously until disease progression or unacceptable toxicity which agrees with the final NICE's scope.

3.3 Comparators

3.3.1 Comparators based on the NICE's final scope

The NICE's final scope identified three types of comparator based on tumour histology:

d) For non-squamous patients, pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin);

e) For people with squamous tumour histology, a third-generation drug (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin); and,

f) For people with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate, single-agent chemotherapy with a third generation drug (for example, gemcitabine or vinorelbine).

3.3.2 Comparators considered by the CS

3.3.2.1 Pemetrexed combination chemotherapy

The CS has considered pemetrexed plus platinum-based therapy as a comparator for the submission in line with the NICE scope. The CS states that cisplatin and carboplatin have the same PFS outcomes so can be considered to be equal; they are treated as a single comparator. However, based on clinical expert's advice, the ERG notes that although the two drugs have similar PFS, they differ significantly in terms of their toxicity level.

Clinical advisors to the ERG advised that 30% of patients receive cisplatin and 70% patients receive carboplatin. This can be compared with the proportion patients who received cisplatin and carboplatin in the PROFILE 1014 trial: 53% and 47% respectively, which therefore may not represent the clinical practice in the UK.

In line with the NICE scope pemetrexed maintenance therapy is not considered as a comparator as NICE guidance was that it was not recommended. However, the ERG notes that, based on its clinical advisor's opinion, pemetrexed maintenance therapy for patients who received first line pemetrexed plus cisplatin was used when available through the cancer Drugs Fund and would be used again if available.

The other comparators included in the NICE scope, a third-generation drug (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin) (for people with squamous tumour histology) and single-agent chemotherapy with a third generation drug (for example, gemcitabine or vinorelbine), (for people with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate) are not considered in the CS because these sub-groups are extremely small and evidence upon which to base an evaluation is not available. The ERG considers that this is reasonable.

The ERG notes that crizotinib second-line therapy is available through CDF and this would mean that pemetrexed combination first-line and crizotinib second-line therapy could represent alternative pathway.

3.4 Outcomes

The CS considered overall survival, progression free survival, objective response rate, adverse events and health-related quality of life outcomes and that appropriate mechanisms for measuring these outcomes were used as outcomes which agree with the list of outcomes in the NICE final scope.

3.5 Other relevant factors

Although this appraisal is of crizotinib as first-line therapy, overall survival is impacted by treatments given postdisease progression. The ERG notes that the second line therapy in the main trial (PROFILE 1014) includes a large number of different agents indicating that the NICE Guideline statement recommending docetaxel as second-line therapy (based on 2005 data) may not be reflective of clinical reality in 2016. The ERG notes that crizotinib second-line therapy is available through CDF and this would mean that pemetrexed combination first-line and crizotinib second-line therapy could represent alternative pathway in the decision model.

4 Clinical Effectiveness

This section contains a critique of the methods of the review(s) of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company performed two separate systematic searches for RCT and non-RCT studies that investigated the efficacy and safety of crizotinib in the treatment of advanced/metastatic ALK-positive NSCLC patients. Searches were carried out using MEDLINE, EMBASE, and the Cochrane library databases. In addition to the electronic databases, the company also performed scanning of reference lists of relevant studies and searches for grey literature and completed and on-going trails.

Details of the searches of RCT and non-RCT were provided in Appendix 2 and Appendix 3 of CS, respectively. Terms and phrases used in each of the electronic databases and grey literature searches as well as hand searches were presented in the appendixes. Thus, based on this evidence, the ERG considers that the search terms and phrases used were adequate to retrieve the relevant published and unpublished data.

Searches were performed in accordance with the PRISMA guidelines, [31] with flow diagrams presented in Figure 5 and Figure 6 although the studies included in the qualitative and quantitative synthesis were not clearly identified. However, the ERG considers that appropriate search steps and guidelines have been followed.

4.1.2 Inclusion criteria

Full inclusion criteria were provided in Table 11 and Table 12 of the CS. In brief; both in RCT and non-RCT systematic literature review, studies were included if they recruited advanced ALK-positive NSCLC adult (≥18 years) patients who were not treated previously with a pharmacological intervention, and used crizitinib and chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) as an intervention and comparator, respectively. For non-RCT evidence, studies were also considered for inclusion if they were single-arm (no comparator). Overall survival, progression free survival, response rate, time to progression, adverse effects and quality of life were considered as outcomes of interest both in RCT and non-RCT studies search.

Studies were excluded, both in RCT and non-RCT, if they did not include patient population of interest, not presented relevant outcomes, or used interventions other than crizotinib. Publications prior to 2007 and Non-English publications were also excluded. Although the inclusion/exclusion

criteria should not have excluded non-English publications the ERG believes it is unlikely that relevant studies have been missed by the search strategy.

4.1.3 Critique of data extraction

The CS presented the number of studies identified as eligible to be included in the SLR but no discussion of any data extraction plan was evidenced. There were, however, baseline data presented in Table 20 and Table 29 of the CS for the RCT and non-RCT studies, respectively.

For the efficacy and safety RCT (PROFILE 1014), data on PFS and its HR (Table 21 of the CS), OS and its HR (Table 23 of the CS), ORR (Table 22 of the CS) and Kaplan-Meier plots (Figure 8, Figure 10 & 11 of the CS) were extracted. Extracted information on patient-reported outcomes and health-related quality of life (Figures 12-15 of the CS), and number adverse events in each treatment options were also evidenced (Tables 32-35 of the CS). In addition, analysis data on pre-specified subgroup For the non-RCTs (PROFILE 1001 and Davis et al 2015) baseline characteristics of individuals were extracted. In addition, PFS data for Davies et al 2015 trial (Table 38 & Appendix 10 of the CS) and number of adverse events for PROFILE 1001 trial were extracted (Appendix 11 of the CS). However, no further data was extracted for the two trials.

Therefore, the ERG considers that, while a data extraction plan for RCT should have been provided, the data reported is appropriate and matches the scope. At the same time, however, it also recognises that there is not enough efficacy and safety information provided for the non-RCTs.

4.1.4 Quality assessment

The CS presented a quality assessment of the a single efficacy RCT (PROFILE 1014) based on adapted tool from the CRD guidance for undertaking of reviews in health care,[32] with assessments of: randomisation, allocation concealment, baseline characteristics, blinding, drop-out rates and type of analysis used (Appendix 7 of the CS). This was appropriate, although the ERG also conducted its own quality assessment based on the Cochrane risk of bias tool for RCTs (see Section 4.2). The CS also presented an appropriate quality assessment of the two non-RCTs (PROFILE 1001 and Davis et al 2015) using the Downs and Black checklist,[33] with assessments of: reporting, external validity, internal validity, internal validity-confounding, and power of the study (see Section 4.2).

4.1.5 Evidence synthesis

Only one trial examining the efficacy of crizotinib in adults with ALK-positive NSCLC was identified, so no synthesis or meta-analysis was carried out.

No indirect or mixed comparison with any other therapies for ALK-positive NSC was conducted, because the company believed that pemetrexed in combination with cisplatin or carboplatin is the only available standard of care as a comparator. The ERG notes that, given that the submission is

based on a pioneering trial that investigates the efficacy of crizotinib only in adult ALK-positive NSCLC previously untreated patients, trials that examined the efficacy of third-generation drugs (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin) and single-agent chemotherapy with a third generation drug (for example, gemcitabine orvinorelbine) could not have been used for indirect treatment comparison.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

One randomised controlled trial was included in the review (PROFILE 1014)[34], which compared crizotinib with pemetrexed chemotherapy in patients with untreated ALK-positive advanced NSCLC. Additional non-RCT evidence was also presented: PROFILE 1001[29] which was a single arm trial of both untreated and previously treated patients, and Davies et al. 2015[10], which is a retrospective cohort study of hospital patients who had received no prior therapy.

4.2.1 *RCT evidence*

The main study on which the CS is based is the Phase III PROFILE 1014 open label RCT. The study design of the trial is summarised below in Table 4.

Table 4 Study design of PROFILE 1014

Study details	PROFILE 1014
Location	247 sites in the UK, Australia, Austria, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Finland, France, Germany, Hong Kong, India, Ireland, Italy, Japan, Republic of Korea, Luxembourg, Mexico, Netherlands, Norway, Peru, Portugal, Russian Federation, Singapore, South Africa, Spain, Switzerland, Taiwan, Ukraine and the United States.
Design	Randomised, two-arm, single-blind
Duration of core study	18 months
Method of randomisation	Randomly assigned in a 1:1 ratio. Stratified by ECOG PS, (0 or 1 vs. 2), Asian or non-Asian race , and presence of absence of brain metastases
Method of blinding	Open-label design made blinding of the patients, care providers and outcomes assessors not feasible. The assessments of tumour response and disease progression were made by independent radiologic review and were blinded to treatment group
Intervention(s)	Oral crizotinib tablet 250 mg twice daily (n = 172)
Comparator(s)	Pemetrexed, 500 mg/m2 BSA; plus either cisplatin, 75 mg/m2 BSA, or carboplatin, target AUC of 5–6 mg/mL/min; administered intravenously every 3 weeks for a maximum of 6 cycles (n = 171)
Primary outcome	Progression-free survival (defined as time from randomisation to RECIST defined progression)
Data cut-off	18 months
Secondary outcomes	Objective response rate (ORR) and best overall response (BOR) Time to tumour response (TTR); Duration of response (DR); Disease control rate (DCR) at Week 12 ; Time to progression (TTP)*; Intracranial time to progression (IC-TTP)*; Extracranial time to progression (EC-TTP)*; Additional secondary outcomes included: Overall survival (OS) – including one-year and 18-months survival probabilities Safety – including type, incidence, severity, seriousness and relationship to study medications of adverse events and any laboratory abnormalities Patient-reported outcomes (PROs): EORTC QLQ-C30; EORTC QLQ-LC13; Time to deterioration (TTD) in either cough, dyspnoea and pain in chest symptoms, as assessed using EORTC QLQ-LC13

	EQ-5D
Duration of follow-up for reported analysis	Follow-up will continue for up to 36 months after the randomisation of the last patient (July 2016). (At the data cut-off (30th November 2013) the median follow-up for the outcome overall survival was 17.4 months (range: [redacted] months) for crizotinib patients, and 16.7 months (range: [redacted] months) for chemotherapy patients)

The trial was conducted at 247 sites, 9 of which are located in the UK, and commenced in January 2011.

Patients (n=343) were randomised on a 1:1 basis to either criztonib 250mg twice daily until disease progression (or until no perceived treatment benefit), or chemotherapy (to pemetrexed 500mg/m^2, plus either cisplatin, 75 mg/m^2, or carboplatin, target area under the concentration-time curve of 5-6 mg/mL/min; administered intravenously every 3 weeks for a maximum of six cycles). Randomisation in the PROFILE 1014 was stratified by the Eastern Cooperative Oncology Group (ECOG) performance, Asian or non-Asian race, and the presence or absence of brain metastases. The stratification variables are reasonable as there has been evidence that each can have a potential impact on prognosis [35]

The quality assessment reported in the CS demonstrated that the trial was appropriately randomised, the groups were similar in terms of baseline characteristics, there was no unexpected imbalance in drop-outs between groups, intention to treat and appropriate censoring methods were implemented during data analyses, and that although the clinical outcome assessor was blinded, care providers and participants were not. The ERG conducted its own quality assessment based on the Cochrane risk of bias tool for RCTs (see Table 5) and agrees with the quality assessment presented by the CS but concluded that whilst this was a well conducted trial, the open label design puts it at a high risk of bias for the primary outcome PFS, and the open label design combined with permitted treatment decisions post disease progression, put the trial at high risk of bias for overall survival. This is discussed further in later sections on PFS and OS.

Table 5 Study quality assessment using Cochrane risk of bias tool for PROFILE 1014 trial

Entry	Judgement	Support for judgment
Random sequence generation	Low risk	Patients were assigned to treatment groups (1:1) based on a random permuted block design using a centralised Interactive Voice Response System (IVRS)/website.
Allocation concealment	High risk	Allocation to treatment was not concealed
Blinding of participants and personnel	High risk	It was open label trial
Blinding of outcome assessment	Low risk	Progression was assessed by independent radiologist
Incomplete outcome data addressed (Short-term outcomes (2-6 weeks))	Low risk	No issues of missing data during this period
Incomplete outcome data addressed (Longer-term outcomes (>6 weeks))	High risk	Patient-reported outcomes and health-related quality of life information was missing substantially for the intervention arm (~84%)
Selective reporting	Low risk	No selective reporting of results was observed.
Other sources of bias: treatment cross-over	High risk	There was a substantial crossing over of patients from intervention drug (crizotinib) to control drug (Pemetrexed combination therapy) and vice versa.

At disease progression patients could be treated with a second-line agent, but the treatment prescribed was not specified in the trial protocol. The ERG notes that this lack of standardisation of post-trial therapy has the potential to confound any comparison of the treatment benefit beyond the treatment period of the trial; the option for patients in the chemotherapy arm to cross-over onto crizotinib following disease progression is of particular concern in this regard. Furthermore, the protocol specified that in the crizotinib arm, crizotinib could continue beyond disease progression and many patients did so. These issues are discussed further in Section 4.2.2.1.

The primary outcome of the trial was progression-free survival (PFS), which was considered to be the time from randomisation to RECIST-defined progression, as assessed by independent radiologic review (IRR) or death. In their clarification response the company confirmed that tumours were assessed at regular intervals, i.e. every 6 weeks from the date of randomisation until radiographic disease progression had been documented by IRR. All scans were then sent to an independent radiology laboratory for a blinded RECIST review. Patients who completed 6 cycles of chemotherapy and/or discontinued treatment prior to RECIST-defined PD were to continue with tumour assessments per the protocol until PD was documented by IRR or additional anticancer therapy was initiated; this included patients who had discontinued study treatment for reasons other than PD but remained in the study. The clinical expert advice to the ERG notes that in clinical practice RECIST criteria which assess tumour size are not used to determine disease progression, instead it is determined by the worsening of symptoms.

There were a range of reported secondary outcomes which are reported in Table 1. For the purposes of this appraisal the most important of these is overall survival.

The CS stated that sub-group analyses would be conducted based on:

- PFS by stratification factors/baseline characteristics
- IC-TTP and EC-TTP by treatment group and baseline brain metastases - these outcomes were not reported in the body of the submission as they are not key to the appraisal.

The key patient inclusion and exclusion criteria for the trial are presented in Table 6, with the full criteria found in Table 16 in the CS. The trial inclusion criteria appear to be fairly appropriate, but were more restrictive than the criteria set out in the NICE scope. Squamous status was not listed in the scope; however, the company stated that non-squamous was included as a criterion as it is extremely rare for squamous patients with ALK-positive status to present in practice. Other criteria not specified in the scope which were applied to the trial were: an ECOG score of ≤2, adequate hepatic, renal and bone marrow function, and brain metastases. Thus the trial population has the potential to be healthier than the real world UK population, though this is uncertain: clinical advice to the ERG indicated that patients with poor ECOG status might not be treated with crizotinib in clinical practice.

Table 6 Eligibility criteria for PROFILE 1014 (based on CS Table 16 which gives full details)

Inclusion criteria	Exclusion criteria
1. Histologically or cytologically proven diagnosis of locally advanced, not suitable for local treatment, recurrent, or metastatic non-squamous NSCLC. 2. Positive for translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as determined by an ALK break-apart FISH test and defined by an increase in the distance between 5' and 3' ALK probes or the loss of the 5' probe. 3. No prior systemic treatment for locally advanced or metastatic disease (exception below): o Prior adjuvant chemotherapy for Stage I-III or combined modality chemotherapy radiation for locally advanced disease allowed if completed >12 months prior to documented PD. 4. Patients with brain metastases were only eligible if treated and neurologically stable with no ongoing requirement for corticosteroids, e.g. dexamethasone, for at least 2 weeks and were not taking medications contraindicated in Exclusion Criteria 12-14. 5. Tumours must have had measurable disease as per RECIST (Version 1.1). 6. Female or male, 18 years of age or older (for patients enrolled in Japan: consent from a legally acceptable representative was required for all patients who were under 20 years old; for patients enrolled in India, the upper age limit was 65 years old). 7. ECOG performance status of 0–2.	1. Current treatment on another therapeutic clinical study. 2. Prior therapy directly targeting ALK. 3. Previous treatment with crizotinib. 4. Prior malignancy (other than current NSCLC): patients were not eligible if they had evidence of active malignancy (other than non-melanoma skin cancer or in situ cervical cancer, or localized and presumed cured prostate cancer) within the last 3 years.

The characteristics of the patient population in the trial are summarised in Table 7. There is no indication of any imbalance between the treatment arms. Almost all patients had adenocarcinoma (94%) and almost all had metastatic disease (98%), and, reflecting the inclusion criterion, almost all were of ECOG status <2 (95%).

Table 7 Patient characteristics of PROFILE 1014

Characteristic	**PROFILE 1014 (n = 343)**	
	Crizotinib (n = 172)	**Chemotherapy (n = 171)**
Median age (range), years	52 (22–76)	54 (19–78)
Male, %	40%	37%
Race % White Asian Other	 53% 45% 2%	 50% 47% 4%
Smoking status % Never smoked Former smoker Current smoker	 62% 33% 6%	 65% 32% 3%
Histologic characteristic of tumour % Adenocarcinoma Nonadenocarcinoma	 94% 6%	 94% 6%
ECOG performance status % 0 or 1 2	 94% 6%	 95% 5%
Extent of disease % Locally advanced Metastatic	 2% 98%	 2% 98%
Time since first diagnosis (months) Median Range	 1.2 0-114.0	 1.2 0-93.6
Brain metastases present %	26%	27%

4.2.2 Summary of the results from the PROFILE 1014 study

An overview of the clinical effectiveness results of PROFILE 1014 are provided in Table 8 for crizotinib compared to pemetrexed chemotherapy.

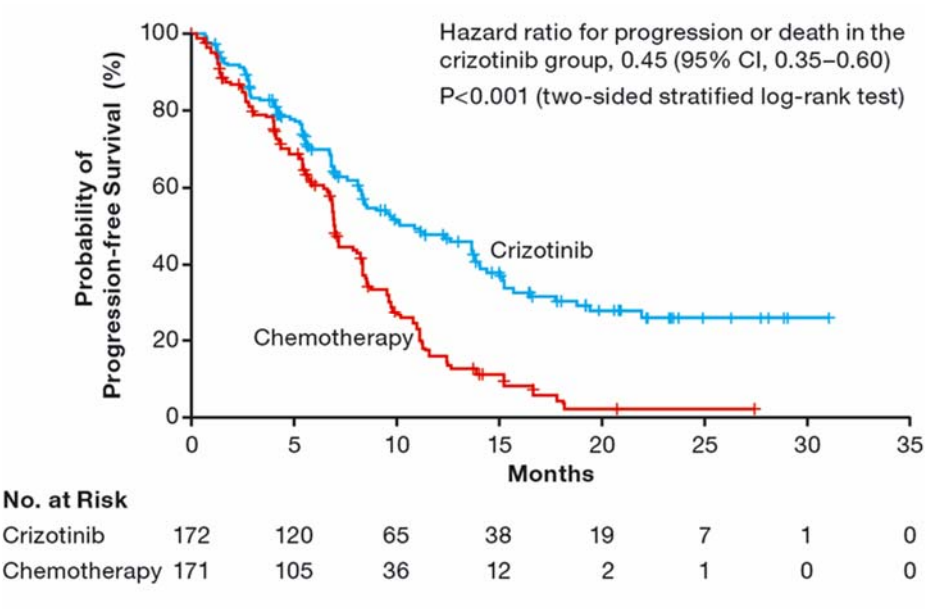
Table 8: Overview of clinical effectiveness results in PROFILE 1014

Outcome		Crizotinib (n=172)	Chemotherapy (n=171)
Progression-free survival (PFS)			
Median PFS, months (95% CI)		10.9 (8.3 to 13.9)	7.0 (6.8 to 8.2)
HR for progression or death with crizotinib (95% CI; P-value)		0.45 (0.35 to 0.60; P<0.001)	
Tumour response			
ORR, % (95% CI)		74 (67 to 81)	45 (37 to 53)
Median best percentage change in target lesions from baseline, %		[redacted]	[redacted]
Overall survival (OS)			
Duration of follow-up		17.4 months (range 12.1 to 23.7)	16.7 months (range 12.2 to 23.4)
Median OS, months		Not reached	Not reached
HR for death with crizotinib, (95% CI; P-value)	**Unadjusted**	0.821 (0.536 to 1.255; P=0.1804, 1-sided)	
	Crossover-adjusted, range using nine models	0.571 to 0.674, across nine parametric models using three methods of analyses.	

4.2.2.1 Progression-Free Survival

At the time of the data cut-off 89 people's cancer had progressed in the crizotinib arm (51.7% of patients) and 132 people had progressed in the chemotherapy arm (77.2%).

Figure 1: Kaplan-Meier plot for progression-free survival in the ITT population in PROFILE 1014



Source: Solomon *et al.* (2014)

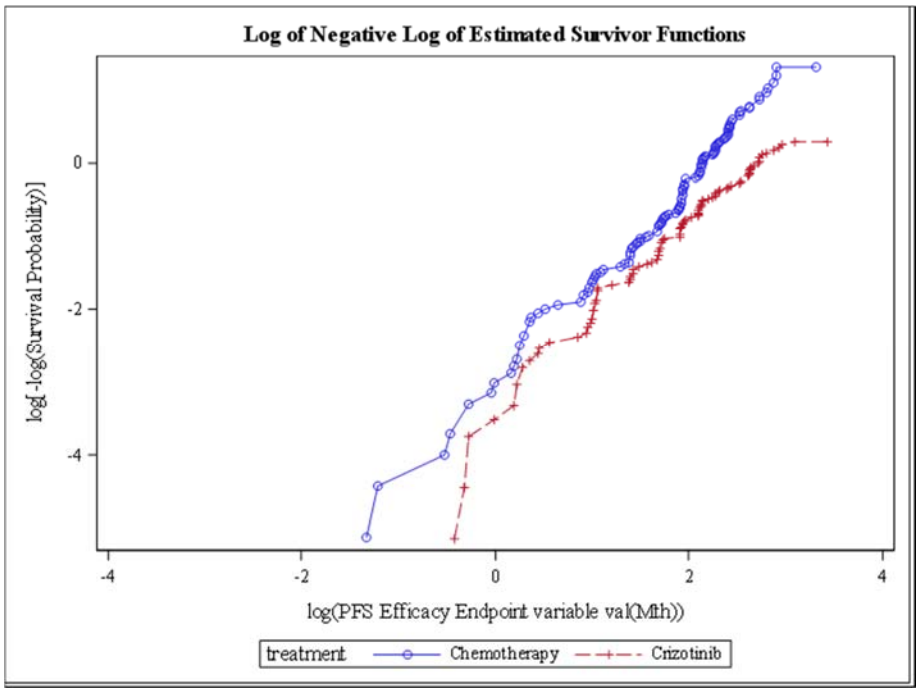
The PFS results show that crizotinib demonstrated a significant improvement in prolonging PFS. Patients in the crizotinib arm had an increase in median PFS of 3.9 months compared to chemotherapy group and a significantly reduced risk of progression or death, with a hazard ratio of 0.45 (95% CI, 0.35 to 0.60; P<0.001). There was no evidence of different effects by sub group (see Appendix 8 of CS).

The PFS data analysed were those available at the data cut at 30th November 2013. This was the date when the pre-specified number of disease progression events had occurred. The ERG notes that at the data cut analysed not all patients had completed the trial; it is anticipated that PFS results from a later data cut will provide a more complete picture of the PFS benefits with crizotinib.

PFS was analysed using the ITT population using the appropriate Kaplan-Meier method. Further details are given in Table 19 of the CS. However, in their clarification response the company stated that the PFS hazard ratio for crizotinib versus chemotherapy was calculated using a Cox proportional hazards model stratified by ECOG performance status (PS), race group, and brain metastases. The one-sided p-value is from the log-rank test stratified by ECOG PS, race group, and brain metastases. In ERG notes that in the analysis of PFS the assumption of Cox proportional hazards assumes that there is a common treatment effect. One hazard ratio therefore applies to the entire period under consideration, assuming that the treatment effect is proportional over time, and therefore the survival curves fitted to each treatment group have a similar shape [36].

The base-case analysis in the CS makes use of the proportional hazards assumption, justifying this by inspecting the log-cumulative hazard plot for PFS (Figure 2). In order for the assumption to hold the plots must remain largely parallel to each other to demonstrate that the hazard ratio is reasonably constant over time. In this case the plot for PFS seems to be unclear, with parts remaining largely parallel, while other sections appear to diverge.

Figure 2: Log-cumulative hazard plot (Progression-Free Survival)



There are a number of reasons why the proportional hazards assumption might not hold for these PFS data: there are differences in the way the two treatment regimen under comparison are given (continuous crizotinib until progression versus a limited number of cycles of pemetrexed + platinum followed by a therapy-free period until progression); the Cox proportional hazards method is only likely to be reasonable when the majority of events in the trial have taken place but at the data-cut for PROFILE 1014 the PFS data, whilst mature, were not complete. Furthermore, with patient-level data available, it was not necessary for the company's analysis to rely on the proportional hazards assumption, as separate parametric models can be fitted which require fewer assumptions. Therefore, the ERG believes that fitting separate parametric models would be likely to produce a more reliable estimate of PFS, and explores this scenario in Section 6.

The company highlights that the PFS results in the chemotherapy arm are higher than those that have been observed in prior studies[1] which they claim may be attributed to the differing patient characteristics, i.e that ALK-positive patients are younger and have a higher proportion on non-smokers. The ERG notes that although the PROFILE 1014 population is younger and has a high proportion of never smoked participants, it is not at all certain that in general ALK-positive patients are younger and healthier than the broader NSCLS population (see Section 4.2.3 for discussion of Davis et al. 2005 'real life' cohort). It is possible that the population in PROFILE 1014 is younger and healthier than real life patients and its results may be favourable for both chemotherapy and crizotinib arms; what this means for the relative treatment effect is unknown. It is also possible that these results indicate that ALK-positive patients have a better prognosis than the broader non-squamous NSCLC population.

The ERG notes that the PFS results from PROFILE 1014 may not be generalisable to clinical practice and therefore should be considered somewhat unreliable. Radiographic criteria might not necessarily be indicative of worsening symptoms and are likely to lead to the earlier identification of progressive disease; they are not generally used in clinical practice to determine progression. Therefore, patients in the chemotherapy arm of the trial may have crossed over to second-line therapy (crizotinib) earlier in PROFILE 1014 than they would likely have done in clinical practice. This was not the case in the crizotinib arm, where patients continued on crizotinib whilst there was still some symptomatic treatment benefit. This potential for imbalance would have been exacerbated by the open label nature of the trial.

4.2.2.2 Tumour Response

The results (Table 9) show that those in the crizotinib arm had a statistically significant higher objective response rate (complete or partial response) than those in the chemotherapy arm (P<0.001). Crizotinib is also shown to have a shorter time to response and a longer duration of response. The clinical significance of the outcome disease control at week 12 is not discussed in the CS.

In their clarification response the company confirmed that all tumour response results are based on data collected prior to disease progression and are not confounded by treatment crossover. The ERG considers that the results for tumour response, being based on IRR and not subject to the problems associated with limited follow-up or post-progression treatment are likely to be reliable.

Table 9 Response to treatment in the ITT population in PROFILE 1014

Response*	Crizotinib (n=172)	Chemotherapy (n=171)
Type of response – no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate (ORR) – % (95% CI)‡	74 (67–81)	45 (37–53)
Disease control rate at Week 12 – % (95% CI)§	[redacted]	[redacted]
Time to response (TTR) – months		
Median (range)	1.4 (0.6–9.5)	2.8 (1.2–8.5)
Duration of response (DR) – months		
Median (95% CI)	11.3 (8.1–13.8)	5.3 (4.1–5.8)

* Tumour responses were assessed using RECIST (version 1.1), and were confirmed by IRR
† Responses could not be evaluated in 4 patients in each group due to early death.
‡ P<0.001 for the comparison between groups (Two-sided Pearson chi-squared test). The 95% CI was calculated with the use of the exact method based on the F-distribution.
§ P=0.0381 for the comparison between groups (Two-sided Pearson chi-squared test). The 95% CI was calculated with the use of the exact method based on the F-distribution.

4.2.2.3 Overall survival

The results for OS are highly uncertain due to the following factors:

- The immaturity of the data
- The high levels of cross-over from chemotherapy to crizotinib at REIST-defined disease progression
- The assumption of proportional hazards
- The imbalance of post-progression follow-up therapy.
-

There is also a potential issue with the very low mortality rate in the chemotherapy arm.

Immaturity of the data

The high uncertainty is driven by the immaturity of the data. At the time of the data cut off (pre-specified point for primary outcome, 30th November 2013) deaths had occurred in only 26% of those who underwent randomisation. In their clarification response the company stated that the number of OS events in PROFILE 1014 was assessed again in [redacted] of the pre-specified number of events had occurred. As median OS had not been reached, the trial protocol was formally amended to continue the collection of survival follow-up information for up to [redacted] after the randomisation of the last patient [redacted] in order to enhance the likelihood to obtain an estimate of the median OS for each treatment arm. As such, the next planned analyses of the trial are planned for [redacted]. If at that time median survival has been reached, an analysis will be conducted. Updated OS analyses will be provided with the final clinical study report [redacted] The earliest date that the company could submit new analyses to NICE would be [redacted]

Cross-over from chemotherapy to crizotinib at RECIST-defined disease progression

The unadjusted OS results shows no significant different in overall survival between patients in the crizotinib arm and those in the chemotherapy arm at the time of the data cut-off (HR, 0.82; 95% CI, 0.54 to 1.25). Of the 171 patients randomly assigned to chemotherapy, 120 patients (70%) subsequently received crizotinib. This high level of cross-over is likely to have had an impact on the results in an under-estimation of the effect of crizotinib. This is supported by the fact that in the subgroup of patients who did not crossover ([redacted]), the HR was [redacted]).

The company therefore adjusted for crossover using three different methods which they considered to be the most appropriate based on the data. The Rank-Preserving Structural Failure Time Model (RPSFT method); two-stage method; and Iterative Parameter estimation (IPE). The RPSFT method was utilised using two types of analysis: one using the Wilcoxon test, and the other using a Log-rank test. The CS showed results for four variations of the IPE method, each using a different parametric function. The parametric functions used were: Weibull, Log-normal, Log-logistic and Exponential. All four of these methods adjusted patients for baseline ECOG PS, brain metastases and smoking status. The Two-stage method made use of a log-normal parametric model and 3 variations of the model were reported in the CS. The first did not adjust for covariates, and the other two were adjusted for baseline smoking status and ECOG PS at progressive disease by IRR. Of these two covariate adjusted models, one adjusted missing ECOG scores as greater than or equal to 2, and the other inputted ECOG scores as the closest value.

The ERG notes that the RPSFT method using two approaches (i.e, the Wilcoxon and log-rank tests) was pre-specified in the clinical trial protocol. [redacted]

The results are presented in Table 10. The adjusted analyses all produced lower hazard ratios than the unadjusted analysis but all still generate wide confidence intervals and only some produce statistically significant results.

Table 10 Summary of overall survival analyses for PROFILE 1014 based on data at the time of final PFS analysis

Method of Analysis	Parametric Model	Adjusted for Crossover	Analysis Details	Hazard Ratio (95% CI)[1]	1-sided p-value[2]
Primary	N/A	No	N/A	0.821 (0.536, 1.255)	0.1804
RPSFTM	N/A	Yes†	Using Wilcoxon test (method **RW**)	0.604 (0.265, 1.420)	NR
			Using Log-rank test (method **RL**)	0.674 (0.283, 1.483)	NR
2-stage	Log-normal	Yes‡	Adjusted for baseline Smoking Status and ECOG PS at PD by IRR, ECOG = closest (method **TSA**)	0.624 (0.405, 0.963)	0.0158
			Adjusted for baseline Smoking Status and ECOG PS at PD by IRR, ECOG = worst (method **TSB**)	0.649 (0.421, 1.000)	0.0242
			Not adjusted for covariates (method **TSC**)	0.610 (0.395, 0.942)	0.0123
IPE	Weibull	Yes†	Adjusted for baseline ECOG PS, baseline Brain Metastases and baseline Smoking Status	0.626 (0.395, 0.992)	0.0230
	Log-normal			0.633 (0.401, 1.000)	0.0251
	Log-Logistic			0.571 (0.349, 0.935)	0.0130
	Exponential			0.674 (0.432, 1.051)	0.0408

ERG comments on methods used for adjustment for crossover

It is normal practice to analyse a trial using the ITT analysis. However, when crossover rates are high the results from the ITT analysis can result in an under-estimation of the treatment effect. Analysing such data adjusting for cross-over is now accepted best practice.[37] A number of methods exist: the rank preserving structural failure time model (RPSFTM), two-stage model; the iterative parameter estimation (IPE); and inverse probability of censoring weights method (IPCW). These are summarised in Table 11.

The ERG has several concerns regarding the crossover adjustment methods used in the CS. The RPSFT and IPE models both assume a common treatment effect, which based on the switching rules of the trial and the characteristics of NSCLC might not hold. This is because those who switched on to the experimental drug when they are at more advanced stage may not have the same benefit as those in the experimental group who received treatment from randomisation. This also applies to those who were in the experimental group and switched on to control group. On the other hand, because in the trial, progression is determined by IRR rather than symptomatic progression, there still may be sizeable capacity to benefit, as patients who were judged to have progressed may not have done so symptomatically. There is also evidence to show that crizotinib is an effective second –line therapy,[38] demonstrating there is still capacity to benefit from the treatment after progression. In their clarification response the company stated that fundamentally, this structural assumption of a common treatment effect, a recognised limitation of the model, is untestable and emphasised that there is no evidence to suggest this assumption doesn't hold. They reiterated that RPSFTM is a widely accepted method to estimate survival time in the presence of crossover, and has been used in a number of oncology clinical trials across different agents and indications.

RPSFTM and IPE models also have problems when the comparator treatment used in the RCT is active (i.e., it prolongs survival).[37] This is because the counterfactual survival models using RPSFTM and IPE require that patients are either "on" or "off" at any one time. If patients in the control group receive an active treatment followed by supportive care upon treatment failure the "off" treatment category represents more than one type of treatment and the counterfactual survival model is not appropriate unless additional causal parameters are added to the model.

The two-stage method assumes no unmeasured confounders and switching should only happen after a disease-related secondary baseline, and that prognostic covariate data were collected at this time-point (NICE TSD16). However, based on the CS evidence (page 82), the ERG understands that models were adjusted for baseline smoking status and ECOG, not for variables that were collected at the progression time point. Thus, the ERG questions the appropriateness of this model for the PROFILE 1014 trial. This method also assumes that there is no time dependant confounding between the time of disease progression and time of switching. The ERG queried the apparent long delay between DP and crossover in some patients. In their clarification response the company stated that although the range was wide (1 to 39 weeks, the median was 4 weeks and the data were highly skewed such that 75% of patients had crossed over by 7 weeks.

The ERG noted that IPCW was not an option for crossover adjustment in the PROFILE1014 trial. The CS stated that this method was not considered as an appropriate analysis after consultation with the EMA. However, the ERG believes that although the IPCW method makes "no unmeasured confounders" assumption and estimates could be biased if almost all patients switch or very few

events are observed in patients who do not switch, there is no indication that this method would perform worse than the RPSFTM and IPE methods in the PROFILE trial.

In summary, none of the methods used in the CS stand out as being the most relevant option. However, of the three methods the two-stage method could be the best available as the assumption of common treatment effect made when utilising the RPSFT model and the IPE method is an assumption which is highly unlikely to hold. In addition, it should be noted that patients received a variety of treatments (more than 10 different drugs) after progression of disease, that is, the switching was not only on to crizotinib or pemetrexed + platinum therapy. Thus, ERG recognises that it is very likely that bias in the risk estimates will not be eliminated whatever crossover adjustment method is used.

The CS highlights how the results from all of the cross-over adjustment methods are fairly consistent, with the mean hazard ratios calculated from the nine methods ranging from 0.571 to 0.674; falling substantially below the unadjusted value of 0.821. The CS states that this provides evidence that the primary OS analysis underestimates the effect of crizotinib, and the narrow range of results reduces the uncertainty around the counter-factual survival estimates of patients on chemotherapy. Although these points may be valid several factors must be taken into consideration. Firstly, although the estimates are fairly consistent, every single method has its limitations and each result has substantial uncertainty associated with it. The confidence intervals around each of the cross-over adjusted hazard ratios are wide, with five of the nine methods producing upper confidence interval values of greater than or equal to one. Secondly, although the values are fairly consistent, the overall survival data which is being adjusted for cross-over is immature, so it is difficult to state how much can be inferred from the results as the data is limited.

Table 11 Summary of methods for adjusting for crossover

Adjustment for crossover method	Outline of method	Main assumptions
Rank preserving structural failure time model (RPSFTM)	Uses a counterfactual framework to estimate the causal effect of treatment. The method uses data on the time people spent on each of the treatment arms, an estimate of treatment effect and an acceleration factor associated with the experimental treatment to estimate counter-factual survival times.	The model assumes that there is a "common treatment effect" meaning that the impact of the treatment is the same regardless of when it was initiated
Iterative parameter estimation (IPE)	An extension of the RPSFT model, making use of the same accelerated failure time model. but a parametric failure time model is fitted to the ITT data in order to calculate an initial estimate of treatment effect. Failure times of switching patients are re-estimated and this process is repeated until the new estimate is close to the previous value and they converge.	it assumes common treatment effect, but because it makes use of a parametric failure time model the method assumes that survival times follow a parametric distribution - relies on finding suitable parametric models (and how suitable these are is difficult to assess)
Two-stage model	Treats the trial as a randomised study until disease progression takes place,	Assumes there are no unmeasured confounders. Parametric assumptions

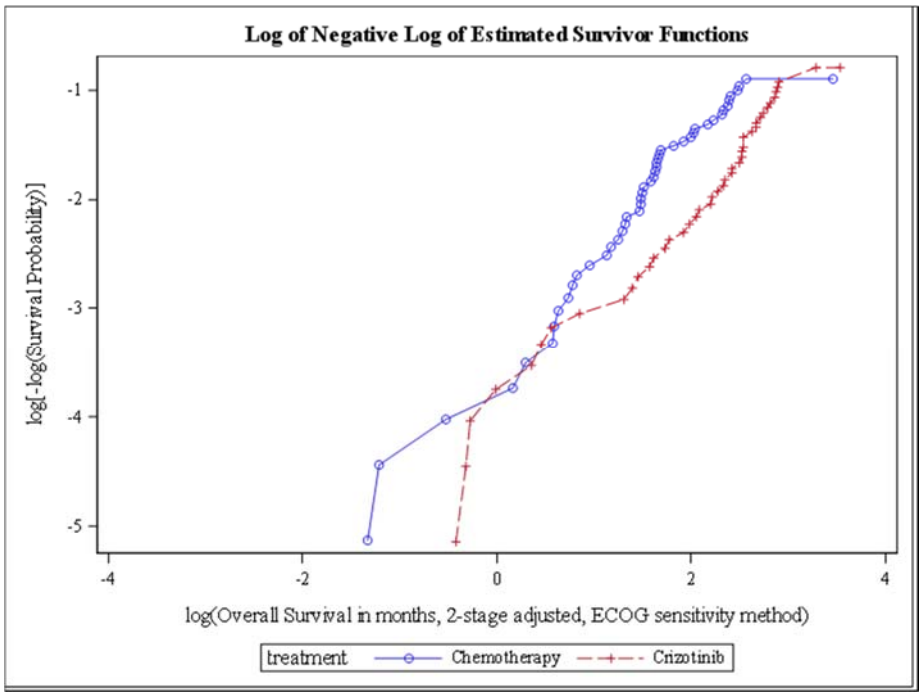
	and as an observational study thereafter (as randomisation is broken). A treatment effect is estimated for those who switch and the survival times for those patients are adjusted accordingly. This then allows for a separate treatment effect to be estimated for those who do not switch. Patients are adjusted for potential confounders, (REF).	which need to be made when choosing which parametric accelerated failure time model is used to estimate the treatment effect in switchers
Inverse probability of censoring weights method (IPCW)	This methods censors patients at the time they switch and weights the remaining observations on covariate values to estimate patients probabilities of being censored in order to correct for selection bias. As the switching rule was based on whether patients had progressed as judged by IRR then this can be considered a predictor which determines crossover.	There are no unmeasured confounders. There must be sufficient numbers of patients under follow-up at all time. Tthe predictors of crossover cannot completely determine who switches to another treatment arm

Assumption of Proportional Hazards

In order to analyse OS data there are two main approaches. One involves fitting separate parametric models for each treatment arm, and the other involves fitting one parametric model to the data and including the treatment group as a covariate in the analysis. The latter approach relies on the assumption of Cox proportional hazards which assumes that there is a common treatment effect. One hazard ratio therefore applies to the entire period under consideration, assuming that the treatment effect is proportional over time, and therefore the survival curves fitted to each treatment group have a similar shape [36].

The base-case analysis in the CS makes use of the proportional hazards assumption, justifying this by inspecting the log-cumulative hazard plots for OS. This plots the log of the hazard ratio against the log of time as shown below in Figure 3. In order for the assumption to hold the plots must remain largely parallel to each other to demonstrate that the hazard ratio is reasonably constant over time. The plot for OS reveals that the curves diverge quite significantly, and remain parallel for only a small section of the data, bringing into question the feasibility of the assumption.

Figure 3: Log-cumulative hazard plot (Overall Survival)



When asked to further justify the assumption of proportional hazards the company cited a UK clinical expert who stated that in his opinion it was clinically reasonable to assume proportional hazards. He went on to say that the only reason that a patient cohort might not follow proportionally extrapolated survival curves was because of crossover between the trial arms. However, no clear clinical rationale was provided to help explain why it is clinically reasonable to make the assumption of proportional hazards. As the OS data has been adjusted for crossover it is also unclear how the issues of treatment switching can be used to explain why a patient group might not follow proportionally extrapolated survival curves.

There are clear differences in the way the two treatments are administered which may help in explaining why the hazard ratios may change over time. Crizotinib is taken twice daily until it is judged that there is no more capacity to benefit from the treatment, whereas chemotherapy is administered in 4 to 6 cycles, after which treatment is ended. Therefore, the observed divergence in the log-cumulative hazard plots could be attributed to the fact that chemotherapy patients receive diminishing benefits from the treatment once it has ended, while crizotinib patients can continue to take treatment for a much longer period of time. In their clarification response the company presented results showing that the PROFILE 1014 trial patients received chemotherapy for a mean of 3.9 months. On the other hand patients in the crizotinib arm received treatment for a mean of crizotinib for a mean of 23.7 months (See section 5.2.8.1 for the calculation of this value). Therefore, due to the differing ways in which the treatments are administered, and the respective durations of the treatments the assumption of common treatment effect and therefore proportional hazards seems unfeasible.

The NICE DSU Technical Support Document 14[36] outlines the circumstances under which it is reasonable to make use of proportional hazard modelling. It states that the Cox proportional hazards method is only likely to be reasonable when the majority of events in the trial have taken place. This is because unless the data is near completion them the method will not produce accurate estimates of mean survival, and will not reflect the full distribution of expected survival times, as these are affected by omitting more extreme extrapolated data points. At the time of the most recent data-cut for PROFILE 1014 the OS data are very immature, with the majority of patients still alive at the time of the analysis (See Section 4.2.2.3). This brings into question the completeness of the data and therefore whether proportional hazard modelling will produce accurate survival estimates.

The document also states that when patient-level data is available, as it is for this analysis, it is not necessary to rely on the proportional hazards assumption, as separate parametric models can be fitted which require fewer assumptions.

In summary, there are good reasons to question the assumptions required for proportional hazard modelling. The ERG believes that fitting separate parametric models is likely to produce more reliable estimates of PFS and OS, and explores this scenario in section 6.

Follow-on therapies and impact on overall survival

The present appraisal requires an evaluation of the effect of first-line therapies and therefore it is important that the outcomes generated from the trial reflect the impact of these first-line therapies only, and not follow-up treatments. However, there are imbalances in the two arms of the trial in the numbers who went onto receive follow-up therapy, and also in the therapies that patients went on to receive (Table 12).

Table 12 Follow-on systemic therapies in PROFILE 1014

	Crizotinib n = 89 (%)	Chemotherapy, n = 132 (%)
Number (%) of subjects with systemic therapy at follow-up	[redacted]	[redacted]
Total number of regimens started		
1 regimen	[redacted]	[redacted]
2 regimens	[redacted]	[redacted]
≥ 3 regimens	[redacted]	[redacted]
Systemic follow-up therapies		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

These post-progression therapies will have impacted on OS, meaning that the estimates for OS may not be reflective of the true impact of crizotinib, but instead a combination of crizotinib and other treatments and the relative treatment effect of crizotinib vs chemotherapy as first-line treatments is uncertain.

The open label nature of the trial and the facility in the trial protocol to allow those randomised to crizotinib to remain on crizotinib after RECIST-defined disease progression has exacerbated the issue around follow-on therapies. This continuation of crizotinib until there was no symptomatic benefit, which occurred in a high proportion of patients, is not considered to be second-line therapy. In contrast, patients randomised to chemotherapy could cross-over to crizotinib at this point, and the

majority did so. Thus the trial design facilitated a delay in the start of second-line therapy in the crizotinib arm compared to that in the chemotherapy arm.

Although cross-over adjustment was conducted for those who switched from chemotherapy to crizotinib, cross-over adjustment was not conducted for those in the crizotinib arm who went on to receive other therapies. Therefore, the cross-over adjusted analysis is likely to adjust the ITT estimate, which *under-estimated* the effect of crizotinib, to a value which *over-estimates* the effect of crizotinib instead.

An alternative approach to investigating the first-line therapies only would be to focus instead on the entire treatment pathway that patients receive. The ITT analysis would then be a fairly good reflection of what happens in UK practice as many patients treated with first line chemotherapy have gone on to receive crizotinib second-line via the CDF. However, the PROFILE 1014 study does not provide a completely accurate representation of UK practice as many of the second-line treatments provided in the trial are not routinely offered in UK practice.

Low mortality rate in the chemotherapy arm

Unadjusted Kaplan-Meier estimates of 1-year and 18-month probabilities of survival with chemotherapy were 79% (95% CI, 71 to 84) and [redacted], respectively (they were. 84% (95% CI, 77 to 89) and [redacted], respectively, with crizotinib). This low mortality rate on chemotherapy in PROFILE 1014 could be assumed to be due to the high rates of crossover to crizotinib at disease progression. However, the ERG notes that, as clear from Figures 10 and 11 in theCS), these estimates are still around 65% to 75% at 1 year and 65% to 70% at 18 months depending on method of adjustment. These estimates can be compared to those reported in other trials of pemtetrexed + platinum in advanced non-squamous NSCLC: for pemetrexed + cisplatin 1 year survival was 50% and 18 month survival was 35%;[1] for pemetrexed + carboplatin 1 year survival was 40% and 18 month survival was 20%.[2] This indirect comparison across different trials raises questions regarding possible explanations for the large differences between the mortality rate for pemetrexed + platinum in the PROFILE trial and the other trials. One certain difference is the population: does this difference indicate that ALK-positive patients have a better prognosis than the broader non-squamous population? Note the difference cannot be attributed to ECOG status as patients in the pemetrexed + cisplatin cohort were of ECOG status 0 and 1 as in PROFILE 1014. If ALK-positive patients have a better prognosis than the broader non-squamous population this brings into question the validity of the current estimates of life expectancy of patients with advanced non-squamous ALK-positive NSCLC: how realistic is an estimate of around 15 months?

4.2.2.4 Patient reported outcomes

A variety of different measures were utilised to measure HRQoL including the EORTC QLQ-C30 and the EORTC QLQ LC-13 (which is a lung cancer-specific module). Completion rates of the EORTC QLQ questionnaire was high: [redacted] for crizotinib patients and [redacted] of chemotherapy patients. From EORTC QLQ-C30 crizotinib produced a small (not clinically significant) improvement from baseline in global HRQoL; compared with the deterioration on chemotherapy this was statistically significant (P<0.001). Similar results were seen for all the individual domains of functioning: physical, social, role, cognitive and emotional.

Crizotinib reduced the symptoms of fatigue, pain, dyspnoea, insomnia, appetite loss, coughing, alopecia, chest pain, arm or shoulder pain and other pain, significantly more than did chemotherapy. Crizotinib did cause significantly greater worsening of nausea and vomiting, diarrhoea and peripheral neuropathy. Further details are given in Figures 12, 13 and 14 in the CS.

Data on EQ-5D were also collected in PROFILE 1014. Completion rates of all questions of the EQ-5D questionnaire from evaluable patients ranged from [redacted] for crizotinib (over the first 30 of a total of 50 cycles) and [redacted] for chemotherapy (over the maximum 6 cycles). All but eight patients in the crizotinib group ([redacted]) and seven patients in the chemotherapy group ([redacted]) from the ITT population completed all questions of the EQ-5D questionnaire at baseline. The CS reports that whereas no statistically significant changes from baseline where observed in the chemotherapy group over 6 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. In a mixed-model analysis, compared to chemotherapy crizotinib was associated with a statistically significant greater improvement in EQ-5D VAS scores ([redacted]) and the overall EQ-5D index score (utility) ([redacted]); improvements from baseline in EQ-5D index scores were also statistically significantly greater in the crizotinib group relative to chemotherapy ([redacted]). In the analysis EQ-5D scores were controlled for baseline differences.

EQ-5D data submitted by the company in their clarification responses showed that mean EQ-5D Health Index Score in the crizotinib arm was [redacted] at baseline and increased to [redacted] at the start of Cycle 2 and remained above that at all later follow-up points. In the chemotherapy arm baseline mean EQ-5D was [redacted] and increased to a maximum of [redacted] over 6 cycles. The ERG notes that as the trial was international in its design with only 9 of the 247 study centres based in the UK, there may be issues of generalisability of the quality of life scores when assuming these scores apply to the UK population.

4.2.3 Non-RCT evidence

Two non-randomised studies were included in the submission: PROFILE 1001 and Davis et al. 2005. The CS presented a quality assessment of these two non-RCTs using the Downs and Black checklist,[33] with assessments of reporting, external validity, internal validity, internal validity-confounding, and power of the study. The CS indicated that with a maximum of 27 points available, each of the trials scored 15 (55.6%), (Appendix 9 of the CS). Given that the trials are non-randomised and unblinded studies, the ERG believes that appropriate quality assessment tool has been used. However, based on the scores, the ERG recognises that there could be a high risk of bias in these studies.

PROFILE 1001

PROFILE 1001 was a single arm, open-label, Phase I study. The study commenced in August 2008 and aimed to determine toxic effects and maximum tolerated dose of crizotinib and to assess the tolerability and efficacy of crizotinib in patients with both previously treated, and untreated ALK-positive stage III or IV NSCLC. Patient inclusion criteria were: Aged ≥18 years old; Measurable ALK-positive NSCLC (as assessed by break-apart FISH assay); Stage III or IV disease; and adequate renal function and ECOG performance status of 0 or 1 (or 2 on agreement by investigator and sponsor). Full inclusion/exclusion criteria are given in the CS Table 27).

The dosing was comparable to the PROFILE 1014 trial, with patients receiving 250mg of crizotinib twice daily.

This study is subject to a number of limitations:

- Only 24 patients (16%) received crizotinib in the first-line setting, raising issues of the generalisability of the study results to the first-line setting.
- The study also included a small number of patients with squamous NSCLC.
- The study was conducted in 8 centres: six in the USA and one each in Australia and South Korea, meaning it is unclear how representative the patient population of the UK population of interest.
- Due to its open label single-arm design there was no blinding of either the intervention or the outcome assessor, making the study at a high risk of bias.
- The inclusion and exclusion criteria PROFILE 1001 are given in Table 27 of the CS.

The patient characteristics for the PROFILE 1001 trial are given in Table 13.

Table 13 Patient characteristics for the PROFILE 1001 trial

Characteristic	PROFILE 1001 Patients receiving crizotinib (n=149)*
Age – years Median (range)	52 (21–86)
Sex – n (%)	
Male	73 (49)
Female	76 (51)
Ethnic origin – n (%)	
White	95 (64)
Asian	41 (28)
Other	13 (9)
Smoking status – n (%)	
Never	106 (71)
Former	42 (28)
Present	1 (<1)
Histological findings – n (%)	
Adenocarcinoma	144 (97)
Large-cell carcinoma	1 (<1)
Squamous-cell carcinoma	2 (1)
Other	2 (1)
ECOG performance status – n (%)	
0	56 (38)
1	75 (50)
≥2	18 (12)
Number of previous treatment regimens for advanced or metastatic disease – n (%)	
0	24 (16)
1	47 (32)
2	31 (21)
3	19 (13)
≥4	28 (19)

***** Baseline characteristics for PROFILE 1001 are presented for the entire study population, including patients who received crizotinib as a second or subsequent line of therapy. Twenty-four patients received crizotinib in the first-line setting.

Adapted from CS Table 29

PROFILE 1001 found that at the latest data cut-off point (median follow-up of 16.3 months) median PFS for patients who had received first line crizotinib (n=24) was found to be 18.3 months (95% CI, 8.3 to 'not reached'). This estimate for PFS is larger than that of PROFILE 1014 (median of 10.9 months), but it should be noted that the results from such a small single-arm trial cannot be considered reliable. The ORR for those who received first-line crizotinib was 63.6% (95% CI, 40.7 to 80.28). This is lower than that in PROFILE 1014 (ORR 74% (95%, 67 to 81).

Davis et al. 2005

The study published as Davis et al. 2005 was a retrospective cohort study of patients with confirmed ALK-positive NSCLC and involved reviewing medical charts of patients receiving crizotinib in a first-line and second-line setting in clinical practice in the US and Canada. The aim of the study was to assess treatment patterns and clinical outcomes of patients with ALK-positive, advanced NSCLC treated with crizotinib in clinical practice. Data was collected on ORR, PFS, OS and treatment patterns including dose changes and reasons for treatment discontinuation.

For the purposes of informing an evaluation of crizotinib as a first-line treatment this study is subject to a number of limitations:

- Around a third (35%) of the study patients had received second-line crizotinib therapy (35%) - the outcomes of these patients may differ from those treated with first-line therapy.
- As the study was retrospective it makes it more prone to bias: selection of patients; response criteria were not dictated by a protocol; and assessments were not done on a uniform scale. The duration of treatment that patients received was not reported.
- The patients in the study were a "convenience" sample as the records were provided from physicians who were willing to participate in the study. As the physicians were not chosen at random, there is potential for selection bias as physicians who have results pointing in one direction may have been more willing to provide data than those who had found different results.
- Data were limited to information available in the patients' medical records which the physicians had access to.
- The study did not provide information on key baseline patient characteristics such as the presence of brain metastases.

The patient characteristics for the Davis et al. 2005 study are given in Table 14, which also compares them to the population in PROFILE1014 and to a UK Cohort details of which were provided by the company in their clarification response to support the generalisability of the Davis cohort to the UK. The ERG notes that the details provided of this cohort are minimal: the age profile is more similar to Davis et al. than the PROFILE trials but other points of comparison (ECOG status, presence of brain metasteses, smoking status, line of therapy) cannot be made. Overall, whilst as a sample of 'real world' data the Davis et al.2005 study may be expected to better reflect the patients to be found in clinical practice than those included in PROFILE 1014 or PROFILE 1001 there is not compelling evidence to suggest the Davis cohort better reflects patients in UK practice.

Table 14: Baseline characteristics of participants in PROFILE 1001, Davis *et al.* (2015), PROFILE 1014 and UK Cohort

			Crizotinib (n=172)	Chemotherapy (n=171)	
Country		**USA**	**International**		**UK**
Age – years					
Median (range)	52 (21–86)	[redacted]	52 (22–76)	54 (19–78)	61
Sex – n (%)					
Male	73 (49)	93 (68)	68 (40)	63 (37)	[redacted]
Female	76 (51)	[redacted]			[redacted]
Ethnic origin – n (%)					
White	95 (64)	103 (75)	91 (53)	85 (50)	[redacted]
Asian	41 (28)	17 (12)†	77 (45)	80 (47)	
Other	13 (9)	16 (12)‡	4 (2)	6 (4)	
Smoking status – n (%)					**NR**
Never	106 (71)	51 (37)	106 (62)	112 (65)	
Former	42 (28)	[redacted]	56 (33)	54 (32)	
Present	1 (<1)	[redacted]	10 (6)	5 (3)	
Histological findings – n (%)					
Adenocarcinoma	144 (97)	[redacted]	161 (94)	161 (94)	
Large-cell carcinoma	1 (<1)	[redacted]	11 (6)	10 (6)	
Squamous-cell carcinoma	2 (1)	[redacted]			
Other	2 (1)	[redacted]			
ECOG performance status – n (%)					**NR**
0	56 (38)	[redacted]	161 (94)	163 (95)	
1	75 (50)	[redacted]			
≥2	18 (12)	30 (22)	10 (6)	8 (5)	
Number of previous treatment regimens for advanced or metastatic disease – n (%)					NR
0	24 (16)	137 (100)	172 (100)	171 (100)	
1	47 (32)	-			
2	31 (21)	-			
3	19 (13)	-			
≥4	28 (19)	-			
Brain metastases present – no. (%)	NR	NR	45 (26)	47 (27)	NR

The results from the Davis et al. 2005 observational study are presented in Table 15; the ORR was 69%, with median PFS of [redacted] and median OS of [redacted]. The CS presented a comparison of key results from PROFILE 1014 and Davis et al. 2015 as shown in Table

15. The findings for median PFS, ORR and 1-year survival rate are similar, with slightly worse outcomes in the Davis et al. 2015 being attributed to the differing patient characteristics in the studies.

In summary, the non-RCT evidence included in the CS are supportive of the results from the PROFILE 1014 trial, but do not resolve the major uncertainties regarding the overall survival benefit with crizotinib relative to current best practice.

Table 15: Clinical effectiveness results from Davis *et al.* (2015) and PROFILE 1014 – in patients who received first-line crizotinib

Outcomes	PROFILE 1014 (n=172)	Davis *et al.* (2015) (n=137)
Median PFS, months (95% CI)	10.9 (8.3 to 13.9)	[redacted]
ORR, % (95% CI)	74 (67–81)	69 (N/A)
Median OS, years (95% CI)	Not reached	[redacted]
1-year survival rate, % (95% CI)†	84 (77 to 89)	85 (79 to 91)
2-year survival rate, % (95% CI)†	Not reported	47 (35 to 60)

† Based on Kaplan-Meier estimates

4.3 Adverse events

Adverse events data in the CS were derived from three sources: PROFILE 1014, PROFILE 1001, and a pooled safety analysis from 1669 patients who received crizotinib across four clinical trials (PROFILE 1014 and 1001 which investigate crizotinib as a first-line therapy, and PROFILE 1005 and 1007 which investigate crizotinib as a second-line therapy).

4.3.1 PROFILE 1014 trial adverse events

In PROFILE 1014 the number of patients suffering a treatment related AE is similar between randomised groups: 98.2% for crizotinib and 92.9% for chemotherapy, and for grade 3 and 4 adverse events, 35.1% in the crizotinib group vs 39.1% in the chemotherapy group. AEs from any cause associated with permanent discontinuation of study treatment occurred in 12% and 14% in the crizotinib and chemotherapy groups respectively (see Table 16).

Table 16 Treatment-emergent adverse events in the AT population in PROFILE 1014

Adverse event, No. of patients (%)*	Crizotinib (n=171)*		Chemotherapy† (n=172)*	
	All causality	Treatment-related	All causality	Treatment-related
Number of patients:‡				
With AEs	[redacted]	[redacted]	[redacted]	[redacted]
With SAEs§	[redacted]	[redacted]	[redacted]	[redacted]
With Grade 3 or 4 AEs	[redacted]	[redacted]	[redacted]	[redacted]
With Grade 5 AEs	[redacted]	[redacted]	[redacted]	[redacted]
With AEs associated with:				
Permanent discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Temporary discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

* No. of patients in the AT population; † Only events that occurred before crossover to crizotinib are included
‡ Patients are only counted once per treatment in each row; § According to investigator assessment; Incidence of AEs were unadjusted for duration of treatment

The most frequently reported AEs in the crizotinib group compared to the chemotherapy group were vision disorders (71% vs 9%), diarrhoea (61% vs 13%) and oedema (49% vs 12%). Conversely the most reported AEs for chemotherapy compared to those on crizotinib were fatigue (38% vs 29%), anaemia (32% vs 9%) and neutropenia (30% vs 21%). The main grade 3 and 4 adverse event reported for crizotinib compared to chemotherapy were elevated levels of aminotransferases (14% vs 2%) and conversely the main ones for chemotherapy were neutropenia (15% vs 11%), anaemia (9% vs 0%) and thrombocytopenia (7% vs 0%).

In PROFILE 1014 patients in the crizotinib group stayed on treatment for a median duration of 10.9 months, and those in the chemotherapy group a median of 4.1 months. Patients randomised to crizotinib received a median of 16 cycles (range 1-50) and those randomised to chemotherapy received a median o 6 cycles (range 1 to 6); the ERG notes that treatment with pemetrexed + platinum is usually limited to 4 cycles: it is possible that the adverse effects profile for chemotherapy presented from this trial overestimates the adverse events that would be experienced in clinical practice.

4.3.2 Pooled analysis of safety data

A pooled safety analysis was also conducted which grouped together results from PROFILE's 1014 and 1001 which investigate crizotinib as a first-line therapy, and PROFILE's 1005 and 1007 which investigate crizotinib as a second-line therapy. The CS reported that the pooled analysis (n= 1,699) showed that the safety profile was relatively consistent across all trials and lines of therapy.[39] From

the pooled analysis the most frequently reported AEs experienced on crizotinib were vision disorders (62%), nausea (57%), and diarrhoea (54%). The complete list by system organ class is given in the CS (Table 37).

In summary, the adverse event profile of crizotinib presents a clinically significant, but as determined by the CHMP a manageable, burden to patients.[39] Given the relatively short-term nature of the evidence base to date the possibility of other as yet unknown adverse effects of crizotinib cannot be discounted.

4.4 Summary of clinical effectiveness critique

The clinical evidence presented addressed the NICE scope but for a slightly restricted population: patients with non-squamous ALK-positive disease.

The systematic review conducted used appropriate methods and included all relevant randomised trials (PROFILE 1014). The submission also included supporting evidence from a single arm trial (PROFILE 1001) and an uncontrolled 'real life' cohort (Davis et al. 2015).

The patient characteristics of the populations in these studies were, in general, generalisable to those in UK clinical practice. Patients in Davis were slightly older and more were/had been smokers than those in the trials. Comparison of the patient characteristics in Davis to those in a UK cohort study suggests that the Davis population may slightly better reflect the UK population than does PROFILE 1014, though there is little information to support this.

PROFILE 1014 was a good quality trial but it was open label and so at high risk of bias. Despite the use of objective criteria for disease progression, many patients in the crizotinib arm remained on crizotinib after PD until symptomatic progression, whilst in contrast patients in the chemotherapy arm crossed at PD to crizotinib therapy.

The results showed a statistically significant benefit for crizotinib in term s of PFS: an increase in median PFS of 3.9 months compared to chemotherapy group and a significantly reduced risk of progression or death (HR 0.45 (95% CI, 0.35 to 0.60; P<0.001). However at the pre-specified data cut analysed not all patients had completed the trial, with 69.2% of patients randomised to crizotinib continuing in the trial. PFS results from a later data cut will provide a more complete picture of the PFS benefits with crizotinib.

Crizotinib produced a statistically significant higher objective response rate, a statistically significant shorter time to response, and a statistically significant longer duration of response than pemetrexed + platinum chemotherapy.

Overall survival data were highly uncertain due primarily to the immaturity of the data (at data cut off only 26% of deaths had occurred). A later more mature data set is anticipated by late 2016/early 2017. In addition, there was a high level (70%) of crossover from the chemotherapy arm to crizotinib at disease progression. Whilst adjustment for crossover in the analysis was performed it is unclear which method is most appropriate: all produced similar hazard ratios but not all were statistically significant. Finally, follow-on therapy administered after progressive disease varied greatly between the treatment arms, in the numbers who went onto receive follow-up therapy, and also in the therapies that patients went on to receive. This imbalance will have confounded to an unknown degree the treatment comparison for overall survival.

The non-RCT evidence included in the CS are supportive of the results from the PROFILE 1014 trial, but do not resolve the major uncertainties regarding the overall survival benefit with crizotinib relative to current best practice.

Crizotinib had statistically significant benefits in terms of HRQoL measures including EORTC QLQ-C30 and the EORTC QLQ LC-13 (which is a lung cancer-specific module), and EQ-5D, which is the measure preferred by NICE.

The adverse event profile of crizotinib presents a clinically significant, but as determined by the CHMP a manageable, burden to patients. [39] The most frequently reported adverse events experienced on crizotinib are vision disorders (62%), nausea (57%), and diarrhoea (54%). Given the relatively short-term nature of the evidence base to date the possibility of other as yet unknown adverse effects of crizotinib cannot be discounted.

4.5 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison and/or multiple treatment comparison was included in the CS.

4.6 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable

4.7 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness undertaken by the ERG

4.8 Conclusions of the clinical effectiveness section

The clinical evidence was based on an appropriately conducted systematic review, and derived primarily from a single well conducted RCT that compared crizotinib to the current standard of care in UK clinical practice, pemterexed + platinum based therapy (except where access to pemetrexed

maintenance therapy is possible). However, the trial was flawed by an open–label design and the facility for different treatment options post-progression.

Objective evidence of a clear treatment benefit in terms of tumour response and a statistically significant benefit in terms of PFS were presented, the data being based on objective RECIST-defined criteria and IRR assessment. However, although a benefit relative to chemotherapy in terms of PFS seems certain, the size and duration of the relative effect is still uncertain. Results from a later more complete data cut are required; these are anticipated in early 2017.

Crizotinib appears to perform better in terms of HRQoL and has a manageable adverse effects profile.

The results for OS are highly uncertain due to the open label design of the trial, the imbalance in post-progression treatment options, the high crossover rates, the method of analysis, and the immaturity of the overall survival data. Whilst mature data are anticipated in early 2017, adjustments for the high levels of crossover from chemotherapy to crizotinib at disease progression and the imbalance in the follow-on therapies will still be required, and results are likely to remain uncertain.

The non-RCT evidence included in the CS are supportive of the results from the PROFILE 1014 trial, but do not resolve the major uncertainties regarding the overall survival benefit with crizotinib relative to current best practice.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided to the ERG following points for clarification. The submission was subject to a critical review on the basis of the company's report and direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to address some remaining uncertainties.

The company's initial economic submission included:

- A description of the search strategy and databases used in the literature review of cost-effectiveness studies (CS, pg. 118 to120), quality-of-life studies (CS, pg. 140 to 142) and resource use studies (CS, pg. 151 to153).
- A report on the *de novo* economic evaluation conducted by the manufacturer. The report outlined the intervention; comparators and patient population; the modelling methodology; the resource components and unit costs; data input sources and assumptions; the base-case results; and sensitivity analysis (CS, pg.122 to 187).
- The company's electronic Excel-based *de novo* model.
- A Patient Access Scheme (PAS) submission describing a price reduction that was subject to approval by the Department of Health was also made available to the ERG. This included a revised cost-effectiveness analysis reporting an ICER using the PAS price in the company's base-case analysis and some sensitivity and scenario analyses.

Following the points of clarification raised by the ERG, a number of addenda were submitted by the company. These included:

- A descriptive reply to the ERG's points for clarification, as well as appendices with additional data requested by the ERG.
- An updated excel based model, which corrected a number of errors identified by the ERG.

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify relevant cost-effectiveness studies for the first-line treatment of advanced NSCLC. The ERG's critique of the systematic review presented by company is given below.

5.1.1 Searches

The CS described the search strategies used to identify relevant cost-effectiveness studies for the first-line treatment of advanced or metastatic NSCLC. The search strategies were briefly described in the main body of the submission in Section 5.1.1 and full details were provided in Appendix 12.

The electronic databases MEDLINE, MEDLINE In Process Citations and Daily Update, EMBASE and EconLit were searched on 17th July 2015, through the Ovid interface. The NHS Economic Evaluation Database and the Health Technology Assessment database were searched on 3rd August 2015, via the Cochrane Library. To supplement the electronic database searches, the company searched the proceedings of six conferences from 2014-2015: American Society of Clinical Oncology (ASCO) Annual Meeting, European Society for Medical Oncology (ESMO) Congress, European Lung Cancer Conference (ELCC), World Conference on Lung Cancer (WCLC), International Society for Cost-effectiveness and Outcomes Research (ISPOR) Annual International Meeting and the ISPOR Annual European Congress. In addition, the National Institute for Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) were searched to identify economic models. The biographies of included articles (including systematic reviews and meta-analyses) were searched for any further relevant studies.

The methods used to identify cost-effectiveness studies were appropriate, with some minor issues noted below. The reporting of the searches was clear with sufficient detail to allow the searches to be reproduced. The databases searched, the service providers used, the date of the searches and complete strategies were all clearly reported. It would have been useful if the company had reported the date segments of each database searched.

The structure of the search strategies presented in Tables 94, 95 and 96 in Appendix 12 is appropriate to capture studies on cost-effectiveness for the advanced or metastatic NSCLC. The correct fields have been searched, the search lines have all been combined correctly and truncation and wildcards have been used appropriately.

Line 11 of the strategy in table 94, Appendix 12 for MEDLINE, MEDLINE in process and EMBASE includes a text word search for advanced or metastatic, however no corresponding subject headings have been used in the strategy. In particular, for EMBASE there are Emtree subject headings available that could have been used: advanced cancer/, metastasis/. The inclusion of these headings would have improved the comprehensiveness of this search.

5.1.2 Inclusion/exclusion criteria used for study selection

The objective of the cost-effectiveness review presented in the CS was twofold:

- To identify previous cost-effectiveness evaluations of crizotinib for first-line treatment of advanced or metastatic NSCLC, with the aim of informing the cost-effectiveness of crizotinib as a first-line treatment;
- To identify cost-effectiveness analyses of any first-line treatment of advanced or metastatic NSCLC, with the aim of informing the development of the presented *de novo* cost-effectiveness model.

The inclusion and exclusions criteria reflect these two objectives. Details of the inclusion and exclusion criteria used for the selection of cost-effectiveness studies can be found on page pg. 119 of the CS, but in brief were as follows:

- **Population:** Individuals with advanced/metastatic NSCLC (regardless of ALK status);
- **Intervention/comparators:** Any pharmacological treatment evaluated as a first-line therapy;
- **Geographic restrictions:** For economic evaluations of crizotinib any country and a UK setting for other interventions;
- **Outcomes:** Costs, life years, QALYs, Incremental costs and QAYs, ICERs;
- **Study designs:** Economic evaluations of the following type: cost-effectiveness, cost utility, cost-benefit, cost-minimisation and cost-consequence;
- **Publication type:** all study types except for comments, editorials and letters and non-systematic reviews/narrative reviews;
- **Other restrictions:** Human studies published in English.

The ERG considers that the inclusion/exclusion criteria used were largely reasonable. The exclusion of non-English studies may, however, have led to some studies being missed, though the ERG considers this unlikely. Furthermore, the criteria relating to outcomes did not include the relevant outcomes net-benefit/net-monetary-benefit. These outcomes are, however, rarely if ever reported in the absence of other measures of cost-effectiveness such as ICERs. It is therefore unlikely that this would lead to any studies not being included.

5.1.3 Studies included and excluded in the cost effectiveness review

In total 20 records were included in the cost effectiveness review. According to the PRISMA flow chart presented in the CS 10 of these were UK evaluations of the cost-effectiveness of first-line therapies for the treatment of advanced or metastatic NSCLC, 5 were systematic literature reviews, 4 were non-UK economic evaluations of crizotinib and 1 was a non-UK economic evaluation of ceritinib. No UK evaluations of the cost-effectiveness of first-line crizotinib for the treatment of advanced or metastatic NSCLC were identified in the review. The details of the 10 UK evaluations of the first-line therapies for the treatment of advanced or metastatic NSCLC, were presented in an appendix to the main CS.

No details were presented of the other 10 records identified in the cost-effectiveness review within the CS. This included the all non-UK economic evaluations of crizotinib that were identified. No explanation or justification was made for the failure to report the details of these studies. At the PFC stage the ERG requested additional information on the 10 unlisted studies included in the cost-effectiveness review. These were provided by the company in their response along with brief data extraction from each study. These additional references are listed in Table 17 below.

Table 17 Additional studies included in the cost-effectiveness review

#	Citation	Reason for not presenting in Submission
1	Djalalov, Sandjar, et al. "Cost effectiveness of EML4-ALK fusion testing and first-line crizotinib treatment for patients with advanced ALK-positive non–small-cell lung cancer." *Journal of Clinical Oncology* 32.10 (2014): 1012-1019.	Not from a UK perspective
2	Gay-Molina, J. G., et al. "PCN73 Economic Analysis of the Use of Crizotinib, a Tyrosine Kinase ALK Inhibitor, in the Treatment of ALK-positive Non-Small Cell Lung Cancer in the Mexican Setting." *Value in Health* 15.7 (2012): A422.	Not from a UK perspective
3	Montero, Alberto J., and Gilberto Lopes. "Cost-effectiveness analysis of crizotinib in metastatic ALK plus non-small cell lung cancer (NSCLC)." J*ournal of Thoracic Oncology*. Vol. 8. 530 Walnut St, Philadelphia, pa 19106-3621 USA: Lippincott Williams & Wilkins, 2013.	Not from a UK perspective
4	Romanus, Dorothy, et al. "Cost-effectiveness of multiplexed predictive biomarker screening in non-small-cell lung cancer." *Journal of Thoracic Oncology* 10.4 (2015): 586-594.	Not from a UK perspective
5	Upadhyay, N., and N. Atreja. "Cost-Effectiveness of Eml4-Alk Gene Targeted First-Line Ceritinib Treatment Among Patients With Advanced Alk-Positive Non–Small Cell Lung Cancer." *Value in Health* 18.3 (2015): A203.	Not from a UK perspective
6	Bongers, Mathilda L., et al. "Cost Effectiveness of Treatment with New Agents in Advanced Non-Small-Cell Lung Cancer." *Pharmacoeconomics*30.1 (2012): 17-34.	Systematic Literature Review
7	Carlson, Josh J., David L. Veenstra, and Scott D. Ramsey. "Pharmacoeconomic evaluations in the treatment of non-small cell lung cancer." *Drugs* 68.8 (2008): 1105-1113.	Systematic Literature Review
8	Chouaid, Christos, et al. "Economics of treatments for non-small cell lung cancer." *Pharmacoeconomics* 27.2 (2009): 113-125.	Systematic Literature Review
9	Lange, Ansgar, et al. "A systematic review of the cost-effectiveness of targeted therapies for metastatic non-small cell lung cancer (NSCLC)."*BMC pulmonary medicine* 14.1 (2014): 1.	Systematic Literature Review
10	Zaim, Remziye, et al. "Molecular screening in advanced non-small cell lung cancer: a systematic review of cost-effectiveness analyses for first-line therapy." *Journal of Thoracic Oncology*. Vol. 8. 530 Walnut St, Philadelphia, PA 19106-3621 USA: Lippincott Williams & Wilkins, 2013.	Systematic Literature Review

The most relevant of the 10 studies listed in Table 18 are the four economic evaluations of crizotinib from a non-UK perspective and an economic evaluation of certanib an alternative ALK-positive targeted therapy, also taking a non-UK perspective. Of these five non-UK economic evaluations, three took a US societal perspective, one a Canadian societal perspective and one a Mexican societal perspective. Four of five studies used Markov structures of various designs and one used micro simulation approach. All five studies reported outcomes in terms of costs per QALY. Comparator treatment regimens varied considerably in the five studies, which included gemcitabine combination therapy, pemetrexed combination therapy and docetexal combination therapy. There was also considerable variation in second/third line therapies modelled which included pemetrexed, doctexal, erlotinib and BSC. Results from the four economic evaluations that assessed crizotinib are reported in Table 18.

Table 18 Results of Non-UK evaluations of crizotinib as first-treatment for ALK-positive NSCLC

	Technologies	Incremental costs (£)	Incremental QALYs	ICER *vs* baseline (QALYs)
Djalalov et al (2014)	Pemetrexed + cisplatin	---	---	---
	Crizotinib	CAD 95,043	0.379	CAD250,632
Gay-Molina et al (2012)	Pemetrexed + cisplatin	---	---	---
	Crizotinib	USD 51,108	1.28	USD 39,928
Romanus et al (2015)	Pemetrexed + cisplatin	---	---	---
	Crizotinib, erlotinib or Pemetrexed + cisplatin dependent on test status.	USD 4082	0.03	USD 136,000
Montero et al 2014	Docetexal	---	---	---
	Crizotinib	USD 77,138	0.14	USD 535,956

5.1.4 Conclusions of the cost effectiveness review

Currently there is a lack of evidence on the cost-effectiveness of crizotinib. The company's search did not identify any relevant economic assessments of crizotinib for the first-line treatment of advanced or metastatic NSCLC in the UK setting. A number of studies evaluating the cost-effective of crizotinib in non-UK settings were identified, however, given the significant variation in international practice non-of these studies is likely to be generalizable to the UK NHS setting. Given above the ERG therefore considers the cost-effectiveness analysis reported in the current submission to be the most relevant source of evidence to inform the decision problem.

5.2 ERG's summary and critique of manufacturer's submitted economic evaluation

An overall summary of the company's approach and signposts to the relevant sections in the manufacturer's submission are reported in Table 19 below:

Table 19 Summary of the company's economic evaluation (and signposts to CS)

	Approach	Source / Justification	Signpost (location in company submission)
Model	Cost-effectiveness (cost-utility) analysis using a semi-Markov model		Section 5.2.2 pg. 122 to 124
States and events	The model contains 3 states: progression free, progressed disease, and death.	Health states are aligned with two primary objectives of treatment (avoiding disease progression and prolonging life), are typical of metastatic oncology models and have been used in previous NICE STA's.	Section 5.2.2 pg. 122 to 124
Comparators	Crizotinib was compared to intravenous pemetrexed.	Consultation with treating UK clinical experts at an advisory board highlighted that the main comparator in clinical practice is pemetrexed in combination with either cisplatin or carboplatin and is offered to the majority of ALK-positive NSCLC patients. Third generation drugs in combination with platinum based chemotherapy was not used as a comparator as this would be very rarely be used in practice Single agent chemotherapy with a third-generation drug for patients with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate was not used as the number of patients eligible for this treatment is very small, around 1-2% of eligible population.	Section 5.2.4 pg. 124 to 125
Subgroups	No subgroup analysis was undertaken.	No subgroup analysis was undertaken as differences in relative efficacy of pre-specified sub groups were minimal.	Section 5.9 pg. 181
Treatment effectiveness	Clinical outcomes included were PFS and OS. PFS was extrapolated from PROFILE 1014 and adjusted using "real world" data from Davis et al (2014) to account for differences between the trial population and target population. OS for crizotinib was extrapolated from the PROFILE 1014 study and adjusted using "real world" data from Davis et al (2014) to account for differences between the trial population and target population. OS for pemetrexed extrapolated from the	PROFILE 1014 was the only RCT that compared crizortinib with pemetrexed in ALK-positive patients with advanced NSCLC. Adjustment for differences between the trial population and the target population were carried following consultation with clinical experts at the advisory board that a non-trial population was likely to less healthy than the patients enrolled in PROFILE 1014. The RPSFT methods of crossover adjustment was pre-specified in the PROFILE 1014 protocol. [redacted]	Section 4.7.2 pg. 78 to 82. Section 5.3 pg. 126 to 139

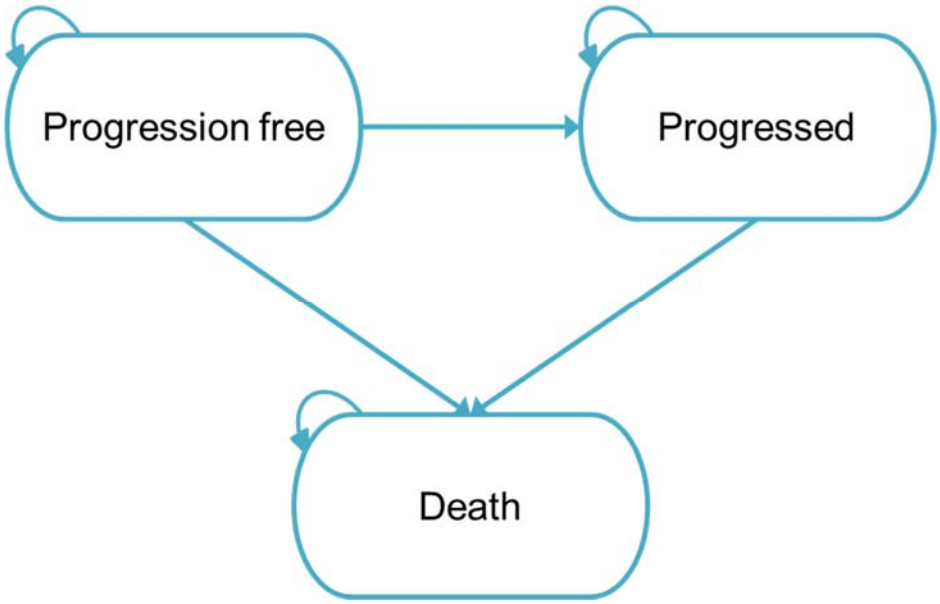
	PROFILE 1014 study and adjusted for crossover. The extrapolation was adjusted using "real world" data from Davis et al (2014) to account for differences between the trial population and target population.	[redacted]	
Adverse events	Adverse events were included if they were grade 3/4 and there was incidence greater than 5% in any of the treatment arms in PROFILE 1014. They were costed, but impact on utility was assumed to be already accounted for in the trial estimates.	Adverse event rates were taken from the PROFILE 1014 trial.	Section 5.5.7 pg. 163 to 165
Health related quality of life	Pre progression utilities were derived from EQ-5D data collected during the PROFILE 1014 trial and converted to QALYs. Utility while on second line therapy derived from EQ-5D data collected during the Profile 1007 trial. Utility while on third line therapy was derived from a published QoL study. A transitional utility was applied for the first cycle following progression from first-line to second line thereapy and from second line therapy to third line therapy. A sustained utility is applied for the duration of treatment beyond progression for patients receiving crizotinib.	EQ-5D utility data was collected pre progression during the PROFILE 1014 trial. Discussion with clinical expert advisory group highlighted that docetexal would be a common second line therapy and therefore utility for second line therapy were obtained from the PROFILE 1007 study. Discussion with a clinical expert advisory group highlighted that chemotherapy would not be given beyond second line and that therefore utility for patients beyond this point was assumed to be consistent with patients with progressive disease following second-line therapy. Transitional utilises were applied to reflect the gradual change in patients utility following progression. This assumption was validated by the clinical expert advisory group. The sustained utility was included to reflect the HRQoL benefits of lower toxicity of patients receiving post progression crizotinib compared with patients receiving docetexal.	Section 5.4 pg. 140 to 150
Resource utilisation and costs	Cost categories were as follows: ALK testing (FISH and IHC); drug acquisition, administration and monitoring; treatment of adverse effects; best supportive care; routine medical management: and terminal care	Drug acquisition costs for crizotinib and pemetrexed were sourced from MIMS. Drug acquisition costs for cisplatin, carboplatin and docetaxel were sourced from eMit. Unit costs for administration; monitoring; and, adverse events were taken from NHS reference costs (2014 to 2015). Terminal care costs were sourced from Georghiou and Bardsley (2014)[40]	Section 5.5 pg.151 to 167

		IHC testing costs were obtained from data on file and FISH costs were sourced from All Wales Genetic Laboratory.[5] Resource use items were obtained using expert opinion	
Discount rates	Costs (apart from ALK testing) and benefits were discounted at 3.5% per annum	In accordance with the NICE reference case.	Section 5.2.3 pg. 124
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic univariate probabilistic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 5.8.3 pg. 178 to 181

5.2.1 Model structure

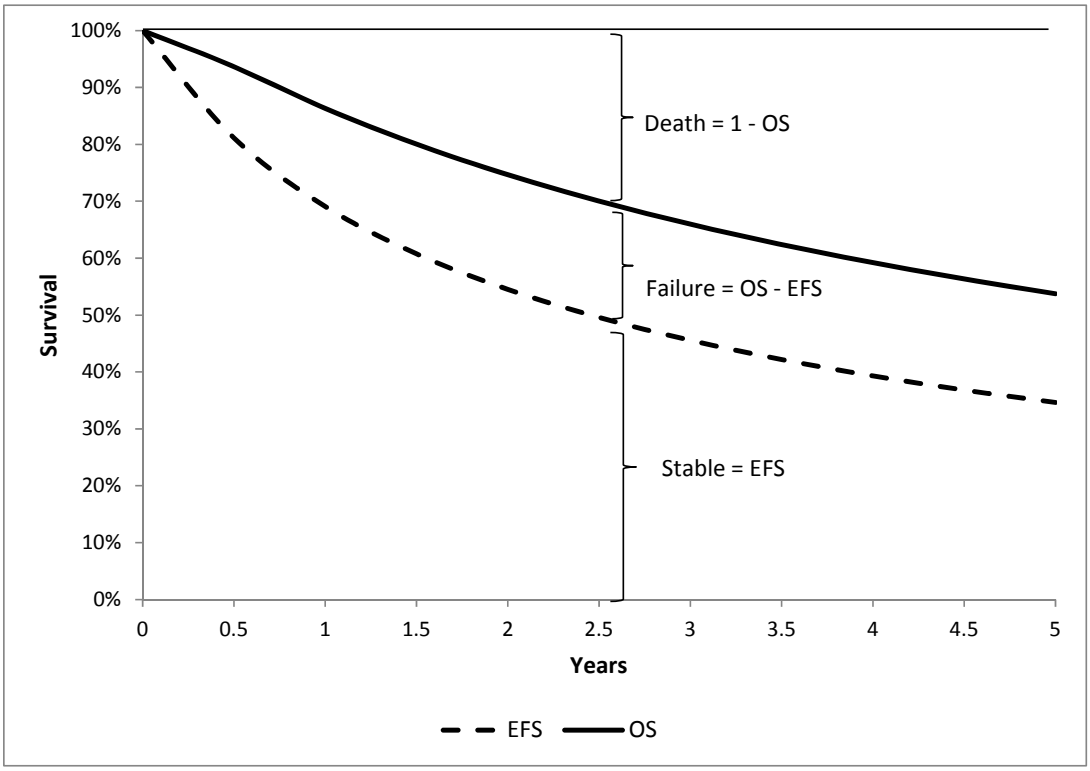
The *de novo* analysis presented by the manufacturer uses a three health state model which the manufacturer refers to as a semi-Markov "area under the curve" analysis (Figure 4). The three states are: (i) Progression free (PF); (ii) Progressed disease (PD); and (iii) Death, which is the absorbing state. Patients enter the model in the PF state and, at each 30 days cycle, they can remain in PF or transition through the model to PD or Death. No reversion from the PD state to the PF state is possible. All patients in the model were assumed to be ALK-positive, as testing was assumed to be performed prior to first-line treatment.

Figure 4: Model structure (Figure 17, Pg.122 in the CS)



Transitions between states are not explicitly incorporated into the analysis using probabilities but the proportion of patients in each state is determined by using estimates of survival over time. The proportion of patients in the progression-free state is based on estimates of PFS, while the proportion of patients in the death state is 1 minus the estimate of OS. The proportion of patients in the failure state is calculated as the difference between OS and PFS. Figure 5 represents a schematic diagram of a survival model.

Figure 5 Schematic diagram of a survival model



Once people progressed (as defined by RECIST) they are moved onto second-line treatment (docetaxel) and then third-line best supportive care before death. The model assumes that treatment beyond progression occurred for a duration in line with what was observed in the PROFILE 1014 trial.

Patients in the progression-free state have different utility values depending on which treatment they receive in line with the findings in PROFILE 1014. Patients in the crizotinib arm experience higher utility than patients receiving first-line pemetrexed. The CS justifies this on the grounds that that crizotinib reduces the symptoms of the disease more than chemotherapy and is associated with fewer, and less severe adverse events. A proportion of those from the crizotinib arm who progressed are assumed to continue on crizotinib for four cycles beyond progression. Crizotinib patients treated beyond progression are assumed to incur an additionality utility compared with untreated progressed patients. Patients in the model are also assumed to experience a transitional utility score for one cycle

when they move health states; this is to represent how a patient's utility does not immediately fall post-progression but declines gradually. This assumption was validated by the company's consultation with clinicians. The post-progression utility scores were assumed to be consistent across the two treatment arms, allowing the differences in modelled results to be reflective of the incremental differences in first-line therapy only.

5.2.2 The manufacturer's economic evaluation compared with the NICE reference case checklist

Table 20 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 20 Features of *de novo* analysis

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	The model complies with the NICE scope which defines the main comparator as pemetrexed combination therapy. Pemetrexed maintenance therapy and pemetrexed combination therapy followed by second-line crizotinib both used widely in practice are not considered as comparators in the model.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account.
Perspective on outcomes	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model follows a time horizon of 15 years. Less than 0.01% of patients are expected to survive beyond this period.
Synthesis of evidence on outcomes	Systematic review and mixed treatment comparison of relative effects.	Partly	No evidence synthesis was used to obtain health benefits estimates, as there were no other studies conducted in the ALK-positive population.
Measure of health effects	QALYs	Yes	Pre progression utilities were derived from EQ-5D data collected during the PROFILE 1014 trial and converted to QALYs. Utility while on second line therapy are derived from EQ-5D data collected during the Profile 1007 trial. Utility while on third line therapy was derived from a published QoL study.
Source of data for measurement of HRQL	Reported directly by patients and/or caregivers	Partly	Utilities for pre-progression and second line therapy were reported directly from patients. Utilises for third line therapy were derived from 100 members of the general public.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes	

Discount rate	Annual rate of 3.5% on both costs and health effects	Yes	Costs and benefits have been discounted at 3.5% per annum.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	No special weighting undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken.

5.2.3 Population

The patient population considered in the base-case economic analysis was untreated, ALK- positive patients with advanced NSCLC of non-squamous histology. This reflects the clinical effectiveness data used in the model which was derived from the PROFILE 1014 trial. This was also reflected in the costs of screening patients for ALK status which was assumed to be based on testing of non-squamous patients only. As stated in Section [redacted], the trial population was broadly in line with the NICE scope which defined the population of interest as people with untreated, ALK- positive, advanced NSCLC which includes patients with both squamous and non-squamous histology . The PROFILE 1014 trial however, excluded patients with squamous ALK- positive NSCLC. The base-case economic analysis therefore reflects a subset of the licenced population as squamous patients are not included. However, as stated in the CS and confirmed by the clinical advisor very few patients (less than 0.1%) with squamous histology are ALK-positive and therefore exclusion of these patients is considered reasonable, equity issues aside. In addition to the base-case analysis a scenario analysis is presented for a population of squamous histology. This was carried out assuming alternative costs for ALK testing (due the different incident rates of ALK-positive mutation in squamous and non-squamous patients) and assuming that PROFILE 1014 was reflective of the prognosis of squamous patients. The latter assumption was considered to be plausible by clinical advisor as no distinction is typically made between squamous and non-squamous patients.

5.2.4 Interventions and comparators

The economic model presented in the CS compares crizotinib with pemetrexed plus platinum based chemotherapy as first-line treatments for untreated non-squamous advanced NSCLC. In the economic model patients initiating on crizotinib may continue therapy beyond progression if in the view of the treating clinician they are deemed to still be benefiting from treatment. Following discontinuation of crizotinib patients are assumed to receive second-line therapy, consisting of docetexal, which is in turn followed by [redacted]. Patients initiating chemotherapy are assumed to have six lines of therapy (as per Profile 1014) and on progression are assumed to receive second-line therapy, consisting of docetaxel, which is in turn followed by [redacted]. The ERG considers the choice comparators to be broadly in line with current practice, but have specific concerns regarding: the spit in combination therapy used; the appropriateness of the comparator given current uncertainty of

treatments on the CDF; and differences in second-line therapies received. These issues are outlined in detail below.

5.2.4.1 Pemetrexed plus platinum chemotherapy

Pemetrexed combination consists of pemetrexed in combination with cisplatin or carboplatin. In the base-case analysis presented in the CS it is assumed that 53.85% of patients will receive cisplatin and 46.15 will receive carboplatin. This assumption is based on the split observed in PROFILE 1014. The CS also presents a scenario analysis, based on expert clincial advice, whereby 25% of patients receive pemetrexed plus cisplatin and 75% receive pemetrexed plus carboplatin on clinical advice that at some centres up to three quarters of patients may receive carboplatin instead of cisplatin. The clinical advisors to the ERG confirmed this scenario was more reflective of clinical practice in the UK suggesting that approximately 30% of patients would receive cisplatin and 70% carboplatin. The distribution of patients receiving carboplatin and cisplatin, however has minimal impact on the ICER (due to similar costs) and is not expected to influence efficacy. The ERG explore this issue further in Section 6.

5.2.4.2 Pemetrexed as a maintenance therapy

The CS assumes patients receiving pemetrexed combination therapy will receive a maximum of six cycles of therapy and then discontinue all treatment until progression. This is in line with the comparator as defined in the scope. The ERG is, however, concerned that this does not reflect current practice in the UK as a significant proportion of ALK-positive NSCLC patients currently receive pemetrexed maintenance therapy. The clinical advisor to the ERG stated that all patients who receive pemetrexed in combination with cisplatin (30% of all patients) would go on to receive pemetrexed maintenance therapy when available via the Cancer Drugs Fund (CDF). The ERG asked the company to respond to the suggestion that pemetrexed maintenance may be an appropriate comparator. Their response emphasised that this was not in the scope and suggested that only about 15% of patients are currently receiving pemetrexed maintenance therapy. The ERG acknowledges that the company complied with scope in this regard and that pemetrexed maintenance was not part of the final scope. However, the exclusion of pemetrexed maintenance potential means that an important comparator used in a significant proportion of patients is currently excluded from the model. The ERG also acknowledges that pemetrexed maintenance was only available under the CDF which is shortly to be discontinued. However, there is the potential for reassessment and approval of pemetrexed maintenance therapy under the proposed transitional procedures. Therefore pemetrexed maintenance therapy may continue to be a part of UK practice. The presented model is therefore only valid in so far as practice does not include pemetrexed maintenance therapy. Due to limited resources available to the ERG and the extensive re-analysis that would be necessary for the ERG to include pemetrexed maintenance therapy in the current model this issue is not explored further in Section 6.

5.2.4.3 Crizotinib as a second line therapy

In the economic model it is assumed that second-line therapy is docetaxel in both treatment arms. The model therefore does not include the use crizotinib as a second-line therapy. The CS justifies the decision to exclude crizotinib as a second-line therapy on the grounds that crizotinib is currently only available via the CDF, and due to uncertainty over the future of the CDF. The ERG considers this a significant omission from the presented model. The use of pemetrexed combination therapy followed by crizotinib as second-line therapy is a clear alternative to the modelled pathway of crizotinib first-line followed by docetaxel second-line. As above, with regards, to pemetrexed maintenance therapy, the presented model is therefore only valid in so far as practice does not include crizotinib as a second-line therapy. Due to limited resources available to the ERG and the extensive re-analysis that would be necessary for the ERG to include crizotinib as a second-line therapy into the economic model the ERG does not explore this issue further in Section 6.

5.2.4.4 Second-line therapies received in PROFILE 1014

As discussed in Section 4.2. 2.3, following discontinuation of first-line therapy a significant number of patients in the PROF ILE 1014 study went on to a receive second-line therapies. For patients who received crizotinib first-line 45/172 (26.2%) received a second-line therapy, this consisted of a wide range of therapies including pemetrexed which is not approved for second-line use in the UK, certainib which has recently received a license from the EMA, but is yet to be appraised by NICE, and a number of unnamed experimental drugs. Patients in the pemetrexed arm of the study in contrast went on to mainly receive crizotinib, with 120 out of 171 patients who had progressed in the pemetrexed arm. Of the remaining 51 patients 47 did not receive any second-line therapy. Details of all the therapies received following discontinuation of first-line therapy are presented in Table 21 along with the proportion patients receiving that therapy. The ERG has significant concerns about this imbalance in the second-line treatments, as the crossover adjusted analysis does not take into account the impact of second-line therapies. Furthermore, whilst differences in follow-on therapies a can be accepted, the PROFILE 1014 trial allowed for beyond progression treatment with crizotinib delaying the start of second-line therapy in the crizotinib arm compared to that in the chemotherapy arm and exacerbating the differences between the treatment arms. It is therefore likely that the comparison of OS is confounded and not fully adjusted for by the adjustment for crossover methods employed. The ERG requested additional analysis to seek to quantify the impact of second-line therapy by asking for separate Kaplan-Meier curves for patients who did and did not receive second-line pemetrexed therapy. The company, however, did not respond to this request on the grounds that the number of patients was too small. As a result of this imbalance the ERG considers the estimated OS subject to unquantifiable uncertainty and is likely to overestimate the benefit of crizotinib over pemetrexed combination therapy. Furthermore, as the cost-effectiveness of crizotinib is driven extensively by the

OS benefits of crizotinib treatment the use of this data is likely to overestimate the cost-effectiveness of crizotinib.

Table 21 Summary of Systemic Anticancer Therapies at Follow-Up Among Patients with Progressive Disease

Therapy	Crizotinib (n=172)	Pemetrexed Combination Therapy (n=171)
	No. of patients (%)	
Any systemic therapy	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5.2.5 Perspective, time horizon

The economic perspective is the National Health Service (NHS) and the Personal Social Services (PSS) in accordance with the NICE reference case. The reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon used was 15 years, which was stated to represent a lifetime horizon. The ERG considered this an appropriate time horizon, as less than 0.001% patients in the model were expected to remain alive beyond 15 years.

5.2.6 Discounting

Costs and benefits in the model were discounted at an annual rate of 3.5% as per the NICE reference case. Implementation of discounting in the economic model was carried out on annual basis, such that all costs and benefits incurred with any given year are discounted by the same amount regardless of whether they occur at the start or the end of that year. The ERG considers this approach to be non-typical and less accurate than the more conventional approach of discounting on a per cycle basis, whereby the discount rate is calculated for every cycle of the model. Discounting on a cyclical basis is more accurate as it more closely reflects the actual time at which benefits and costs occur and is more theoretically sound as the principal behind discounting is essentially one of preferences over the timing of consumption and that future consumption is less valuable than immediate consumption. The current formulation of the model, however, implies that consumption 11 months from now is equivalent to immediate consumption which seems to stand in contrast to this underlying principle. The ERG therefore considers this as an error in the executable model and is rectified in the ERG revised model, see Section 6.

5.2.7 Treatment effectiveness and extrapolation

Both PFS and OS are considered in the company's economic model with data for both sourced from PROFILE 1014. The model generated the proportion of patients in the progression free and progressive disease states: the proportion of patients in the progression free health state was taken directly from the extrapolated PFS curve; the proportion of patients with progressive disease was calculated by subtracting PFS from OS.

As discussed in Sections 4.2.2, the ERG has a number of concerns regarding the analysis of the PFS and OS specifically the assumption of proportional hazards and the methods of crossover adjustment used to analysis the OS survival data from PROFILE 1014. Each of these issues is discussed in turn with specific focus on how these assumptions may impact on the estimated ICER.

5.2.7.1 Proportional hazards

As discussed in Section 4.2.2.1 extrapolation of PFS was carried out assuming proportional hazards and a single parametric survival curve was fitted to the Kaplan-Meier plots for the crizotinib and pemetrexed arms of PROFILE 1014, with a covariate for the treatment effect. This assumes that that the treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape. This assumption was justified in the CS with reference to plots of log hazards against log time. As discussed in Section 4.2.2.1, the ERG questions the plausibility of this assumption in the present context noting in particular that the mode of action for the two therapies is quite different and that administration of crizotinib is ongoing until lack of continuing benefit, whereas pemetrexed combination therapy is administered for a fixed number of cycles. As such the ERG considers that the conservative approach of using independent functions is likely to be more

appropriate in the present context. The impact of this assumption on the estimated economic model is potentially profound as the estimated ICER is particular sensitive to these clinical inputs, as demonstrated by the sensitivity analysis presented in the CS. The ERG therefore presents a additional analysis in Section 6 where independent parametric survival functions are fitted to the Kaplan-Meier plots of PFS for the crizotinib and pemetrexed arms of PROFILE 1014.

5.2.7.2 Adjustment for crossover

In the economic model the company consider five alternative methods of cross-over adjustment, three based on the two stage method of crossover adjustment and two based on the RPSFT method of crossover adjustment. The company did not consider the IPE method of adjustment presented in the clinical section. This was justified on the basis that the IPE method makes the same common treatment effect assumption as the RPSFT method. The estimated hazard ratios using the IPE method were similar to those obtained using the other methods of cross-over adjustment. Details of the five methods of adjustment are discussed in Section 4.2.2.3 of the CS. The hazard ratios from each method of adjustment and the respective impact on cost-effectiveness of the different crossover adjustment methods are shown in Table 22. The ERG

Table 22 Overall survival cross-over adjustment methods: treatment effect estimates and ICER estimates

Crossover adjustment method	Analysis	Crizotinib versus pemetrexed plus cisplatin/carboplatin Hazard Ratio (95% CI)	ICER
Two stage adjusted model	Adjustment for treatment switching and additional covariates (ECOG base-case imputation)	0.624 (0.405, 0.963)	[redacted]
	Adjustment for treatment switching and additional covariates (ECOG sensitivity imputation)	0.649 (0.421, 1.000	[redacted]
	Adjustment for treatment switching only	0.610 (0395, 0.942)	[redacted]
RPSFT	Log-rank test method	0.674 (0.283, 1.483)	[redacted]
	Wilcoxon test method	0.604 (0.265, 1.420)	[redacted]

The CS notes the consistency in the estimated hazard ratio and the absence of any methodological or clinical reason select the median value using a two stage approach for the base-case. As stated in Section 4.2.2.3 the choice of two stage model A over the other methods of adjustment is largely arbitrary and as can be seen from Table 22 while the hazard ratio does not vary significantly according to the model selected, the choice of method does have a significant effect on the estimated

ICER as the economic model is particularly sensitive to any change in OS benefit. Given the lack of any methodological or clinical reason to select one model over another it important to consider that there is significant uncertainty surrounding the presented base-case ICER not accounted for in the probabilistic analysis. Furthermore, as discussed in Section 4.2.2.3 all of the methods of adjustment make strong and largely untestable assumptions and it should not be assumed that estimates of OS based on the presented methods of cross-over adjustment are correct simply because there is a degree of consistency in the estimates: it is quite possible that the estimates are simply consistently wrong. Indeed, as argued in Section 4.2.2.3 all of the adjustment options presented by the company are potentially biased. As such, the ERG consider there to be significant and unquantifiable uncertainty surrounding the estimated OS benefits and by extension to the estimated ICER.

5.2.8 Duration of therapy

5.2.8.1 Duration of crizotinib therapy

The duration of therapy for patients within the economic model is dependent on whether patients continue therapy past progression. Based on PROFILE 1014 it is assumed that 73% of patients in the crizotinib arm continue to receive therapy beyond progression while the remaining 27% discontinue crizotinib therapy on transition to progressive disease. Within the economic model duration of treatment for patients who discontinue treatment at progression is determined by time to progression, where time to progression is based on the extrapolation of PFS data from PROFILE 1014 adjusted to the UK population using the Davis study[10]. Duration of treatment for patients who continue treatment *beyond* progression is also linked to time to progression, but it is assumed that patients receive a further 4 cycles of crizotinib (based on data from the PROFILE 1014 trial of time on crizotinib post-progression).

The ERG considers the approach taken by the company to be reasonable with regards to patients who discontinue treatment to progression, but has identified a number of issues regarding the assumptions made for patients treated beyond progression and the way 'time on treatment' is implemented in the electronic model for these patients.

The assumption that patients receive a further 4 cycles of crizotinib beyond progression is based on the median time on crizotinib post progression reported in PROFILE 1014 of 3.1 months. The ERG notes that use of the 3.1 month figure is incorrect for a number of reasons. Firstly, it is inappropriate to use a median instead of a mean value within cost-effectiveness analysis, and based on the analysis present in the CSR[34], the mean duration of treatment beyond progression is [redacted] months, conservatively equivalent to [redacted]. Secondly, both these median and mean values R are based on truncated data set in which it is assumed that all patients who are still on crizotinib treatment discontinue therapy upon being censored. As [redacted] of crizotinib patient were still on therapy at the time of the analysed data cut of 30th November 2013, these estimates dramatically underestimate the

true median/mean time on crizotinib treatment beyond progression. To calculate a more accurate estimate of mean time on treatment following progression the ERG requested the Kaplan-Meier of discontinuation of treatment for crizotinib patients at the PFC stage. As the Kaplan-Meier provided in the company's response was incomplete the ERG fitted a series of parametric survival curves were fitted to the data to calculate mean duration of treatment, see Figure 6 below.

Figure 6 Discontinuation curve for crizotinib fit of parametric survival curves

Based on AIC (Akaike information criterion) and BIC (Bayesian information criterion) the ERG considered the most appropriate parametric curve to be the exponential curve, see Table 23 below (lower values are preferred for best fit). Based on the exponential curve mean duration of treatment for all crizotinib a patient is estimated to be [redacted] months. This compares with [redacted] using the truncated data reported in the CSR. Using this value and mean time to progression it is possible to calculate mean time on crizotinib post progression, which the ERG calculate to be [redacted]. The company model therefore dramatically underestimates the time on treatment beyond progression and as a consequence also underestimates the ICER.

Table 23 Assessment of parametric survival models for crizotinib discontinuation

Model	AIC	BIC
Exponential	437.04	440.18
Generalised Gamma	438.80	448.22
Gompertz	438.30	444.59
Log-logistic	436.96	443.24
Log-normal	437.59	443.87
Weibull	439.04	445.32

In addition to the above a further issue was identified by the ERG with regards to the implementation of treatment beyond progression in the economic model. As described above the model assumes that newly progressed patients will go on to receive for 4 cycles of treatment. However, the way that the model is constructed means not all patients that progress will go on receive four cycles of treatment beyond progression because in each period a proportion of the patients die, based on mortality in that cycle. Consequently, the actual mean number of cycles of treatment received beyond progression is not 4, but 2.2. The intended 4 cycles of treatment beyond progression therefore does operate as mean number of cycles, but instead as maximum number of cycles and does not recognise that some patients receive many cycles of treatment beyond progression. This misspecification of the model leads to an underestimation of time on treatment beyond progression, reducing total QALYs accrued by crizotinib patients and also reducing total costs of treatment, with a net effect of underestimating the ICER.

To correct the model and accurately reflect the duration of treatment beyond progression it is necessary to substantially reprogram the model and to implement a full area under the curve model in which time on treatment is sourced from the observed time on treatment for patients in the PROFILE 1014 trial. The ERG we able to fix this issue and the results of the new ERG model are presented in Section 6. This fix, however, has implications for other parts of the model relating to time on second-line therapy that the ERG were not able to fix. Further details on this issue are included in our discussion of duration of second-line treatments.

5.2.8.2 Duration of treatment with pemetrexed combination therapy

Duration of treatment with pemetrexed combination is based on the PROFILE 1014 study in which patients received a median of six cycles of therapy. The implementation of this in the model assumes that patients receive therapy for the first four cycles of the model for all patients that are alive (the

difference in cycles in model with cycles of therapy is due to the model cycle not aligning with treatment cycle).

The ERG has two specific concerns about the duration of treatment with pemetrexed combination therapy. The first issue concerns the implementation of the duration of pemetrexed therapy in the model. Patients are assumed to receive therapy for the first four cycles assuming that they are alive. This effectively implies that all patients discontinued pemetrexed therapy because of death; this does reflect the actual number of cycles of therapy received in the PROFILE 1014 trial. However, there is a discrepancy between the mean number of cycles of therapy received according to the model ([redacted]) and the actual mean number of cycles therapy received in PROFILE 1014 ([redacted]). Similarly to the issues highlighted above relating to duration of crizotinib therapy, the ERG considers the company's approach regarding the modelling of time on pemetrexed therapy of far from ideal and suggest a better approach would have been to implement a full area under the curve model in which time on therapy was based on the observed discontinuation curve. The influence of this issue is likely to relative modest, but will have led to an overestimate the cost-effectiveness of crizotinib. The ERG therefore implements a full area under the curve using discontinuation data provided by the company in their clarification response.

A second issue regarding the duration of pemetrexed combination treatment is the assumption that patients would be initiated on a six cycle regimen of chemotherapy in the UK and that the PROFILE 1014 trial is reflective of UK practice. Discussions with the clinical advisors to the ERG suggested that there is some variation in UK practice with one clinical advisor stating they more typically use a 4 cycle regimen, while a second advised that while the aim is to administer six cycles of therapy, this not always achievable, and that fewer cycles are often received in practice. Furthermore, the SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy.[41] The model therefore may overestimate the number of cycles of pemetrexed combination therapy. Further evidence presented in TA181 suggests that the clinical benefits of additional cycles of chemotherapy is often marginal and that median PFS and OS are similar whether a four or six cycles of chemotherapy are used. This may imply that a four cycle regimen is more cost effective than a six cycle regimen due to a significant reduction in drug acquisition and administration costs for a marginal reduction in QALYs. The ERG therefore presents a series of scenario analyses in Section 6 in which it is assumed that fewer rounds of pemetrexed plus cisplatin/carboplatin are given; this sensitivity analysis is optimistic as it assumes no change to efficacy.

5.2.8.3 Duration of Second-line therapy and time spent on BSC

For both crizotinib and pemetrexed patients it was assumed in the economic model that patients would receive second-line therapy consisting of docetaxel. For crizotinib patients that discontinued therapy at progression, second-line therapy was initiated immediately following progression and for crizotinib

patients that continued crizotinib therapy beyond progression, second-line therapy was initiated immediately following discontinuation of crizotinib. For pemetrexed patients second-line therapy was assumed to be initiated following progression. The duration of second-line therapy was assumed to be the same in for all patients regardless of first-line therapy or continuation of first-line therapy beyond progression. Further, it was assumed that all patients would receive therapy. The duration of time spent on second line therapy (docetaxel) in the economic model was assumed to be 3 cycles based on the median progression-free survival of 2.6 months observed in the Profile 1007 trial.

The implementation of duration of second-line therapy follows the same method as for treatment beyond progression for crizotinib patients and similarly flawed. Due to the design of the PROFILE 1014 study it is, however, not possible to obtain a treatment discontinuation curve for second–line therapy as few patients received docetaxel as their second-line therapy. As such, it is not possible to implement a full area under the cover model for second-line therapy. An alternative would potentially use the treatment discontinuation curve from PROFILE 1007, however, as discussed below, this is far from ideal, and the ERG does not consider there to be a simple way of fixing the economic model to correct for this flaw. The impact of this issue on the resulting ICER is, however, likely to be considerably smaller than that of crizotinib treatment for number of reasons. Firstly, docetaxel is given for a much shorter duration and therefore the cumulative effects of mortality will be smaller. Secondly, the model may be incorrect in terms of assessing time on second-line, but is approximately equally incorrect for both treatment arms and therefore it does not favour crizotinib over pemetrexed or vice versa.

The ERG has number of additional concerns regarding the assumptions made regarding second-line therapies received by patients. Firstly, is not clear that all patients would in fact receive second-line therapy as evidenced by PROFILE 1014 in which [redacted] and [redacted] of crizotinib and pemtrexed patients respectively received no further treatment. Further there is no reason to suggest that mean duration of second-line therapy would be the same for both crizotinib and pemetrexed patients. The use of PROFILE 1007 data where patients received first-line pemetrexed is therefore not necessarily reflective of the duration of second-line treatment for crizotinib patients. Given the issues highlighted above and the difficulty of addressing them, the ERG entirely removes second-line treatment in the ERG base-case and patients are assumed to move directly to BSC. ERG does not consider this ideal, but considers this to be as reasonable as assuming all patients receive the same second-line treatment. It This assumption is likely to favour pemetrexed as more of these patients went on to receive second-line treatment in the PROFILE 1014 study.

5.2.9 Health related quality of life

5.2.9.1 Source of health-related quality of life data

To assign appropriate utility values to the health states within the model the company consider a number of sources of utility data, an overview of which is provided below.

The primary source of utility data considered by the company was the PROFILE 1014 trial which collected health-related quality of life (HRQoL) evidence from the trial participants using EQ-5D questionnaire. At the baseline the mean utility in the two arms were similar [redacted] (SD [redacted]) for the crizotinib and [redacted] (SD [redacted]) for the pemetrexed plus cisplatin/carboplatin. Mean progression free utility for the each arms was estimated using repeated measures mixed-effects analysis controlling for baseline (i.e. the methods contained a baseline covariate). The mean progression free utilities were [redacted] (SE [redacted]) for crizotinib arm and [redacted] (SE [redacted]) for the pemetrexed plus cisplatin/carboplatin.[34]

The collection of utility data in the PROFILE 1014 trial was limited to when patients were on first-line treatment, and therefore the company carried out a systematic search of the literature to identify HRQoL data to inform the other health state within the cost-effectiveness model. A detailed description and critique of the searches carried out are presented in Appendix 10.1. The literature search was an update of a previous systematic review in 2012 was carried out to identify the HRQoL and utilities associated with advanced/metastatic lung cancer; this previous review was used to inform HTA submissions in the UK for crizotinib for the treatment of previously-treated ALK-positive NSCLC, which included NICE TA296. The updated systematic literature review identified 13 unique citations (eight full text publication and five conference abstracts). The details are presented in the company submission section 5.4.3 (pg. 140-143) and summary of the design and key results of included studies reporting HRQoL data are presented in the CS in Appendix 18 (pg. 268 – 286).

The company did not consider any of the utilities identified in the included studies to be superior in terms of relevance to the HRQoL data collected in PROFILE 1014. Therefore, where feasible, HRQoL data from PROFILE 1014 were used exclusively in the base-case analysis. The CS, however, did present a comparison of the utility values obtained from PROFILE 1014 and those in the literature (NSCLC), and concluded that utility values identified in the literature were broadly similar to the utility values for chemotherapy patients from the PROFILE 1014 study. It was, however, noted that the utilities in PROFILE 1014 were higher than values previously reported (CS, Table 115 in Appendix 18, pg. 268-285).

The systematic review of utilities data also considered the impact on HRQoL of adverse events as this data was not collected in PROFILE 1014. A number of studies were identified as part of this search. A summary of the design and results of these studies is presented in Table 24. Doyal et al. (2008)[42] demonstrated that symptoms such as pain, cough and dyspnoea have a detrimental effect on HRQoL. Nafees et al. (2008)[43] reported that all toxicities were associated with a significant decline in utility

compared to stable disease with no toxicity. Thomas et al. (2011)[44] reported that a Common Terminology Criteria for Adverse Events (CTCAE) score of >2 was associated with a greater risk of worsening HRQoL. Another study by Billingham et al. (2011)[45], reported an association between improvements in pain, cough, haemoptysis, insomnia, appetite loss and emotional functioning, and improvements in measures of global HRQoL.

Table 24 Summary of the studies indicated that symptoms or adverse events have an impact on HRQoL

Studies	Country	Sample size and population	Method of elicitation	Utility values for health states	Utility decrements associate with symptoms/adverse events, (parameter estimate, SE)
Doyal et al. (2008)[42]	United Kingdom	101 healthy participants from the Greater London	Standard gamble interview and a mixed model was used for analysis	0.712 for treatment response (no additional symptoms); and 0.626 for stable disease (no additional symptoms)	Symptoms: Cough (-0.046, 0.011) Dyspnoea (-0.050, 0.012) Pain (-0.069, 0.012)
Nafees et al. (2008)[43]	United Kingdom	100 participants from UK general population	standard gamble interviews and mixed model with random effects on the participant level was used for the analysis	0.653 for stable disease with no toxicity; 0.67 for responding disease with no toxicity; and 0.47 for progressive disease	Adverse events: Neutropenia (-0.090, 0.015) Febrile Neutropenia (-0.090, 0.016) Fatigue (-0.073, 0.018) Nausea & vomiting (-0.048, 0.016) Diarrhoea (-0.047, 0.016) Hair loss (-0.045, 0.015) Rash (-0.032, 0.012)
Thomas et al. (2011)[44] Abstract only	Multinational (Belgium, France, Germany, Greece, Italy, Portugal, Spain, Turkey)	1626 patients with confirmed NSCLC	Not clear	Not reported	Values are not reported. Although, it was reported that a Common Terminology Criteria for the Adverse Events (CTCAE) score of >2 was associated with a greater risk of worsening HRQoL.
Billingham et al. (2011)[45] Abstract only	United Kingdom	1363 patients with advance NSCLC	Not clear	Mean utility score of 0.66	Values are not reported. Although, reported an association between improvements in pain, cough, haemoptysis, insomnia, appetite loss and emotional functioning and improvements in global measures of QoL.

SE = standard error

5.2.9.2 HRQoL values used in cost-effectiveness analysis

Table 25 summaries the HRQoL utility values that were assigned to the progression free and progressed disease health states in the economic model. With regards to the progression free health states utility were sourced from PROFILE 1014. No adjustments had been made to these values. Health state utility estimates for the progressed disease were used from different source of data:

PROFILE 1014 to inform treatment beyond progression with crizotinib; PROFILE 1007 to inform progressed disease second-line treatment with docetaxel; and, Nafees (2008) to inform progressed disease second-line treatment with docetaxel.[43]

Table 25 Summary of utility values used for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI
Progression free		
Progression free –crizotinib (PROFILE 1014)	[redacted]	[redacted]
Progression free – pemetrexed plus cisplatin/carboplatin (PROFILE 1014)	[redacted]	[redacted]
Progressed disease		
Treatment beyond progression with crizotinib: Sustained utility for 4 cycles (PROFILE 1014 & PROFILE 1007)	[redacted]	[redacted]
Progressed disease: second-line treatment with docetaxel (PROFILE 1007)	0.66 (0.04)	(0.58, 0.74)
Progressed disease: third-line treatment with BSC Nafees *et al.* (2008)	0.47 (0.05)	(0.38, 0.57)

ALK: anaplastic lymphoma kinase; BSC: best supportive care; NSCLC: non-small cell lung cancer; CI: confidence interval; SE: standard error.

Progression free utilities

Within the cost-effectiveness model, patients were assigned different utility values in the progression free health state dependent on the first-line treatment received. Patients receiving crizotinib were assigned a higher utility than patients receiving pemetrexed plus cisplatin/carboplatin ([redacted] vs. [redacted] as observed in PROFILE 1014). The company explains that this difference is in utility values observed in PROFILE 1014 was likely because crizotinib leads to better symptom control and is associated with fewer and less severe side effects.

The ERG considers this differential utility broadly plausible, however, notes some problems with the way in which HRQoL data were collected for patients on chemotherapy which may partly explain this differential. This issue relates to the fact that HRQoL data was collected only while patients were on first-line treatment and therefore not necessarily reflective of average utility throughout the pre-progression period: pemetrexed combination therapy is a fixed cycle regimen and for a potentially substantial period prior to progression patients would not have been on active treatment. For the patients who received crizotinib first-line this data collection policy can be considered appropriate as patients continue to receive therapy for the entire period prior to progression and therefore utilities

reflect HRQoL throughout the pre-progression period. The analysis therefore implicitly assumes that HRQoL for pre-progressed pemetrexed patients would be the same both on and off treatment. As noted by in the CS chemotherapy is associated with frequent side effects and is therefore plausible that patients receiving chemotherapy treatment would have lower utility than those who have finished treatment. Discussion of this issue with the clinical advisor to the ERG suggested that patients who have finished chemotherapy treatment are likely to have higher utility than patients on chemotherapy treatment and potentially higher utility than patients receiving crizotinib due the lack of side-effects. The ERG therefore considers that it is plausible that patients in pemetrexed arm who are not progressed and off treatment will have substantially higher utility. To explore this issue the ERG therefore conducts scenario analysis in Section 6 in which it is assumed that post completion of treatment and prior to progression pemetrexed patients receive the higher utility of [redacted] as currently assumed to be experienced by crizotinib patients.

Sustained utility during treatment beyond progression

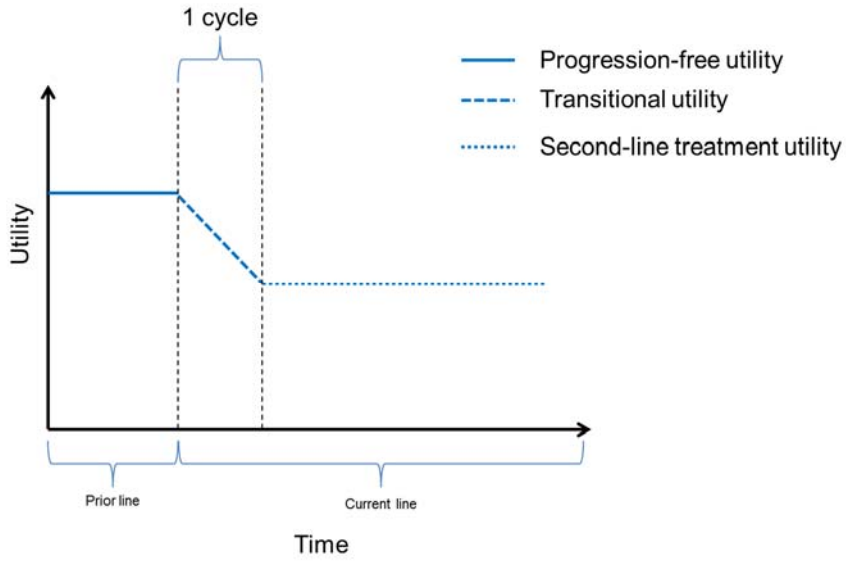
In the cost-effectiveness model, a proportion of patients were assumed to receive crizotinib treatment beyond progression (based on PROFILE 1014). The company justified this on the basis of that treating clinicians will continue to prescribe crizotinib while they perceive a continued benefit to a patient's HRQoL. This may be in the form of limiting the speed of disease progression or to allow the patient to continue to benefit from the superior toxicity profile of crizotinib compared with the next line of treatment (docetaxel). In order to reflect this, the economic model applied a 'sustained' utility for the duration of treatment beyond progression (assumed to be 4 cycles). The CS assumed that it is unlikely patients would achieve the same utility score as pre-progression due to some degree of disease progression and potential symptom worsening. However, the company considered that is similarly unlikely the utility score would decrease to that of a second-line patient (as this defeats the point of treating beyond progression). Hence, the model assumed that for the 73% of patients treated beyond progression with crizotinib would have a utility score of [redacted] based on the midpoint between pre progression utility ([redacted]) and post progression utility (0.66). While the ERG consider that it is plausible that patients treated beyond progression may experience some utility benefit, it has some concerns regarding the value chosen. Firstly, basing the utility value on the midpoint between pre and post progression is largely arbitrary and no clinical evidence is provided to support this assumption. Secondly, it seems clinically unlikely that progressed patients receiving crizotinib would have higher utility than pre-progressed patients receiving pemetrexed patients given that symptom load for these patients will be lower. Given the lack of alternative data to provide a utility value for this group of patients the ERG carries out a series of scenario analysis in Section 6 to evaluate the impact of uncertainty surrounding this parameter.

Transitional utility following progression between lines of treatment

In the CS base-case analysis, a 'transitional' utility was applied when moving between health states during the first cycle following transition in order to best reflect the patient pathway in reality. The values of the transitional utility were estimated as the mid-between health state they have left and the health state they have entered. This rule was applied when transitioning between first-line and second-line treatment as well as transitioning between second-line treatment and BSC. The intent behind this assumption is to represent the idea that following progression between lines of treatment, it is implausible that a patients' utility will drop immediately to the utility associated with the next line of treatment. The CS considered that it is logical and clinically rational to assume there is a period of transition in HRQoL between states.

Figure 7 illustrates this transitional utility when moving between states.

Figure 7 Transitional utility following progression



The ERG does not consider the inclusion of transitional utilities appropriate as this is likely to double count the higher utility described following transition to the new health state. This is because the utility data collected to populate these values is based upon an average or individuals in that health state. This would include individuals who have just entered that state who may have be experience higher utility than other patients in that health state and individuals who are about to leave that health state who may have lower utility than other patients in that health. The average utility for a particular health state therefore already accounts for variation in patients' utility within that health state. The CS presented a sensitivity analysis where transitional utility between health states was not applied. This was however based on probabilistic analysis and therefore in Section 6 the ERG carries out additional deterministic sensitivity analysis removing these transitional utility values.

Progressed disease utilities

A set of assumptions were made in the model while including utility values for the progressed disease. In order 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 arm. The CS model assumed (based on discussions with the UK clinical experts at the advisory board) that docetaxel would be a common second-line therapy. Therefore, the utility value of 0.66 is used for patients receiving second-line treatment with docetaxel in ALK-positive NSCL. This value was obtained from the PROFILE 1007 trial.[46] Following discontinuation of second-line therapy it was assumed that patients would not go on to receive further active therapy and that patients would receive BSC until their death. For this period it was assumed that patients in both treatment arms would receive utility of 0.47 based on the value for progressive disease following second-line treatment from Nafees et al. (2008). [43] While it would preferable that utilities were derived from a trial the ERG considers that these assumptions are plausible.

5.2.9.3 HRQoL associated with adverse events

In the CS base-case, no disutility due to adverse events was applied. The company justified this on the basis that this would double-count health effects as the HRQoL estimates included in the PROFILE 1014 trial whereby estimates taken from patients whilst on treatment, and therefore already reflect the effects on HRQoL of adverse events. The CS considered that this assumption was a conservative one, because crizotinib has a more favourable adverse event profile than pemetrexed plus cisplatin/carboplatin. The CS, however, also presented a sensitivity analysis whereby disutilities from adverse events are applied to each treatment arm during cycle 1. The disutilises used were based on values identified in the literature and are summarised Table 26. Adverse events rates were based on those observed in PROFILE 1014 and were included if they were of Grade ¾ severity and occurred in ≥5% of either treatment arm. Grade 1 and 2 adverse events were not considered as these would not be expected to require active intervention or have a large impact on quality of life. The estimated total disutility from the adverse event profiles was 0.01 for crizotinib patients and 0.03 for pemetrexed plus cisplatin/carboplatin patients. The ERG considers the assumption made in the company's base-case of no disutility adjustment to be appropriate.

Table 26 Disutilities due to adverse events and proportions of patients experiencing each adverse event

Adverse event	Utility decrement	% patients with adverse event	
		Crizotinib	Pemetrexed plus cisplatin/carboplatin
Elevated transaminases	0.00	14.04%	2.37%
Neutropenia	0.09	11.11%	15.38%
Anaemia	0.07	0.00%	8.88%

Leukopenia	0.09	1.75%	5.33%
Thrombocytopenia	0.09	0.00%	6.51%

5.2.10 Resources and costs

The CS gave a detailed description of a wide range of resources and costs. These included:

- Drug acquisition and administration costs for crizotinib and pemetrexed combination therapy;
- Resources and costs of treatment received following disease progression
- Resources and costs related to monitoring and palliative care (Health state costs)
- Resources and costs related to adverse reaction management
- Cost of ALK-testing

The company's model adopted an NHS and PSS cost perspective. To identify cost and resource use data to inform the assessment of cost-effectiveness, the company performed a systematic review of the literature for advanced/metastatic ALK-positive NSCLC patients, as described in section 5.5.2 of the CS. A detailed description and critique of the searches carried out are presented in Appendix 10.2. In total 24 studies met the inclusion criteria of this review reporting a number of cost valuations or health resource use consumption, which are presented in Appendix 20: Table 123 & 124 (p.g. 290 – 303) of the CS.

5.2.10.1 Drug acquisition cost for crizotinib and comparator treatments

Table 27 presents the drug costs used in the model per 30 day cycle. The CS economic model, assumes crizotinib patients were given 2 tablets daily (in total 500mg per administration). This is based on the dosage used in the PROFILE 1014 study. Drug costs were sourced from MMIS.

With regards to pemetrexed patients in the economic model, pemetrexed and cisplatin dosing was based on the body surface area (BSA), which was assumed to be 1.73 m^2. This value was sourced from the BSA of patients in PROFILE 1014 trial. Carboplatin dosing is based on a target area under the curve (AUC) of 5–6. In the absence of data from PROFILE 1014 to estimate the target AUC, previous NICE submissions were reviewed for their assumptions regarding the dosing of carboplatin. TA181 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.[47, 48] The CS selected a dose of 500 mg in the base-case as a conservative assumption as this results in the lower cost for carboplatin. The model does not assume any impact on efficacy. Drug costs for pemetrexed were sourced from MIMS and for cisplatin and carboplatin from eMit. The ERG considers these assumptions reasonable and conservative with respect cost-effectiveness of crizotinib.

Table 27 Drug cost and vial/tablet used per cycle in the base-case analysis

Treatment	Unit	Unit cost (list price)	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Crizotinib[*]	60 x 200mg tablets	£4,689.00	2x 250mg per day (30 days)	£4,689.00
	60 x 250mg tablets	£4,689.00		
Pemetrexed[*]	100mg vial	£160.00	500 mg/m2 = 500/1.73 = 866 mg (21 days)	£1,440.00 with wastage £1,385.40 without wastage
	500mg vial	£800.00		
Cisplatin[$]	10mg (10ml vial)	£3.24	75mg/m2 = 75/1.73 =130mg (21 days)	£47.00 with wastage £25.72 without wastage £19.98 without wastage
	50mg (50ml vial)	£6.97		
	100mg (100ml vial)	£12.53		
Carboplatin[$]	50mg (5ml vial)	£4.36	Target AUC = 5, dose = 500 mg (21 days)	£34.18 with wastage £28.27 without wastage £22.41 without wastage
	150mg (15ml vial)	£9.90		
	450mg (45ml vial)	£29.82		
	600mg (65ml vial)	£33.92		

[*]Reference: MIMS (Monthly Index of Medical Specialities), [$]Reference: eMit (electronic market information tool)

With respect to both crizotinib and pemetrexed no drug wastage was assumed for either treatment. The ERG considers this to unrealistic. With regards crizotinib tablets come in 60 tablet pack which last 30 days. It is reasonable to assume once a pack has been started these would not be reused should patient discontinue therapy part way through a pack. To account for this drug wastage, costs should be based not on the number of patients receiving treatment half-way through the cycle as modelled, but rather based on the number of patients receiving treatment at the beginning of each cycle of model. The impact of adding drug wastage for crizotinib is to increase total costs of crizotinib treatment and hence increase the ICER.

Similarly with regards to pemetrexed combination therapy, therapy is given at the beginning of each cycle of therapy and therefore costs should reflect the number patients eligible for treatment on that day rather than the number eligible half way through a cycle. Given the lack of alignment between the cycle length used in the model and the treatment cycle this more difficult to calculate, but can be done by assuming a linear pattern of discontinuation within cycles. The impact of drug wastage for chemotherapy on the ICER serves to increase the total costs of pemetrexed treatment and therefore reduces the ICER. The impact of drug wastage for chemotherapy is, however smaller than for crizotinib due to lower per cycle treatment costs and because of the lack of alignment between the

cycle length in the model and the treatment cycle. The ERG presents a series of scenario analyses including drug wastage for both crizotinib and pemetrexed patients in Section 6.

5.2.10.2 Drug administration costs for crizotinib and comparator treatments

The costs associated with administration of crizotinib and pemetrexed are summarised in Table 28. The CS base-case analysis assumes no ongoing administration costs for crizotinib as it is an oral therapy and does not require hospital administration. This assumption is justified by referring to a previous appraisal of nintedanib for previously treated locally advanced, metastatic, or locally recurrent NSCLC (TA 347)[48]. This treatment is similar in characteristics to crizotinib, as it involves taking a 200mg tablet twice daily and is for the same disease. In the appraisal no administration costs were included and no issue was raised by the ERG or the committee. The company base-case instead includes a one-off cost of oral administration during the first model cycle. The reason for this is to reflect where patients are given instructions on how to take the tablets by a nurse the first time they are first prescribed the treatment. Following administrations are assumed to only require the patient to collect their prescription during regular check-ups, and therefore are assumed to carry no cost. The health resource group code for oral chemotherapy SB11Z was used in the scenario, with a cost of £163.

However, in the appraisal of crizotinib for previously treated NSCLC ALK-positive patients (TA 296),[23] the committee were in agreement that there would be an administrative cost to the NHS associated with crizotinib therapy. It was concluded that the SB11Z healthcare resource group code for oral chemotherapy should be applied for each cycle of crizotinib therapy in the progression-free survival state. This was concluded in spite of the fact that the same arguments presented in the CS against the inclusion of administration costs were considered by the committee.

In summary, there appears to be inconsistency in prior appraisals in regards to whether administration costs are relevant and should be applied to crizotinib therapy, meaning the correct approach to adopt is unclear. The ERG considered that previous crizotinib appraisal was the most relevant to the current decision problem, and therefore followed the committee's rationale from TA 296. The £163 administration cost was therefore applied to each cycle of crizotinib therapy in the ERGs revised base-case analysis presented in Section 6.

With regards to the administration of chemotherapy based regimens, cisplatin-containing regimens were assumed to incur a day case appointment (unit cost £413.58)[49], whereas carboplatin-containing regimens were assumed to incur an outpatient appointment (unit cost £325.94)[49]. This is based on

assumptions made in a previous NICE technology appraisal for pemetrexed due to the more complex administration required for cisplatin.[47]

Table 28 costs associated with the technology in the CS economic model base-case

Items	Crizotinib (confidence interval)	Pemetrexed plus cisplatin /carboplatin (confidence interval)
Technology Cost per treatment cycle	£4,689.00 list price	£1,467.76 (£1,467.56, £1,467,95)
Mean cost of technology treatment	£51,579.00; assuming median duration of treatment is 11 cycles (accounts for wastage) of 30 days	£8,806.54 (£8,805.37, £8,807.71); assuming median duration of 6 cycles of 21 days
Administration Cost per treatment cycle	£0	£373.13 (£228.08, £399.85)
Mean cost of technology administration	£0	£2,238.79 (£1,368.46, £2,399.08)
Monitoring cost	N/A – monitoring is expected to be based on health state rather than treatment	N/A – monitoring is costed in the health state
ALK-testing, cost per treated patient	[redacted]	N/A – no testing costs are required for pemetrexed treatment
Total	£53,223.60 (£52,917.11, £53,561.22) with PAS]	£11,045.33 (£10,173.83, £11,206.78)

5.2.10.3 Resources and costs of treatment received following disease progression

The CS assumed all patients received second-line treatment with docetaxel following progression of disease. The assumption was based on expert clinical opinion and stated that this is the most reflective of clinical practice in UK. 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.[23] Following treatment with docetaxel all patients were assumed to receive best supportive care (consisting of monitoring only) until death. The unit costs of docetaxel are provided in Table 29. An administration cost of £325.94 per treatment cycle was included in the company's model based on an outpatient appointment.

Table 29 Unit costs of Docetaxel treatment following progression

Unit of Docetaxal	Unit cost[$]	Does per cycle (treatment cycle)	Cost per treatment cycle
20 mg (1 ml Vial)	£4.55	75 mg/m2 (21 days)	£21.49 with wastage £19.44 without wastage
80 mg (4 ml Vial)	£12.39		

140 mg (7 ml Vial)	£20.95		
160 mg (16 ml Vial)	£44.84		

[$]Reference: eMit (electronic market information tool)

5.2.10.4 Resources and costs related to monitoring and palliative care (Health state costs)

The CS incorporated monitoring costs in the model consisting cost of outpatient visit/oncologist visit, GP visit, cancer nurse, complete Blood Count, biochemistry, CT scan and chest X-ray. The costs and resources used were assumed to be same in patients in the progression free health state and the progressed disease health state whilst receiving second-line treatment. The company's clinical experts confirmed that resource utilisation is expected to be the same for patients receiving first-line and second-line treatment for NSCLC. The costs and resources used were estimated separately for the patients in the progressed disease health state who are receiving BSC. Resource utilisation assumptions were derived from TA296, which used values from TA162 and TA258.[23, 50, 51] 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 three previous occasions and, although not all specifically focusing on patients with an ALK mutation, are applicable for second-line NSCLC patients receiving treatment with an oral agent. The unit costs for all resource items, other than drugs, were updated to most recently available values (2014-2015).

Total cost of monitoring were £192.75 per month in first line and second line treatment, and £195.13 per month for patients on BSC. The resources used and unit cost are presented in Table 30. The ERG considered the general approach here to be reasonable.

Table 30 Frequency of resources used in different health states and associated unit costs

Resources used	Frequency of resources used (TA296):		Unit cost*
	Patients in progression free health state and patients in progressed disease health state receiving second-line treatment	Patients in progressed disease health state receiving third-line treatment	
Outpatient Visit	0.75 visits per month	N/A	£158.54
Oncologist visit	N/A	1 visit	£158.54
GP visit	10% of patients per month	28% patients (1 visit)	£50.00
Cancer nurse	20% of patients receive 1 per month	10% patients (1 visit)	£66.42
Complete Blood Count	0.75 per month	All patients, 1 per month	£3.01
Biochemistry	0.75 per month	All patients, 1 per month	£1.19
CT scan	30% patients receive 0.75 per month	5% of patients, 0.75 per month	£132.18

Chest X-ray	0.75 per month	30% of patients, 0.75 per month	£30.23

*Unit costs are based on NHS reference costs 2014-15 except GP visits which is based on Curtis (2014). N/A: not applicable

The CS model included a standard cost for palliative care for all patients before death. The costs of palliative care included hospital care cost for the final 90 days of life[40], and other services costs such as district nurse, nursing and residential care, hospice care and Marie Curie nursing. The total cost of £7,253 was applied in the economic model as a one-off cost at the point of death (see Table 31).

Table 31 Cost of palliative care

Cost	Unit cost (confidence interval)
District nurse	£278 (£226, £335)
Nursing and residential care	£1,000 (£814, £1,205)
Hospice care – inpatient	£550 (£448, £663)
Hospice care – final 3 months of life	£4,500 (£3,661, £5,424)
Marie Curie nursing service	£550 (£448, £663)
District nurse	£278 (£226, £335)
Total cost	**£7,253 (£5,901, £8,742)[$]**

Reference: Georghiou and Bardsley (2014); [$] the total cost of £6,878 was inflated to 2014/15 in line with PSSRU

The ERG did not identify any areas of concern regarding the company's derivation of the health state costs.

5.2.10.5 Resources and costs related to management of adverse events

Adverse events were considered for inclusion in the CS model if they had an incidence of ≥5% in any group of the PROFILE 1014 trial. The justification given for this was that grade I or II adverse events would not be expected to require active intervention. Adverse events were applied as one-time events, occurring in the first 30 days of treatment. Five adverse events met these inclusion criteria: elevated transaminases, neutropenia, anaemia, leukopenia and thrombocytopenia (See section 4.3. The proportions of patients experiencing each adverse event are provided in Table 26 (pg. 91).

Of these, three of these adverse events elevated transaminases, leukopenia and neutropenia were assumed to require no active intervention and therefore incur no costs. The company justified this, based on clinical expert opinion, that these adverse events would be managed through dose reduction/ interruption, or "watch and wait" monitoring. Costs assigned to anaemia and thrombocytopenia were based on costs used in previous NICE technology appraisals. The costs associated with treating each adverse events are described in Table 32. The total cost of treating adverse events was derived using the proportions of patients experiencing each adverse event and costs associated with treating adverse events. The total cost of treating adverse events for crizotinib were estimated to be £0.00 as no patients experienced anaemia and thrombocytopenia. Total cost of treating adverse events for

pemetrexed were estimated to be £163.20. These were applied within the model as a one-off cost during the first cycle of the model for simplicity. The CS conducted a scenario analysis whereby the adverse event costs set to £0 in the pemetrexed arm; this had minimal impact on the ICER.

Table 32 Cost of treating adverse events due to chemotherapy with pemetrexed

Adverse event	Resource required*	Unit cost$	Total cost
Anaemia	1.7 hospitalisation days	£220.16 per day	£374.27
Thrombo-cytopenia	2.0 hospitalisation days	£375.05 per day	£758.50
Neutropenia	Managed by dose reduction	N/A	N/A

*Reference: TA296; $Reference: NHS reference costs 2014-15; N/A=not applicable

5.2.10.6 Cost of ALK-testing

The base-case testing strategy presented in the CE model assumes that every non-squamous NSCLC patient receives an IHC test, and that those who score +1 or +2 go on to then receive a confirmatory FISH test. Two other scenarios were also presented in the CS, one which assumes that everyone who receives a positive IHC score (+1/+2/+3) goes on to receive a FISH test, and the other that everyone receives a FISH test only. Table 33 presents the costs of identifying one ALK-positive patient for each of these three strategies and the subsequent impact on the ICER of changing the testing regime.

Table 33 Impact of Testing Strategy on ICER

Test	Cost of identifying one ALK-positive patient	ICER
IHC followed by ALK for scores = 1+/2+	[redacted]	[redacted]
IHC followed by ALK for all positive scores	[redacted]	[redacted]
FISH only	[redacted]	[redacted]

The proposed testing strategy presented in the base-case analysis is considered to be reasonable (See Section 2.3.2). However, the clinical advisors to the ERG suggested that there is some variation in practice, with some centres testing all patients with IHC, followed by a subsequent FISH test for those with a positive score (+1/+2/+3). This suggests that testing costs may be higher than modelled in practice.

The reported cost of IHC was supplied from data on file and is reported at [redacted] per test. However, it is difficult to estimate what the true cost to the NHS would be as this price does not include laboratory and overhead costs due to a lack of publically available data. This means that the cost of IHC is potentially underestimated. The cost of FISH was taken from the All Wales Genetics Laboratory pricing list which reports a price of £120.[5] However, the cost supplied applies to NHS referrals but might not represent the true total cost of FISH, but rather an internal NHS price for FISH testing. Further it not entirely clear whether this cost would include laboratory and overhead costs to the NHS making the value uncertain. The ERG requested further justification for the costs of ALK testing

from the company at the PFC stage, but did not receive any further substantive justification for the selected values in the response.

An alternative source for the cost of testing for ALK is a study conducted by Cancer Research UK investigating molecular diagnostic provision in England[52]. The research involved sending a survey to every laboratory in England that conducted molecular diagnostic tests. Of those laboratories which conducted tests in solid tumours, 15 out of 25 responded, covering a catchment population of 34.3 million out of a total population of 53.5 million. The estimated total cost of ALK testing per patient was estimated to be £153, based on survey findings received in 2015. When this value is divided by the prevalence of ALK (3.4%) it provides the cost of identifying one ALK-positive patient which is estimated to be £4,500. This cost is substantially higher than the base-case result of [redacted]. The ERG explores the impact of including this alternative cost of testing in section 6.

5.2.11 Cost effectiveness results

5.2.11.1 Base-case results

The company presented results for the base case analysis based on the November 2013 cut of the PROFILE 1014 trial. The company also presented results for the base case analysis with a confidential PAS applied to the list price of crizotinib. This PAS has, however yet to be approved by the department of health and therefore ICER values reported in this section are based on the current list price of cizotinib. The results with the proposed PAS applied are reported in Appendix 10.3. The results of the company base case analysis are presented in Table 34. The company found crizotinib to be more costly [redacted] but also more beneficial (gain of [redacted] QALYs) compared with pemetrexed chemotherapy. The resulting incremental cost-effectiveness ratio (ICER) is [redacted] per QALY gained.

Table 34 Company's base case deterministic results (without PAS)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£) *vs* baseline (QALYs)
Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	---	---	---	---
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2.11.2 Probabilistic mean pairwise cost-effectiveness analysis results

The incremental results from the company's probabilistic analyses are presented in Table 35. The probabilistic ICER value of [redacted] per QALY is very similar to the deterministic base case result of [redacted]. This suggests that the model is linear with regard to uncertainty around input parameters.

Table 35 Company's base case probabilistic results (without PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) *vs* baseline (QALYs)
Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	---	---	---
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 8 shows the probability that crizotinib is cost-effective at a range of different threshold values. The probability of crizotinib being cost-effective using a threshold £20,000, £30,000 and £50,000 per QALY was [redacted] and [redacted] respectively.

Figure 8 Cost-effectiveness acceptability curve: crizotinib versus pemetrexed plus cisplatin/carboplatin

5.2.11.3 One way sensitivity analysis

The company presented the results of a variety of one-way deterministic sensitivity analysis to highlight the uncertainty around different model input parameters impacts on the ICER. Figure 9 shows a tornado diagram of the model parameters which the company considered to have the most influence on the assessment of cost-effectiveness of crizotinib compared with pemetrexed with cisplatin/carboplatin. The model parameters were varied between upper and lower bounds. This analysis highlights how the curve fit parameters for the overall survival curve have the biggest impact on the ICER, with the covariate parameter varying the ICER from [redacted] to [redacted] per QALY.

Figure 9 One-way sensitivity analysis tornado diagram (without PAS)

5.2.11.4 Probabilistic scenario and sensitivity analyses

A range of parameters and assumptions were also varied in the probabilistic sensitivity analysis, with the results presented on page 180 of the CS. Twenty two different parameters and assumptions were varied in the analysis, with the ICER being most sensitive to the time horizon of the analysis, and the inclusion of squamous patients. A time horizon of one year increased the ICER to [redacted], while a five year horizon increased it to [redacted].

An exploratory analysis which included squamous patients was presented as this population was included in the scope. This caused the ICER to increase to [redacted]. Under this scenario it is assumed that every squamous would be tested which would greatly increase the cost of screening, while very few ALK+ patients would likely be identified. The ICER is also fairly sensitive to the patient characteristics selected, with the ICER falling to [redacted] if the patient characteristics from PROFILE 1014 are used in the analysis. There is also sensitivity present when the RPSFT-Wilcoxon cross-over method is adopted to adjust for treatment switching (ICER = [redacted]), and when different combinations of parametric functions are used for PFS and OS.

5.2.12 Model validation and face validity check

5.2.12.1 Validation by the company

The CS states that a number of quality control measures to validate the model including internal quality control process on behalf of the developers and review of the model by an external independent health economist.

The company also externally validated the result of the model against predicted PFS and OS in the Davis, FRAME and JMBD studies the results of this analysis show the models predictions of median PFS are largely consistent with these studies and indicate broad face validity of the model predictions regards PFS and OS. The predicted PFS is also compared with the observed PFS in the PROFILE 1014 trial (adjusted for baseline covariates) used to populate the model. In general the model aligns with the observed data, but there are some differences, these are likely due to the parametric functions used to model PFS.

Further to the external validity assessments described above, the company also stated that model assumptions and results were presented to 4 UK lung clinicians to validate assumptions made in the adjustment of PFS and OS analysis; assumptions made on the resource use and monitoring regimes, HRQoL assumptions and treatments relevant to UK practice.

5.2.12.1 Validation by the ERG

The ERG carried out additional checks of the internal and external validity of the submitted economic model. The internal validation of the model included the use of check list to carry out a series of series of black box tests to evaluate the internal validity of the model. These black box test the internal logic of the model as well checking the predictive validity of parameter inputs (e.g. that increasing effectiveness of the treatment lowers cost-effectiveness). Further to this, the code of the model was examined for potential errors, this included tracking how parameters fed into the model and an examination of the calculation sheets, with a view to understanding how QALYs and costs are accumulated in the model. This review identified a significant number of errors and/potential inconsistencies early in the STA process which the ERG corrected and sent to the company for validation. Additionally, following the clarification stage a large number of further errors were identified in the company model. A brief overview of the errors is described below:

- Cost and benefits were discounted on an annual rather per cycle basis;
- Time zero was included as a complete cycle in the model;
- One-off administration cost for crizotinib were not included;
- Arbitrary administration costs included in both crizotinib and pemetrexed arms'
- QALY calculations for time on second-line treatment and BSC care were incorrect;

- Calculation of number of patients at 8 cycles beyond progression incorrectly calculated for crizotinib patients;
- Duration of time on crizotinib post progression was mis-specified;
- Duration of time on docetaxel mis-specified for both crizotinib and pemetrexed patients (note the ERG has not been able to rectify this error, due to lack of appropriate data);
- Duration of time on BSC mis-specified for both crizotinib and pemetrexed (note the ERG has only been able to partially rectify the mis-specification, due to lack of appropriate data).

Although the company appears to have undertaken a thorough approach to the internal and external validation of their results, the ERG is has serious concerns regarding the internal validity of the model, particularly as simple checks would have ensured that the many errors remaining in the model would have been identified. With regards to the external validity the ERG has some concerns regarding the (face-validity) of the projected survival gains observed in the model which appear to be inconsistent with data on survival rates in the UK presented in the background section of the CS. These data suggest that the 1 year survival rate of stage 3 patients would be 35%, this compares with a predicted survival rate on pemetrexed of 52% in the model which is assumed to include both stage 3 and 4 patients. The ERG would also have liked an examination of the model against the four non-UK economic evaluations identified in the cost-effectiveness review with a particular focus on drivers of cost-effectiveness.

5.3 Conclusions of the cost effectiveness section

A limited number of cost-effectiveness analyses of crizotinib were identified in the systematic review presented in CS, however none of these took UK perspective and were unlikely to generalizable to the UK NHS. Consequently, the manufacturer's model represents the most relevant source of existing evidence. The economic model described in the CS is considered by the ERG to meet the NICE reference case and is broadly in-line with the decision problem specified in the scope. The ICER presented in the CS was [redacted] per QALY; including a yet to be approved PAS the ICER was [redacted] per QALY.

The ERG identified that the electronic economic model submitted by the company contained a significant number of errors. Of these the most important was mis-specification duration of treatment with crizotinib post progression, which was significantly underestimated in the company model. As a consequence the ICER presented in the CS are incorrect and should not be relied upon. In addition to these interval validity issues the ERG also identified a number of uncertainties surrounding assumptions made in the company model. These are outlined in brief below:

1. *Reliability of OS data and assumption of proportional hazards*

The clinical evidence supporting the estimated OS benefits is subject to a number of uncertainties these relate to the immaturity of the OS data; the extensive cross-over that occurred; and imbalances in the second-line treatments received once cross-over had been accounted for. Further to the above, in both the analysis of PFS and OS proportional hazards assumption is made and therefore a single parametric survival function is fitted to the data with a covariate for the treatment effect. This assumption is justified by inspecting the log-cumulative hazard plots for both PFS and OS. The ERG, however, consider there to be a number of reasons why the assumption required for proportional hazard modelling do not hold. Most significant of these is the different duration over which treatment is received suggesting fundamental differences in the mode of action.

1. *Duration of chemotherapy*

The company model assumes six cycles of pemetrexed in combination with platinum-based chemotherapy. The SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy.[41] Discussions with the clinical advisors to the ERG suggest there is some variation practice as regards the typical number of cycles of therapy used. The ERG therefore considers it plausible that company model overestimates the number of cycles of pemetrexed + cisplatin/carboplatin with associated impacts on cost and QALYs.

2. *Transitional utilities*

The company model assumes a transitional utility when moving between lines of treatment to reflect a gradual change in utility. The ERG however, considers that this is likely to double count the potentially higher utility patients in subsequent health states as the average utility figures already account for variation in utility within than health state.

3. *Differential HRQoL for pre-progressed patients*

The company model assumes differential utility rates for pre-progressed patients receiving crizotinb first-line compared with patients receiving pemetrexed combination therapy first-line. This is based on utility values observed in the PROFILE 1014 study. The ERG, however consider that PROFILE 1014 may underestimate the HRQoL of pemetrexed patients as data was only collected while they patients were on treatment. The data on HRQoL in the PROFILE 1014 study will therefore not capture potentially higher HRQoL experienced by patients after diconintauation of treatment, but prior to progression.

4. *Costs of ALK testing*

   Costs of ALK testing were sourced from data on file for IHC testing and from the All Wales Genetics Laboratory pricing list for FISH testing in the company model. It was uncertain whether the costs used include laboratory and overhead costs. Further, the ERG identified alternative source of testing costs that were substantially higher than those identified by the company.

5. *Administration costs associated with crizotinib*

   The company model assumes no on-going administration costs for crizotinib as it is an oral therapy and does not require hospital administration. The ERG, however, noted that in TA296 that the committee considered that on-going administration costs for crizotinib should be included.

6. *Drug wastage*

   With respect to both crizotinib and pemetrexed no drug wastage was assumed for either treatment. The ERG considers this to unrealistic and considers that drug wastage costs should be included for both crizotinib and pemetrexed groups.

In summary, the ERG considers the manufacturer's base-case ICERs even correcting for the identified calculation errors to be overly optimistic towards crizotinib. Additional analyses undertaken by the ERG are presented in Section 6, which consider the potential impact of the remaining uncertainties on the cost-effectiveness results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost-effectiveness analysis presented in Section 5. This section is organised in five parts. Section 6.2 details the impact of critical corrections to company model identified in ERG's validation of the electronic model, this includes changes to the duration patients spend on crizotinib post progression. Section 6.3 details a series of exploratory analyses considering a number of assumptions in the company model. The exploratory analyses in these sections focus on the following issues and uncertainties:

1. Exploration of the impact of alternative treatment strategies for pemetrexed patients;
2. Drug wastage for patients who die part way through a cycle of treatment;
3. Removal of assumed transition utilities;
4. Exploration of alternative assumption regarding post progression utility for patients receiving crizotinib therapy beyond progression;
5. Exploration of alternative utility assumptions regarding pre progressed patients who have completed chemotherapy treatment;
6. Impact of alternative assumptions regarding use of cisplatin and carboplatin;
7. Alternative costs for ALK testing;
8. Addition of administration costs for crizotinib

In Section 6.4, based on a combination of the exploratory analyses presented in Section 6.3, the ERG then presents an alternative ERG base-case that can be considered as plausible as the base-case presented by the company. Section 6.5 then goes on to presented a further series of exploratory analyses in which assumptions regarding the proportional hazards in the analysis of PFS and OS are explored. In this section a range of scenarios are presented where independent parametric survival functions are fitted to the Kaplan-Meier plots of PFS and OS for crizotinib and pemetrexed. Section 6.6 presents a brief conclusion summarising the ERG's additional analyses. All analysis in this section is presented without the company's proposed PAS as it is yet to be approved by the Department of Health. The ERG, however, has also conducted all the analysis presented in this section using the company's proposed PAS , the results of this analysis are presented in Appendix 10.3.2.

6.2 ERG corrections and adjustments to the manufacturer's base-case model

The CS original economic model was corrected by ERG and, also by company during the clarification stage of the assessment. Details of the all errors are presented in section 5.2.12.

The impact of these corrections on the resulting ICER is significant, increasing the ICER from [redacted] per QALY to [redacted] per QALY (See Table 36). The majority of the impact of the corrections on the model is to substantially increase the total costs associated with crizotinib. This is due a significant increase in total drug acquisition costs. This occurs because in the original company model the mean duration of crizotinib treatment was estimated at approximately [redacted] compared with [redacted] in the corrected model.[redacted]

Table 36 Incremental cost-effectiveness ratios incorporating all corrections and adjustments to the manufacturer's base-case model

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's original base-case presented in the CS document	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 Additional ERG analyses

6.3.1 Exploration of the impact of alternative treatment strategies for pemetrexed patients

In the CS base-case analysis, up to 6 cycles of chemotherapy are assumed (pemetrexed plus cisplatin/carboplatin), based on the median number of cycles of pemetrexed plus cisplatin/carboplatin received in the PROFILE 1014 trial.[34] the SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy.[41], Discussions with the clinical advisors to the ERG suggest there is some variation practice as regards the typical number of cycles of therapy used. Therefore, ERG explored the impact of this assumption on the ICER.

Table 37 shows the results for alternative treatment strategies for pemetrexed patients. This analysis, however, only accounts for changes in costs and does not account for any effect on clinical benefits resulting from the use of fewer cycles of chemotherapy; this analysis should therefore be considered conservative with respect to the cost effectiveness of crizotinib. The impact of these alternative treatment strategies on the resulting ICER is small: an approximate £1,200 increase when patients had 5 cycles of pemetrexed plus cisplatin/carboplatin; and approximately £2,900 increase when patients had 4 cycles.

Table 37 impact of alternative treatment strategies for pemetrexed patients (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.2 Drug wastage for patients who die part way through a cycle of treatment

As noted in Section 5, the company base case assumes no drug wastage for either crizotinib of pemetrexed. The ERG consider it likely that for both treatment groups there would be some, albeit limited drug wastage when a patient discontinues treatment part was through a treatment cycle. The ERG therefore has undertaken an analysis including drug wastage in both arms. For crizotinib this was done by assuming that drug costs are based on the proportion of patients on treatment at the beginning of a model cycle rather than halfway through a cycle. For chemotherapy this was done by assuming drug costs are based on the proportion of patients eligible for treatment at the time of delivery of the next cycle of chemotherapy assuming a linear decline in treatment discontinuation within model cycles. The results of this analysis are presented in Table 38. This analysis shows that drug wastage has a modest impact on the resulting ICER, increasing it by approximately £1000 per QALY.

Table 38 Results of drug wastage (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st line crizotinib wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st line pemetrexed wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st line crizotinib and pemetrexed both wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.3 Removal of assumed transition utilities

In the CS base-case analysis, a 'transitional' utility was applied when moving between health states during the first cycle following progression. The CS presented a sensitivity analysis whereby the

transitional utility was applied to patients receiving treatment beyond progression when they progressed. In this scenario it is assumed that utility drops immediately to the utility value for that health state.

The ERG has concerns about the use of such transitional utilities as this is likely to double count higher utility after progression. The ERG therefore considers the scenario analysis presented by the company in which no transitional utilities are included to be more plausible than the company base-case. The results of this analysis using the ERG corrected model are presented in Table 39. Excluding transitional utilities results in a small reduction in QALYs accrued in both treatment groups compared with the CS's corrected base-case and results in a slight reduction in the ICER (<£600).

Table 39 Results assuming no transitional utility (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No transitional utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.4 Exploration of alternative assumption regarding post progression utility for patients receiving crizotinib therapy beyond progression

The CS model assumed that the 73% of patients who receive treated beyond progression with crizotinib have a utility score of ([redacted]) based on the midpoint between pre progression utility ([redacted]) and post progression utility (0.66). While the ERG consider it is plausible that patients treated beyond progression may experience some utility benefit, it considers that the value chosen is probably too high, as it implies that progressed patients receiving crizotinib would have a higher utility than pre-progressed patients receiving pemetrexed patients. Given that symptom load for pre-progressed patients would likely be significantly lower, the ERG considers this unlikely. In the absence of appropriate data to populate this utility value the ERG presents an alternative analysis in which it is assumed that patients being treated beyond progression receive a utility value of [redacted] based on utility of pre-progressed patients receiving pemetrexed. The resulting ICERs with this assumption are presented in Table 40. The results show that it has only a modest impact on the ICER.

Table 40 Results of alternative utility assumption for post progression patients receiving crizotinib therapy beyond progression (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative post progression utility for crizotinib patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.5 Exploration of alternative assumptions of utility regarding pre progressed patients who have completed chemotherapy treatment;

As noted in the section 5, chemotherapy is associated with frequent side effects and is therefore plausible that patients receiving treatment would have lower utility than those who have finished treatment. However, discussion with clinical advisors suggests that once treatment has been completed that patients who received first-line chemotherapy will experience a significant increase in HRQoL. Due to the way data was collected in PROFILE 1014 the ERG did not think this is adequately reflected in the HRQoL data used in the model. The ERG therefore present and alternative scenario which retains a differential utility between crizotinib and chemotherapy patients while the latter are on treatment, but once chemotherapy patients have discontinued treatment chemotherapy patients receive the higher utility of [redacted] currently assumed to be experienced by crizotinib patients. The results of this analysis are presented in Table 41. This analysis shows that there is a 0.02 of QALY gain in the pemetrexed + cisplatin/carboplatin patient group compared with the CS's base-case leading to modest increase in the estimated ICER.

Table 41 Results of alternative assumptions of utility regarding pre progressed patients after chemotherapy treatment completed (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progressed utility adjustment for chemotherapy patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.6 Impact of alternative assumptions regarding use of cisplatin and carboplatin

In the CS base-case, it is assumed that [redacted] of patients on pemetrexed combination therapy will receive cisplatin and [redacted] will receive carboplatin, which is based on the split observed in PROFILE 1014. The CS also presented a scenario analysis whereby 25% of patients receive pemetrexed plus cisplatin and 75% receive pemetrexed plus carboplatin; this is based on clinical

advice that some centres up to three quarters of patients may receive carboplatin instead of cisplatin. The clinical advisors to the ERG confirmed this scenario was more reflective of clinical practice in the UK suggesting that approximately 30% of patients would receive cisplatin and 70% carboplatin. Hence, ERG considered that the proportion of 25% of cisplatin and 75% of carboplatin are more plausible scenario. The ERG therefore present the results of this scenario analysis (Table 42) carried out by the company as the ERG include this in assumption in the ERG base-case analysis .The results show that it has minimal impact on the ICER.

Table 42 Results of alternative assumptions regarding use of cisplatin and carboplatin (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25% use of cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.7 Alternative costs for ALK testing

As described in section 5, the CS base-case testing strategy assumed that every non-squamous NSCLC patient receives an IHC test, and that those who score +1 or +2 go on to then receive a confirmatory FISH test. Based on this testing strategy the cost of identifying one ALK-positive patient is estimated to be [redacted]. The costs this is based on are however, subject to a degree of uncertainty as it is unclear whether laboratory and overhead costs are included. The ERG therefore sought to identify alternative source of costs and identified a survey of UK laboratories conducted by Cancer Research UK that suggested that the mean cost of ALK testing was £153 per patient. Given the incidence of ALK-positive patients, this would imply a cost of £4,500 to identifying one ALK-positive patient. The results of an analysis including this alternative cost of testing are presented in Table 43. This analysis shows that the alternative cost of ALK testing has moderate impact on the resulting ICER increasing it by £3,500 compared with the CS's base-case.

Table 43 Results assuming alternative costs for ALK testing (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative costs for ALK testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.8 Addition of administration costs for crizotinib

The CS base-case analysis assumes no ongoing administration costs for crizotinib as it is an oral therapy and does not require hospital administration, and only includes a one-off cost to reflect where patients are given instructions on how to take the tablets by a nurse the first time they are prescribed the treatment. However, as noted in Section 5, in the previous appraisal of crizotinib as second-line treatment the committee (TA 296) the committee considered that there would be an administrative cost to the NHS associated with crizotinib therapy. The ERG therefore present an analysis in which an on-going per cycle administration costs is included. The results of this analysis are presented in Table 44.This analysis shows that addition of the per cycle administration costs of crizotinib has modest impact on the resulting ICER.

Table 44 Results assuming additional per cycle administration costs for crizotinib (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-going administration costs for crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 ERG's preferred base-case

Table 45 presents the ERG's preferred base-case this combines a number of the changes to the company base-case explored in Section 6.3. Specifically, the ERG base-case makes the following amendments to the CS's base-case:

1. Drug wastage for patients who die part way through a cycle of treatment in both crizotinib and chemotherapy group;
2. Removal of assumed transition utilities;
3. Alternative utility of [redacted] for the pre progressed patients who have completed chemotherapy treatment;
4. Alternative assumptions regarding use of 25% cisplatin and 75% carboplatin;
5. Alternative costs of £4,500 for ALK testing
6. Per cycle drug administration costs for crizotinib

The ERG considers this alternative base-case to be at least as plausible as the company's base-case. Combining these modifications to the company model leads to a substantial increase in the ICER from [redacted] in the corrected base-case to [redacted] in the ERG's alternative base-case.

Table 45 Incremental cost-effectiveness ratios of the CS's corrected base-case and ERG's preferred base-case (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 Exploratory analysis on PFS and OS

The base-case analysis in the CS makes use of the proportional hazards assumption, justifying this by inspecting the log-cumulative hazard plots for both PFS and OS. In the CS's base-case, the generalised gamma curve for PFS and the Weibull curve for OS were selected for both crizotinib and pemetrexed. However, the ERG believes that fitting separate parametric models is likely to produce more reliable estimates of PFS and OS (Sections 4.2.2.1 and 4.2.2.3). TThe ERG has therefore explored a range of scenarios where independent parametric survival curves are fitted to PFS and OS for crizotinib and pemetrexed patients.

The ERG conducted analyses uses the fully stratified model provided by company in its clarification response. The fully stratified model which comprises independent models for each treatment with separate covariates for prognostic factors, included the following assumptions

- Survival model parameters and baseline covariate parameters are estimated separately for each treatment arm
- The underlying shape and the impact of important prognostic factors are allowed to be different by treatment arm
- Uses two subsets of PROFILE 1014 data to fit the models for each treatment arm (smaller sample size)

6.5.1 Exploration of uncertainty around choice of parametric curves and estimated PFS

The AIC and BIC for the PFS curves (including covariates for treatment and prognostic factors) are provided in Table 46 (lower values are preferred for best fit). The PFS curve fits for crizotinib are shown in Figure 10 and the PFS curve fits for pemetrexed plus cisplatin/carboplatin are shown in

Figure 11 along with their respective Kaplan-Meier curves, which have each been adjusted for separate covariates for prognostic factors.

The AIC and BIC indicate that there is no great difference between different curve fits in terms of fit to the data in two treatments. However, the generalised gamma, loglogistic and lognormal curves had the lowest values for crizotinib, and therefore best fit to the observed Kaplan-Meier data for crizotinib; and the generalised gamma and Weibull curves had the lowest values for pemetrexed, and therefore best fit to the observed Kaplan-Meier data for pemetrexed. Therefore, ERG explores the impact of those curves on ICREs using combination of the curves for both treatments.

Table 46 AIC and BIC for PFS (models including separate covariates for prognostic factors)

	Crizotinib		Pemetrexed	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	766.13	791.31	864.58	889.71
Generalised gamma	762.57	794.05	834.21	865.62
Gompertz	768.12	796.45	840.47	868.75
Log-logistic	761.60	789.93	845.23	873.51
Log-normal	760.95	789.28	850.60	878.88
Weibull	764.67	793.00	832.49	860.77

AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 10 PFS parametric curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

Figure 11 PFS parametric curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)

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The PFS curves for both treatments were adjusted to the real-world data patient characteristics. The estimated mean PFS varies between [redacted] to [redacted] months for crizotinib and [redacted] to [redacted] months for pemetrexed patients (Table 47). The progression free survival in crizotinib patients are greater than pemetrexed patients in all fitted models.

Table 47 Mean progression free survival (PFS) in months estimated from different fitted curves (adjusted to the real-word patients characteristics)

Model	Crizotinib	Pemetrexed
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

The ERG conducted analysis to explore impact on ICERs using the following selected combination of curves for PFS:

- 1st assumption - including parametric curves of loglogistic for crizotinib and gamma for pemetrexed
- 2nd assumption - including parametric curves of lognormal for crizotinib and gamma for pemetrexed
- 3rd assumption - including parametric curves of gamma for crizotinib and gamma for pemetrexed
- 4th assumption - including parametric curves of loglogistic for crizotinib and Weibull for pemetrexed
- 5th assumption - including parametric curves of lognormal for crizotinib and Weibull for pemetrexed
- 6th assumption - including parametric curves of gamma for crizotinib and Weibull for pemetrexed

The results of the analysis are presented in Table 48. The results show that there is significant difference in QALYs. The QALYs are higher compared with the ERG's base-case in all assumptions in both treatments. The fully stratified model assumptions for PFS have moderate impact on resulting ICERs. The ICERs are lower than the ERG's base-case. The resulting ICERs vary between [redacted] and [redacted] per QALY.

Table 48 Incremental cost-effectiveness ratios of different combination of parametric curves for PFS (without PAS)

	PFS fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		ICERs
	Crizotinib	**Pemetrexed**	**QALYs**	**Costs**	**QALYs**	**Costs**	
ERG's preferred base-case (proportional hazard assumption)	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st assumption	Loglogistic	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd assumption	Lognormal	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd assumption	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th assumption	Loglogistic	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th assumption	Lognormal	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5.2 Uncertainty around choice of parametric curves and estimated OS

The AIC and BIC for the OS curves (including covariates for treatment and prognostic factors) are provided in Table 49; lower values are preferred for best fit. The OS curve fits for crizotinib are shown in Figure 12 and the OS curve fits for pemetrexed plus cisplatin/carboplatin are shown in

Figure 13 along with their respective Kaplan-Meier curves, which have each been adjusted for separate covariates for prognostic factors.

The AIC and BIC indicate that there is no great difference between different curve fits in terms of fit to the data in two treatments. However, the generalised gamma, gompertz and Weibull curves had the lower AIC and BIC values and visually more plausible for crizotinib. The exponential and Weibull curves had the lower AIC and BIC values, and visually more plausible for pemetrexed. Therefore, ERG explores the impact of those parametric curves on ICREs using combination of the curves for both treatments.

Table 49 AIC and BIC for OS (models including separate covariates for prognostic factors)

	Crizotinib		Pemetrexed	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	433.88	459.06	406.78	431.91
Generalised gamma	433.05	464.53	409.45	440.87
Gompertz	434.12	462.44	407.57	435.84
Log-logistic	436.79	465.12	407.49	435.76
Log-normal	440.43	468.76	408.40	436.67
Weibull	433.34	461.66	408.65	436.93

Figure 12 OS curve fits – crizotinib; predicted curves estimated using patient characteristics from PROFILE 1014 crizotinib arm (models including separate covariates for prognostic factors)

Figure 13 OS (using crossover method TSA) curve fits – pemetrexed plus cisplatin/carboplatin; predicted curves estimated using patient characteristics from PROFILE 1014 pemetrexed plus cisplatin/carboplatin arm (models including separate covariates for prognostic factors)

The OS curves for both treatments were adjusted to the real-world data patient characteristics. The mean OS varies between [redacted] to [redacted] months for crizotinib and [redacted] to [redacted] for pemetrexed patients (Table 50). The estimated mean OS varies significantly between the treatments. Notably, the gompartz curve fitted model for pemetrexed has greater overall survival than any of the fitted model for crizotinib.

Table 50 Mean overall survival (OS) in months in months estimated from different fitted curves (adjusted to the real-word patients' characteristics)

Model	Crizotinib	Pemetrexed
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

The ERG conducted analysis to explore impact on ICERs using the following selected combination of curves for OS:

- 1st assumption - including parametric curves of gamma for crizotinib and exponential for pemetrexed
- 2nd assumption - including parametric curves of gompertz for crizotinib and exponential for pemetrexed
- 3rd assumption - including parametric curves of weibull for crizotinib and exponential for pemetrexed
- 4th assumption - including parametric curves of gamma for crizotinib and weibull for pemetrexed
- 5th assumption - including parametric curves of gompertz for crizotinib and weibull for pemetrexed
- 6th assumption - including parametric curves of weibull for crizotinib and weibull for pemetrexed

Results of the analysis are presented in Table 51. The results show that the fully stratified model has significant impact on QALY gains. The QALY gains are lower for crizotinib patients and higher in pemetrexed compared with the ERG's preferred base-case. Therefore, the resulting ICERs are substantially higher than the ERG's preferred base-case.

Table 51 Incremental cost-effectiveness ratios of different combination of parametric curves for OS (without PAS)

	OS fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		
	Crizotinib	**Pemetrexed**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard assumption)	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st assumption	Gamma	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd assumption	Gompertz	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd assumption	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th assumption	Gompertz	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th assumption	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52 shows further illustration of uncertainty around the proportional hazard model vs. fully stratified model. There is approximately £28,000 increase in the ICER in the fully stratified model

compared with proportional hazard model keeping the fitted curves same for both treatments. The ICERs increases further to [redacted] when the fitted curves are selected based on lowest AIC.

Table 52 Incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model (without PAS)

	Fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		
	PFS	OS	QALYs	Costs	QALYs	Costs	ICER
ERG's preferred base-case (proportional hazard model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model and curves selected using lowest AIC)	Log-normal – crizotinib; and gamma - pemetrexed	Gamma – crizotinib; and exponential - pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.6 Conclusions from ERG analyses

In this Section the ERG has presented a number of additional analyses. These analyses were carried in a number of stages. The first stage address critically important errors in the electronic model submitted by the company which meant that total duration of treatment with crizotinib was significantly underestimated. The ICER from the correct base-case model was [redacted] per QALY which was significantly higher than the ICER in original model provide by the company [redacted]) due a substantial increase in total drug acquisition costs for crizotinib. Using the correct model the ERG then presented a number of sensitivity analyses to explore a number of issues raised in Section 5. This concluded with the presentation of an alternative ERG base-case which combined a number scenarios presented by the company and the alternative assumptions explored in this section. The ERG's base-case analysis suggests that the ICER for crizotinib compared with pemetrexed plus cisplatin/carboplatin is around [redacted] per QALY. This base-case is considered to be as plausible as the one presented by the company (corrected for calculation errors).

The final part of this section carried a further series of exploratory analyses that explored the impact of the proportional hazards assumption made in the analysis of PFS and OS. The results of this analysis show the ICER is generally robust to this assumption with regards to PFS, but is very sensitive with respect to this assumption with regards to OS producing significantly higher ICERs than when proportional hazards is assumed. This is part due to the immaturity of the OS data which

leads to considerable uncertainty around the extrapolation. Using the same parametric functions fitted in the company's base where proportional hazards is assumed this analysis gives a ICER of [redacted] per QALY (assuming ERG assumptions) and where the best statistically fitted curves are selected this analysis produces an ICER of [redacted].

7 End of life

NICE 'end of life' criteria are as follows: that the treatment is indicated for patients with a short life expectancy, normally 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 to current NHS treatment; and that the treatment is licensed or otherwise indicated, for small patient populations.

The ERG notes that whether crizotinib for first-line treatment of advanced non-squamous ALK-positive NSCLC meets NICE end-of life criteria is unclear.

The life expectancy for patients with ALK-positive NSCLC is not known with any certainty. The CS presented four estimates of median overall survival without crizotinib. Two were of patients treated with pemetrexed + platinum but were of non-squamous but not specifically ALK-positive patients (median OS = 11.8 (95% CI 10.4, 13.2) [1] and 10.6 (95% CI 9.4 to 12.0).[21] The ERG identified a further trial in non-squamous advanced NSCLC with a relevant treatment arm (pemetrexed + carboplatin); this reported median OS of 7.8 (95% CI 5.4, 10.1). [2] It is unclear how ALK-positive patients compare with the wider non-squamous population. One estimate specific to ALK-positive patients (20 (95% CI 13, 26) was based on 36 crizotinib naïve patients but most had received previous treatments for advanced disease, i.e. they were not a first-line population. [22] The estimate given by UK clinical experts is an expected life expectancy of around 15 months. The results from the main RCT of crizotinib PRIOFILE 1014 reported high survival rates of 65% to 75% at 1 year and 65% to 70% at 18 months depending on method of crossover adjustment. These estimates are very high when compared to those reported in other trials of pemtetrexed + platinum in advanced non-squamous NSCLC. Does this difference indicate that ALK-positive patients have a better prognosis than the broader non-squamous population? If ALK-positive patients have a better prognosis than the broader non-squamous population, this brings into question the validity of the current estimates of life expectancy of patients with advanced non-squamous ALK-positive NSCLC: how realistic is an estimate of around 15 months? The median OS is estimated to be [redacted] months for pemetrexed + platinum in economic model base case, with a plausible range between [redacted] and [redacted] months.

The life extension from treatment with first-line crizotinib is highly uncertain. Available results from a single RCT (PROFILE 1014) indicate an increase in median PFS of 3.9 months. How this translates into an OS benefit is not known. The hazard ration for OS calculated after crossover adjustment is around 0.6, which is less than the HR of 0.45 for PFS – but it is unclear what means in terms of OS survival duration benefit. In the economic model base case, the median OS estimated to be [redacted] months for pemetrexed + platinum and [redacted] months for crizotinib patients. This indicates an increase in median OS of [redacted] months. However, it is plausible that the estimated value varies as median OS changes on the choice of the parametric fitted curves: the plausible range of OS for pemetrexed platinum is between [redacted] and [redacted], and for crizotinib is between [redacted] and [redacted] months.

Crizotinib is indicated for a small patient population: it is estimated by the company that fewer than 500 patients per year will be eligible for first-line crizotinib.

8 Overall conclusions

The principal source of the evidence on the efficacy and safety of crizotinib was the PROFILE 1014 RCT which compared crizotinib with pemetrexed in combination with either cisplatin or carboplatin.

PROFILE 1014 showed crizotinib to have a significant benefit in terms of median PFS compared to the pemetrexed group (HR 0.30, 95% CI 0.21 to 0.43). In terms of adverse events, the most frequently reported AEs experienced on crizotinib were vision disorders (62%), nausea (57%), and diarrhoea (54%). The company considered the OS data from PROFILE 1014 immature and median OS was not reached. The unadjusted hazard ratio for death with crizotinib was 0.821 (0.536 to 1.255). A number of methods of adjustment for crossover were implemented and the crossover adjusted hazard ratios ranged from 0.571 to 0.674, across nine parametric models using three methods of analyses; not all were statistically significant.

The main limitations of the clinical evidence presented were:

- The immaturity of OS data from the PROFILE 1014 study;
- The high rate of crossover seen in the PROFILE 10147 trial, and limitations regarding the methods used to adjust for this in an attempt to derive an absolute survival gain for crizotinib;
- Extensive differences between crizotinib and chemotherapy patients in proportion and of patients receiving second-line therapy and the type of therapy received once crossover had been accounted for.

There are several remaining uncertainties surrounding the evaluation of the clinical evidence. The main ones are:

- The size and duration of the PFS benefits of crizotinib compared with chemotherapy;
- The OS benefits of crizotinib compared with chemotherapy;
- The comparability of the populations in PROFILE 1014 with the UK ALK positive NSCLC population;
- The clinical characteristics and prognosis of a typical population of patients with advanced non-squamous ALK-positive NSCLC;
- The efficacy and safety of crizotinib in a population who are not eligible for chemotherapy;
- The efficacy and safety of crizotinib in who are ALK postive and patients who do not have adenocarcinoma NSCLC.

The Company's *de-novo* economic analysis was considered by the ERG to provide the most relevant evidence for the decision problem. The model structure was appropriate for the decision-problem. The company presented both deterministic and probabilistic analysis. The deterministic incremental cost-

effectiveness ratio (ICER) in the base-case analysis was [redacted] per QALY and [redacted] per QALY in the probabilistic analysis.

The major weakness of the cost-effectiveness model presented in the CS related to the modelling of duration of crizotinib treatment beyond progression. As outlined above, this mean that the model underestimated total time on crizotinib and therefore total costs associated with crizotinib treatment. Further, to these calculation errors the ERG did not consider that the manufacturer had adequately justified a number of assumptions made in the economic model. These main weakness and uncertainties in the model are as follows:

- Uncertainties regarding estimated OS benefits due the immaturity of the OS data; the extensive cross-over that occurred; and imbalances in the second-line treatments received once cross-over had been accounted for.
- Assumption of proportional hazards for PFS and OS data;
- The HRQoL of patients initiate pemetrexed combination therapy, post treatment pre-progression;
- Costs associated with ALK testing.

The ERG presented a number of additional analyses correcting for critical calculation errors and considering alternative plausible assumptions. ICERs from these analyses were [redacted] and [redacted] per QALY, respectively. The ERG also carried out further exploratory analysis around the assumption of proportion hazards which was made in the company's analysis of PFS and OS. This analysis showed the ICER to be very sensitive to this assumption with the resulting analysis producing ICER's in excess of [redacted] per QALY. In light of the sensitivity of the model to estimated OS benefits the ERG considers the cost-effectiveness of crizotinb to be highly uncertain and potentially considerably higher than presented in the company model even once corrected for calculation errors.

Finally, it should be noted that the assessment of clinical and cost-effectiveness of crizotinib presented in this report matches the NICE scope but ignores the possible future use of pemetrexed maintenance therapy as a more effective comparator than pemetrexed plus platinum therapy alone. The possibility of using crizotinib as a 2nd line treatment in ALK-positive NSCLC patients has also been ignored.

8.1 Implications for research

Long-term follow-up data are being collected for the PROFILE 1014 trial and are anticipated to be available in early 2017. This long term-data will provide further data on the effectiveness of crizotinib and particularly the impact of crizotinib on OS, which is currently highly uncertain due to the immaturity of the currently available data.

Due to extensive cross-over in the PROFILE 1014 trial and other design issue which led to significant imbalance in second-line treatments receive by crizotinib and chemotherapy, further clinical studies evaluating the effectiveness of crizotinib are warranted to confirm the results of PROFILE 1014. High crossover is likely to be the case in any future RCT comparing crizotinib with chemotherapy, a well-designed prospective cohort study may therefore be more appropriate. This study should have an appropriately long duration of follow-up and mandate complete reporting of second- and greater-line therapy.

Further research into the characteristics and prognosis of a typical population of patients with advanced non-squamous ALK-positive NSCLC is also required as there is currently uncertainty regarding the typical population and results from the PROFILE 1014 trial suggest that ALK positive patients may have significantly different prognosis than ALK negative patients.

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10 Appendices

10.1 Description and critique on searches conducted for measurement and valuation of health effects

The CS described the search strategies used to identify relevant HRQoL data for people with advanced/metastatic ALK-positive NSCLC treated with critizotinib or relevant comparators. The search strategies were briefly described in the main body of the submission in Section 5.4.3 and full details were provided in Appendix 17.

The company updated the searches from a similar previous systematic review carried out in 2012 on crizotinib for the treatment of previously-treated ALK-positive NSCLC. The electronic databases MEDLINE, MEDLINE In Process Citations and Daily Update, EconLit and EMBASE were searched on 31st July 2015, via the Ovid interface. The NHS Economic Evaluations database and the Health Technology Assessment database were searched on 3rd August 2015, via the Cochrane Library. A date limit to restrict retrieval to records from 2012 onwards was applied. To supplement the electronic database searches, the manufacturer reported scanning the reference lists of included articles, searching the grey literature and searching for completed and on-going trials.

The methods used to identify HRQoL studies were appropriate, with some minor issues noted below. The reporting of the database searches was clear with sufficient detail to allow the searches to be reproduced. The databases searched, the service providers used, the date of the searches and complete strategies were all clearly reported. However, there were no details reported in Appendix 17 about the search for grey literature or the search for completed and on-going trials. It also would have been useful if the manufacturers had reported the date segments of each database searched.

The structure of the search strategies presented in tables 113, 114 and 115 in Appendix 17 is appropriate to capture studies on HRQoL in people with advanced/metastatic lung NSCLC. The correct fields have been searched for the most part. However, the date limit used at line 14 in Table 112 uses the entry date (ed) field. Not all records in Medline In Process are assigned an entry date. Therefore any relevant records from Medline In Process without an entry date would not have been identified by this search. The search lines have all been combined correctly and truncation and wildcards have been used appropriately. The range of textwords searched for the HRQoL terms in Table 112 at line 7 is fairly limited and including further synonyms for HRQoL and associated measures would have improved this search.

10.2 Description and critique on searches conducted for healthcare resource identification, measurement and valuation

The MS described 1) the search strategies used to identify relevant costs and resource use data for people with advanced/metastatic ALK-positive NSCLC and 2) the search strategies used for the identification of costs and resource use associated with molecular or diagnostic testing for genetic mutations in patients with advanced/metastatic lung cancer. The search strategies were briefly described in the main body of the submission in Section 5.5.2 and full details were provided in Appendix 19.

The manufacturer updated the searches from a similar previous systematic review carried out in 2012 on crizotinib for the treatment of previously-treated ALK-positive NSCLC. The electronic databases MEDLINE, MEDLINE In Process Citations and Daily Update, EconLit and EMBASE were searched on 31st July 2015, through the Ovid interface. The NHS Economic Evaluations database and the Health Technology Assessment database were searched on 3rd August 2015, via the Cochrane Library. A date limit to restrict retrieval to records from 2012 onwards was applied. A further limit to UK only studies was applied to some of the searches. To supplement the electronic database searches, the manufacturer reported scanning the reference lists of included articles, searching the grey literature and searching for completed and on-going trials.

The methods used to identify the cost and resource use studies were appropriate, with some minor issues noted below. The reporting of the database searches was clear with sufficient detail to allow the searches to be reproduced. The databases searched, the service providers used, the date of the searches and complete strategies were all clearly reported. However, there were no details reported in Appendix 19 about the search for grey literature or the search for completed and on-going trials. It also would have been useful if the manufacturers had reported the date segments of each database searched.

The structure of the search strategies presented in tables 117, 118, 119, 120 and 121 in Appendix 19 were appropriate to capture cost and resource use studies in people with advanced/metastatic ALK-positive NSCLC. The correct fields have been searched for the most part. However, the date limit used at line 11 in Table 117 and again at line 8 in Table 121 uses the entry date (ed) field. Not all records in Medline In Process are assigned an entry date. Therefore any relevant records from Medline In Process without an entry date would not have been identified by these searches. The search lines have all been combined correctly and truncation and wildcards have been used appropriately.

The range of text words and subject headings searched is generally appropriate. However in table 117 (MEDLINE search) at line 7 and table 118 (EMBASE search) at line 7 a fairly limited range of text

words has been used to limit to UK only studies. Further synonyms could have been used, for example GB, "G.B.", "U.K." and also the inclusion of major UK cities would have improved the sensitivity of this search. The search strategy in table 121 at line 6 has only included the subject heading for clinical laboratory techniques to try and capture studies of molecular or diagnostic testing. It would have been better to include text word searches for molecular or diagnostic testing in addition, to avoid missing potentially relevant studies.

10.3 Cost-effectiveness results (confidential PAS applied)

10.3.1 Results of CS's base case with PAS

Table 53: Deterministic results with PAS applied summarises the deterministic results with the PAS applied, and Table 54 the probabilistic results. The PAS is yet to be approved and is therefore not included in the base-case results.

Table 53: Deterministic results with PAS applied

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£) *vs* baseline (QALYs)
Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	---	---	---	---
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,306

Table 54: Probabilistic results with PAS applied

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) *vs* baseline (QALYs)
Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	---	---	---
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	£45,488

10.3.2 Corrected model with PAS

Table 55 shows the results of corrections to the company's electronic model with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.2.

Table 55 Impact of model corrections to company's base-case (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Original model)	[redacted]	[redacted]	[redacted]	[redacted]	£46,306
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847

10.3.3 Results of sensitivity analyses with PAS

Table 56 shows the results of alternative treatment strategies for pemetrexed patients with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.1.

Table 56 impact of alternative treatment strategies for pemetrexed patients (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
5 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	£65,134
4 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	£66,952

Table 57 shows the results of drug wastage analysis with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.2.

Table 57 Results of drug wastage analysis (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
1st line crizotinib wastage	[redacted]	[redacted]	[redacted]	[redacted]	£65,325
1st line pemetrexed wastage	[redacted]	[redacted]	[redacted]	[redacted]	£63,636
1st line crizotinib and pemetrexed both wastage	[redacted]	[redacted]	[redacted]	[redacted]	£65,114

Table 58 shows the results assuming no transitional utility with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.3.

Table 58 Results assuming no transitional utility (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
No transitional utility	[redacted]	[redacted]	[redacted]	[redacted]	£63,560

Table 59 shows results of alternative utility assumption for post progression patients receiving crizotinib therapy beyond progression with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.4.

Table 59 Results of alternative utility assumption for post progression patients receiving crizotinib therapy beyond progression (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
Alternative post progression utility for crizotinib patients	[redacted]	[redacted]	[redacted]	[redacted]	£64,915

Table 60 shows results of alternative assumptions of utility regarding pre progressed patients after chemotherapy treatment completed with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.5.

Table 60 Results of alternative assumptions of utility regarding pre progressed patients after chemotherapy treatment completed (With PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
Pre-progressed utility adjustment for chemotherapy patients	[redacted]	[redacted]	[redacted]	[redacted]	£65,335

Table 61 shows results of alternative assumptions of proportion used for cisplatin (25%) and carboplatin (75%) with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.6.

Table 61 Results of alternative assumptions regarding use of cisplatin and carboplatin (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
25% use of cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	£63,748

Table 62 shows results assuming alternative costs for ALK testing with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.7.

Table 62 Results assuming alternative costs for ALK testing (With PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative costs for ALK testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 63 shows results additional per cycle administration costs for crizotinib with the CS'sproposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.8.

Table 63 Results assuming additional per cycle administration costs for crizotinib (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
On-going administration costs for crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	£68,168

Table 64 shows incremental cost-effectiveness ratios of the CS's corrected base-case and ERG's preferred base-case with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.4.

Table 64 Incremental cost-effectiveness ratios of the CS's corrected base-case and ERG's preferred base-case (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£63,847
ERG's preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	£74,225

Table 65 shows incremental cost-effectiveness ratios of different combination of parametric curves incorporated to estimate PFS with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.5.1.

Table 65 Incremental cost-effectiveness ratios of different combination of parametric curves for PFS (with PAS)

	PFS fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		ICER
	Crizotinib	Pemetrexed	QALYs	Costs	QALYs	Costs	
ERG's preferred base-case (proportional hazard assumption)	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£74,225
1st assumption	Loglogistic	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£73,043
2nd assumption	Lognormal	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£73,007
3rd assumption	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£73,799
4th assumption	Loglogistic	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£72,939
5th assumption	Lognormal	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£72,903
6th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£73,692

Table 66 shows incremental cost-effectiveness ratios of different combination of parametric curves incorporated to estimate OS (with the CS's proposed PAS applied). The results are equivalent to the without PAS results presented in Section 6.5.2.

Table 66 Incremental cost-effectiveness ratios of different combination of parametric curves for OS (with PAS)

	OS fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		
	Crizotinib	**Pemetrexed**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard assumption)	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£74,225
1st assumption	Gamma	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£130,548
2nd assumption	Gompertz	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£109,831
3rd assumption	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£95,156
4th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£119,528
5th assumption	Gompertz	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£102,638
6th assumption	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£90,191

Table 67 shows incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.5.2.

Table 67 Incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model (with PAS)

	Fitted curves		**Crizotinib**		**Pemetrexed + cisplatin/carboplatin**		
	PFS	**OS**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	£74,225
ERG's preferred base-case (fully stratified model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	£89,592
ERG's preferred base-case (fully stratified model and curves selected using lowest AIC)	Log-normal – crizotinib; and gamma - pemetrexed	Gamma – crizotinib; and exponential - pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	£130,088

1 Summary

Crizotinib is a first-in-class, inhibitor of anaplastic lymphoma kinase (ALK) and is indicated for adults with ALK-positive advanced non-small-cell lung cancer (NSCLC).

Based on tumour histology, there are two types of lung cancers: NSCLC and small cell lung cancer (SCLC). NSCLC can be further grouped into: adenocarcinoma (approximately 40%), squamous cell carcinomas (25-30%), large cell carcinoma (10-15%) and other subtypes (e.g. adenosquamous carcinoma and sarcomatoid carcinoma). About 4% and 10% of adenocarcinoma patients are believed to have ALK gene rearrangement (ALK-positive NSCLC) and EGFR gene mutations, respectively. ALK-positive NSCLC is characterised by alterations (translocations) of ALK gene and is more commonly related with adenocarcinomas although it can occur in any of the NSCLC: estimates are 3.4% of non-squamous and 0.08% of squamous tumours, though these are uncertain and could be higher.

Prognosis for patients with advanced NSCLC is poor and although only limited information is available regarding the prognosis of ALK-positive patients specifically, estimated life expectancy is around 15 months.

1.1 Critique of the decision problem in the manufacturer's submission

The population in the NICE scope is patients with untreated, advanced ALK-positive NSCLC that included both squamous and non-squamous patients. The company's decision problem restricts this to non-squamous disease. This is acceptable as the vast majority (97.7%) of ALK-positive patients are expected to be of non-squamous tumour histology. This reflects the population of the main randomised controlled trial presented as evidence. The cost-effectiveness of crizotinib in squamous patients is considered in a scenario analysis.

The NICE scope also included the population with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate. This subgroup is not considered in the CS because expert clinical advice to the company highlighted that this sub-group accounts for less than 2% of the ALK-positive patient population. Furthermore, there is a lack of evidence for standard therapy and it is not possible to conduct an evaluation of the cost-effectiveness of crizotinib in this sub-group.

The CS statement of the decision problem adheres to the intervention specified in the NICE scope: crizotinib 200 and 250 mg capsules and is administered orally, 250mg twice daily taken continuously until disease progression or unacceptable toxicity.

The NICE's final scope identified three types of comparator based on tumour histology:

a) For non-squamous patients, pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin);
b) For people with squamous tumour histology, a third-generation drug (for example, gemcitabine or vinorelbine) in combination with platinum chemotherapy (cisplatin or carboplatin); and,
c) For people with non-squamous or squamous tumour histology for whom treatment with a platinum drug is not appropriate, single-agent chemotherapy with a third generation drug (for example, gemcitabine or vinorelbine).

As only the first patient population is considered fully in the CS, only pemetrexed plus platinum-based therapy is included as a comparator. This is in line with the NICE scope. The CS states that cisplatin and carboplatin have the same PFS outcomes so can be considered to be equal; they are treated as a single comparator. However, based on clinical expert's advice, the ERG notes that although the two drugs have similar PFS, they differ significantly in terms of their toxicity level.

Clinical advisors to the ERG advised that 30% of patients receive cisplatin and 70% patients receive carboplatin. This can be compared with the proportion patients who received cisplatin and carboplatin in the PROFILE 1014 trial: 54% and 46% respectively, which therefore may not represent the clinical practice in the UK.

In line with the NICE scope, pemetrexed maintenance therapy is not considered as a comparator as NICE guidance was that it was not recommended. However, the ERG notes that, based on its clinical advisor's opinion, pemetrexed maintenance therapy for patients who received first line pemetrexed plus cisplatin was used when available through the Cancer Drugs Fund and would be used again if available.

The CS statement of the decision problem adheres to the outcome measures specified in the NICE scope: progression free survival, objective response rate, overall survival, adverse events and health-related quality of life outcomes.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission presented data from three clinical studies: one open label randomised controlled trial of crizotinib with pemetrexed plus a platinum based agent (cisplatin or carboplatin) in patients with advanced non-sqauamous ALK-positive NSCLC (PROFILE 1014); a single-arm trial of crizotinib in patients with both previously treated, and untreated ALK-positive stage III or IV NSCLC (PROFILE 1001); and a retrospective cohort study of patients with confirmed ALK-positive NSCLC, which involved reviewing medical charts of patients receiving crizotinib in a first-line and second-line setting in clinical practice in the US and Canada (Davis et al. 2015).

criteria should not have excluded non-English publications the ERG believes it is unlikely that relevant studies have been missed by the search strategy.

4.1.3 Critique of data extraction

The CS presented the number of studies identified as eligible to be included in the SLR but no discussion of any data extraction plan was evidenced. There were, however, baseline data presented in Table 20 and Table 29 of the CS for the RCT and non-RCT studies, respectively.

For the efficacy and safety RCT (PROFILE 1014), data on PFS and its HR (Table 21 of the CS), OS and its HR (Table 23 of the CS), ORR (Table 22 of the CS) and Kaplan-Meier plots (Figure 8, Figure 10 & 11 of the CS) were extracted. Extracted information on patient-reported outcomes and health-related quality of life (Figures 12-15 of the CS), and number adverse events in each treatment options were also evidenced (Tables 32-35 of the CS). In addition, analysis data on pre-specified subgroup were also extracted (Appendix 8 of the CS).

For the non-RCTs (PROFILE 1001 and Davis et al 2015) baseline characteristics of individuals were extracted. In addition, PFS, OS and ORR data from Davies et al 2015 (Table 30 & Appendix 10 of the CS) and the number of adverse events for PROFILE 1001 trial were extracted (Appendix 11 of the CS). PFS and ORR data from PROFILE 1001 were only reported in text in the CS.

Therefore, the ERG considers that, while a data extraction plan for RCT should have been provided, the data reported is appropriate and matches the scope. At the same time, however, it also recognises that there is not enough efficacy and safety information provided for the non-RCTs.

4.1.4 Quality assessment

The CS presented a quality assessment of the a single efficacy RCT (PROFILE 1014) based on adapted tool from the CRD guidance for undertaking of reviews in health care,[32] with assessments of: randomisation, allocation concealment, baseline characteristics, blinding, drop-out rates and type of analysis used (Appendix 7 of the CS). This was appropriate, although the ERG also conducted its own quality assessment based on the Cochrane risk of bias tool for RCTs (see Section 4.2). The CS also presented an appropriate quality assessment of the two non-RCTs (PROFILE 1001 and Davis et al 2015) using the Downs and Black checklist,[33] with assessments of: reporting, external validity, internal validity, internal validity-confounding, and power of the study (see Section 4.2).

4.1.5 Evidence synthesis

Only one trial examining the efficacy of crizotinib in adults with ALK-positive NSCLC was identified, so no synthesis or meta-analysis was carried out.

4.2.2.4 Patient reported outcomes

A variety of different measures were utilised to measure HRQoL including the EORTC QLQ-C30 and the EORTC QLQ LC-13 (which is a lung cancer-specific module). Completion rates of the EORTC QLQ questionnaire was high: [redacted] for crizotinib patients and [redacted] of chemotherapy patients. From EORTC QLQ-C30 crizotinib produced a small (not clinically significant) improvement from baseline in global HRQoL; compared with the deterioration on chemotherapy this was statistically significant (P<0.001). Similar results were seen for all the individual domains of functioning: physical, social, role, cognitive and emotional.

Crizotinib reduced the symptoms of nausea, vomiting, fatigue, pain, dyspnoea, insomnia, appetite loss, coughing, alopecia, chest pain, arm or shoulder pain and other pain, compared with chemotherapy. Crizotinib, however, cause significantly greater worsening of diarrhoea and peripheral neuropathy compared to chemotherapy. Further details are given in Figures 12, 13 and 14 in the CS.

Data on EQ-5D were also collected in PROFILE 1014. Completion rates of all questions of the EQ-5D questionnaire from evaluable patients ranged from [redacted] for crizotinib (over the first 30 of a total of 50 cycles) and [redacted] for chemotherapy (over the maximum 6 cycles). All but eight patients in the crizotinib group ([redacted]) and seven patients in the chemotherapy group ([redacted]) from the ITT population completed all questions of the EQ-5D questionnaire at baseline. The CS reports that whereas no statistically significant changes from baseline where observed in the chemotherapy group over 6 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. In a mixed-model analysis, compared to chemotherapy crizotinib was associated with a statistically significant greater improvement in EQ-5D VAS scores ([redacted]) and the overall EQ-5D index score (utility) ([redacted]); improvements from baseline in EQ-5D index scores were also statistically significantly greater in the crizotinib group relative to chemotherapy ([redacted]). In the analysis EQ-5D scores were controlled for baseline differences.

EQ-5D data submitted by the company in their clarification responses showed that mean EQ-5D Health Index Score in the crizotinib arm was [redacted] at baseline and increased to [redacted] at the start of Cycle 2 and remained above that at all later follow-up points. In the chemotherapy arm baseline mean EQ-5D was [redacted] and increased to a maximum of [redacted] over 6 cycles. The ERG notes that as the trial was international in its design with only 9 of the 247 study centres based in the UK, there may be issues of generalisability of the quality of life scores when assuming these scores apply to the UK population.

The most relevant of the 10 studies listed in Table 1 are the four economic evaluations of crizotinib from a non-UK perspective and an economic evaluation of ceritinib an alternative ALK-positive targeted therapy, also taking a non-UK perspective. Of these five non-UK economic evaluations, three took a US societal perspective, one a Canadian societal perspective and one a Mexican societal perspective. Four of five studies used Markov structures of various designs and one used micro simulation approach. All five studies reported outcomes in terms of costs per QALY. Comparator treatment regimens varied considerably in the five studies, which included gemcitabine combination therapy, pemetrexed combination therapy and docetexal combination therapy. There was also considerable variation in second/third line therapies modelled which included pemetrexed, doctexal, erlotinib and BSC. Results from the four economic evaluations that assessed crizotinib are reported in Table 1.

Table 1 Results of Non-UK evaluations of ALK targeted therapies as first-treatments for ALK-positive NSCLC

	Technologies	Incremental costs (£)	Incremental QALYs	ICER *vs* baseline (QALYs)
Djalalov et al (2014)	Pemetrexed + cisplatin	---	---	---
	Crizotinib	CAD 95,043	0.379	CAD250,632
Gay-Molina et al (2012)	Pemetrexed + cisplatin	---	---	---
	Crizotinib	USD 51,108	1.28	USD 39,928
Romanus et al (2015)	Pemetrexed + cisplatin	---	---	---
	Crizotinib, erlotinib or Pemetrexed + cisplatin dependent on test status.	USD 4082	0.03	USD 136,000
Montero et al 2014	Docetexal	---	---	---
	Crizotinib	USD 77,138	0.14	USD 535,956
Upadhyay et al 2015	Gemcitabine +cisplatin	---	---	---
	Ceritinib	USD 1898	0.09	USD 21,263

5.1.4 Conclusions of the cost effectiveness review

Currently there is a lack of evidence on the cost-effectiveness of crizotinib. The company's search did not identify any relevant economic assessments of crizotinib for the first-line treatment of advanced or metastatic NSCLC in the UK setting. A number of studies evaluating the cost-effective of crizotinib in non-UK settings were identified, however, given the significant variation in international practice non-of these studies is likely to be generalizable to the UK NHS setting. Given above the ERG therefore considers the cost-effectiveness analysis reported in the current submission to be the most relevant source of evidence to inform the decision problem.

to respond to the suggestion that pemetrexed maintenance may be an appropriate comparator. Their response emphasised that this was not in the scope and suggested that only about 15% of patients are currently receiving pemetrexed maintenance therapy. The ERG acknowledges that the company complied with scope in this regard and that pemetrexed maintenance was not part of the final scope. However, the exclusion of pemetrexed maintenance potential means that an important comparator used in a significant proportion of patients is currently excluded from the model. The ERG also acknowledges that pemetrexed maintenance was only available under the CDF which is shortly to be discontinued. However, there is the potential for reassessment and approval of pemetrexed maintenance therapy under the proposed transitional procedures. Therefore pemetrexed maintenance therapy may continue to be a part of UK practice. The presented model is therefore only valid in so far as practice does not include pemetrexed maintenance therapy. Due to limited resources available to the ERG and the extensive re-analysis that would be necessary for the ERG to include pemetrexed maintenance therapy in the current model this issue is not explored further in Section 6.

5.2.4.3 Crizotinib as a second line therapy

In the economic model it is assumed that second-line therapy is docetaxel in both treatment arms. The model therefore does not include the use crizotinib as a second-line therapy. The CS justifies the decision to exclude crizotinib as a second-line therapy on the grounds that crizotinib is currently only available via the CDF, and due to uncertainty over the future of the CDF. The CS also noted that crizotinib is currently not avialable in Wales. The ERG considers this a significant omission from the presented model. The use of pemetrexed combination therapy followed by crizotinib as second-line therapy is a clear alternative to the modelled pathway of crizotinib first-line followed by docetaxel second-line. As above, with regards, to pemetrexed maintenance therapy, the presented model is therefore only valid in so far as practice does not include crizotinib as a second-line therapy. Due to limited resources available to the ERG and the extensive re-analysis that would be necessary for the ERG to include crizotinib as a second-line therapy into the economic model the ERG does not explore this issue further in Section 6.

5.2.4.4 Second-line therapies received in PROFILE 1014

As discussed in Section 4.2.2.3, following discontinuation of first-line therapy a significant number of patients in the PROF ILE 1014 study went on to a receive second-line therapies. For patients who received crizotinib first-line 45/172 (26.2%) received a second-line therapy, this consisted of a wide range of therapies including pemetrexed which is not approved for second-line use in the UK, certainib which has recently received a license from the EMA, but is yet to be appraised by NICE, and a number of unnamed experimental drugs. Patients in the pemetrexed arm of the study in contrast went on to mainly receive crizotinib, with 120 out of 171 patients who had progressed in the pemetrexed arm. Of the remaining 51 patients 47 did not receive any second-line therapy. Details of

[redacted]	[redacted]	[redacted]
[redacted]	1 [redacted]	[redacted]

5.2.5 Perspective, time horizon

The economic perspective is the National Health Service (NHS) and the Personal Social Services (PSS) in accordance with the NICE reference case. The reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon used was 15 years, which was stated to represent a lifetime horizon. The ERG considered this an appropriate time horizon, as less than 0.001% patients in the model were expected to remain alive beyond 15 years.

5.2.6 Discounting

Costs and benefits in the model were discounted at an annual rate of 3.5% as per the NICE reference case. Implementation of discounting in the economic model was carried out on annual basis, such that all costs and benefits incurred with any given year are discounted by the same amount regardless of whether they occur at the start or the end of that year. The ERG considers this approach to be non-typical and less accurate than the more conventional approach of discounting on a per cycle basis, whereby the discount rate is calculated for every cycle of the model. Discounting on a cyclical basis is more accurate as it more closely reflects the actual time at which benefits and costs occur and is more theoretically sound as the principal behind discounting is essentially one of preferences over the timing of consumption and that future consumption is less valuable than immediate consumption. The current formulation of the model, however, implies that consumption 11 months from now is equivalent to immediate consumption which seems to stand in contrast to this underlying principle. The approach taken by the company of discounting by year is inconsistent with the near universal approach taken in health economic modelling of discounting by cycle and while not strictly a calculation error the ERG consider this as an error in the executable model and is rectified in the ERG revised model, see Section 6.

5.2.7 Treatment effectiveness and extrapolation

Both PFS and OS are considered in the company's economic model with data for both sourced from PROFILE 1014. The model generated the proportion of patients in the progression free and progressive disease states: the proportion of patients in the progression free health state was taken directly from the extrapolated PFS curve; the proportion of patients with progressive disease was calculated by subtracting PFS from OS.

Table 2 Overall survival cross-over adjustment methods: treatment effect estimates and ICER estimates

Crossover adjustment method	Analysis	Crizotinib versus pemetrexed plus cisplatin/carboplatin Hazard Ratio (95% CI)	ICER
Two stage adjusted model	Adjustment for treatment switching and additional covariates (ECOG base-case imputation)	0.624 (0.405, 0.963)	[redacted]
	Adjustment for treatment switching and additional covariates (ECOG sensitivity imputation)	0.649 (0.421, 1.000	[redacted]
	Adjustment for treatment switching only	0.610 (0395, 0.942)	[redacted]
RPSFT	Log-rank test method	0.674 (0.283, 1.483)	[redacted]
	Wilcoxon test method	0.604 (0.265, 1.420)	[redacted]

The CS notes the consistency in the estimated hazard ratio and the absence of any methodological or clinical reason select the median value using a two stage approach for the base-case. As stated in Section 4.2.2.3 the choice of two stage model A over the other methods of adjustment is largely arbitrary and as can be seen from Table 2 while the hazard ratio does not vary significantly according to the model selected, the choice of method does have a significant effect on the estimated ICER as the economic model is particularly sensitive to any change in OS benefit. Given the lack of any methodological or clinical reason to select one model over another it important to consider that there is significant uncertainty surrounding the presented base-case ICER according to the choice of adjustment method selected. This uncertainty is not accounted for in any probabilistic analysis presented by the company. Furthermore, as discussed in Section 4.2.2.3 all of the methods of adjustment make strong and largely untestable assumptions and it should not be assumed that estimates of OS based on the presented methods of cross-over adjustment are correct simply because there is a degree of consistency in the estimates: it is quite possible that the estimates are simply consistently wrong. Indeed, as argued in Section 4.2.2.3 all of the adjustment options presented by the company are potentially biased. As such, the ERG consider there to unquantifiable uncertainty surrounding the estimated OS benefits and by extension to the estimated ICER due to potential bias in the method of analysis.

5.2.8 Duration of therapy

5.2.8.1 Duration of crizotinib therapy

The duration of therapy for patients within the economic model is dependent on whether patients continue therapy past progression. Based on PROFILE 1014 it is assumed that 74% of patients in the crizotinib arm continue to receive therapy beyond progression while the remaining 26% discontinue

crizotinib therapy on transition to progressive disease. Within the economic model duration of treatment for patients who discontinue treatment at progression is determined by time to progression, where time to progression is based on the extrapolation of PFS data from PROFILE 1014 adjusted to the UK population using the Davis study[10]. Duration of treatment for patients who continue treatment *beyond* progression is also linked to time to progression, but it is assumed that patients receive a further 4 cycles of crizotinib (based on data from the PROFILE 1014 trial of time on crizotinib post-progression).

The ERG considers the approach taken by the company to be reasonable with regards to patients who discontinue treatment at progression, but has identified a number of issues regarding the assumptions made for patients treated beyond progression and the way 'time on treatment' is implemented in the electronic model for these patients.

The assumption that patients receive a further 4 cycles of crizotinib beyond progression is based on the median time on crizotinib post progression reported in PROFILE 1014 of 3.1 months. The ERG notes that use of the 3.1 month figure is incorrect for a number of reasons. Firstly, it is inappropriate to use a median instead of a mean value within cost-effectiveness analysis, and based on the analysis present in the CSR[34], the mean duration of treatment beyond progression is [redacted] months ((20.2 weeks/7)*30), conservatively equivalent to [redacted]. Secondly, both these median and mean values are based on truncated data set in which it is assumed that all patients who are still on crizotinib treatment discontinue therapy upon being censored. The company's clarrication response stated that [redacted] of crizotinib patient were still on therapy at the time of the analysed data cut of 30th November 2013, these estimates therefore dramatically underestimate the true median/mean time on crizotinib treatment beyond progression. To calculate a more accurate estimate of mean time on treatment following progression the ERG requested the Kaplan-Meier of discontinuation of treatment for crizotinib patients at the PFC stage. As the Kaplan-Meier provided in the company's response was incomplete the ERG fitted a series of parametric survival curves were fitted to the data to calculate mean duration of treatment, see Figure 1 below.

Figure 1 Discontinuation curve for crizotinib fit of parametric survival curves

Note Weibull curve hidden behind Exponential curve.

Based on AIC (Akaike information criterion) and BIC (Bayesian information criterion) the ERG considered the most appropriate parametric curve to be the exponential curve, see Table 23 below (lower values are preferred for best fit). Based on the exponential curve mean duration of treatment for all crizotinib a patient is estimated to be [redacted] months. This compares with [redacted] using the truncated data reported in the CSR. Using this value and mean time to progression it is possible to calculate mean time on crizotinib post progression, which the ERG calculate to be [redacted]. The company model therefore dramatically underestimates the time on treatment beyond progression and as a consequence also underestimates the ICER.

Table 3 Assessment of parametric survival models for crizotinib discontinuation

Model	AIC	BIC
Exponential	437.04	440.18
Generalised Gamma	438.80	448.22
Gompertz	438.30	444.59
Log-logistic	436.96	443.24
Log-normal	437.59	443.87
Weibull	439.04	445.32

Table 4 Drug cost and vial/tablet used per cycle in the base-case analysis

Treatment	Unit	Unit cost (list price)	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Crizotinib[*]	60 x 200mg tablets	£4,689.00	2x 250mg per day (30 days)	£4,689.00
	60 x 250mg tablets	£4,689.00		
Pemetrexed[*]	100mg vial	£160.00	500 mg/m2 = 500/1.73 = 866 mg (21 days)	£1,440.00 with wastage £1,385.40 without wastage
	500mg vial	£800.00		
Cisplatin[$]	10mg (10ml vial)	£3.24	75mg/m2 = 75/1.73 =130mg (21 days)	£47.00 with wastage £25.72 without wastage £19.98 without wastage
	50mg (50ml vial)	£6.97		
	100mg (100ml vial)	£12.53		
Carboplatin[$]	50mg (5ml vial)	£4.36	Target AUC = 5, dose = 500 mg (21 days)	£34.18 with wastage £28.27 without wastage £22.41 without wastage
	150mg (15ml vial)	£9.90		
	450mg (45ml vial)	£29.82		
	600mg (65ml vial)	£33.92		

[*]Reference: MIMS (Monthly Index of Medical Specialities), [$]Reference: eMit (electronic market information tool)

With respect to both crizotinib and pemetrexed no drug wastage due to discontinuation of therapy was assumed for either treatment. The ERG considers this to be unrealistic. With regards crizotinib tablets come in 60 tablet pack which last 30 days. It is reasonable to assume once a pack has been started these would not be reused should patient discontinue therapy part way through a pack. To account for this drug wastage, costs should be based not on the number of patients receiving treatment half-way through the cycle as modelled, but rather based on the number of patients receiving treatment at the beginning of each cycle of model. The impact of adding drug wastage for crizotinib is to increase total costs of crizotinib treatment and hence increase the ICER.

Similarly with regards to pemetrexed combination therapy, therapy is given at the beginning of each cycle of therapy and therefore costs should reflect the number patients eligible for treatment on that day rather than the number eligible half way through a cycle. Given the lack of alignment between the cycle length used in the model and the treatment cycle this more difficult to calculate, but can be done by assuming a linear pattern of discontinuation within cycles. The impact of drug wastage for chemotherapy on the ICER serves to increase the total costs of pemetrexed treatment and therefore reduces the ICER. The impact of drug wastage for chemotherapy is, however smaller than for crizotinib due to lower per cycle treatment costs and because of the lack of alignment between the cycle length in the model and the treatment cycle. The ERG presents a series of scenario analyses including drug wastage for both crizotinib and pemetrexed patients in Section 6.

- The HRQoL of patients who initiate pemetrexed combination therapy, post treatment pre-progression;
- Costs associated with ALK testing.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG's primary concern with the company's base case estimate of cost-effectiveness related to the large number of calculation errors, most particularly errors in the calculation of duration of crizotinib treatment beyond progression. Correcting for these calculation errors significantly increases the estimated ICER from [redacted] in the company's base-case to [redacted]. Note these ICER estimates do not include a PAS which is currently awaiting approval with the Department of Health.

In addition to correcting the calculation errors identified in the company model the ERG carried out series of sensitivity analyses, the result of which are summarised in the Table 1 below. The ERG also presented an alternative base-case based on a combination of a number of these scenario analyses. The ERG base-case made the following assumptions:

- Drug wastage for both crizotinib and pemetrexed was include;
- Transitional utilities were exclude for the model with the exception for crizotinib patients treated beyond progression;
- A higher utility was assigned to patients who initiating on chemotherapy who had completed treatment, but were yet to transition to progressive disease;
- An alternative split regarding the number of patients receiving cisplatin and carboplatin was assumed based a scenario analysis presented in the CS;
- Alternative higher ALK testing costs;
- Inclusion of on-going administration costs for crizotinib.

Table 1 Summary of results from additional analyses carried out by the ERG (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
Analysis	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's base-case (corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including drug wastage for both crizotinib and pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removing transitional utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including a higher utility value for chemotherapy patients post discontinuation of first-line treatment and prior to progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assuming a 25%/75% split in the use of cisplatin and carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including alternative higher ALK testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including on-going administration costs for crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ICER for the ERG base-case analysis was [redacted] per QALY not including any PAS. The ERG also carried a series of exploratory analyse using the ERG base-case in which the impact of the assumption of proportional hazards on the estimated ICER was explored. The results of the most plausible estimates of cost-effectiveness are summarized in Table 2 below. Due to the lack of any clinical or statistical justification for selecting one curve over another the ERG could not select any individual analyses as being the most plausible, but consider the analysis assuming a generalised gamma for PFS and Weibull for OS to be particularly relevant for comparative purposes as these were the distributions used in the company's base-case analysis in which proportional hazards was assumed.

Table 2 Incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model (without PAS)

	Fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		
	PFS	**OS**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model and curves selected using lowest AIC)	Log-normal – crizotinib; and gamma - pemetrexed	Gamma – crizotinib; and exponential - pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.8 Conclusions from the ERG analyses

The ERG corrections of calculation errors suggest that the ICER for crizotinib compared with pemetrexed combination therapy is [redacted] per QALY gained. The ERG's additional exploratory analyses using a range of alternative assumptions indicate that this ICER is likely to represent a lower bound. The results from the ERG base-case which can be considered as plausible as the base-case see's this ICER increase [redacted]. Further, additional exploratory analysis carried out by the ERG in which independent parametric survival curves are fitted have substantial impact on the ICER which varies between [redacted] and [redacted] per QALY in these analyses.

Finally, it should be noted that the assessment of clinical and cost-effectiveness of crizotinib presented in this report matches the NICE scope but ignores the possible future use of pemetrexed maintenance therapy as a more effective comparator than pemetrexed plus platinum therapy alone. The possibility of using crizotinib as a 2nd line treatment in ALK-positive NSCLC patients is similarly not included.

true median/mean time on crizotinib treatment beyond progression. To calculate a more accurate estimate of mean time on treatment following progression the ERG requested the Kaplan-Meier of discontinuation of treatment for crizotinib patients at the PFC stage. As the Kaplan-Meier provided in the company's response was incomplete the ERG fitted a series of parametric survival curves were fitted to the data to calculate mean duration of treatment, see **Error! Not a valid bookmark self-reference.** below.

Figure 6 Discontinuation curve for crizotinib fit of parametric survival curves

Note Weibull curve hidden behind Exponential curve.

Based on AIC (Akaike information criterion) and BIC (Bayesian information criterion) the ERG considered the most appropriate parametric curve to be the exponential curve, see Table 23 below (lower values are preferred for best fit). Based on the exponential curve mean duration of treatment for all crizotinib a patient is estimated to be [redacted] months. This compares with [redacted] months using the truncated data reported in the CSR. Using mean duration of treatment and mean time to progression (adjusted for base-line covariates) it is possible to calculate mean time on crizotinib post progression, which the ERG calculate to be [redacted] months. The company model therefore dramatically underestimates the time on treatment beyond progression and as a consequence also underestimates the ICER.

Table 23 Assessment of parametric survival models for crizotinib discontinuation

Model	AIC	BIC
Exponential	437.04	440.18
Generalised Gamma	438.80	448.22
Gompertz	438.30	444.59
Log-logistic	436.96	443.24
Log-normal	437.59	443.87
Weibull	439.04	445.32

In addition to the above a further issue was identified by the ERG with regards to the implementation of treatment beyond progression in the economic model. As described above the model assumes that newly progressed patients will go on to receive for 4 cycles of treatment. However, the way that the model is constructed means not all patients that progress will go on receive four cycles of treatment beyond progression because in each period a proportion of the patients die, based on mortality in that cycle. Consequently, the actual mean number of cycles of treatment received beyond progression is not 4, but 2.42. The intended 4 cycles of treatment beyond progression therefore does operate as mean number of cycles, but instead as maximum number of cycles and does not recognise that some patients receive many cycles of treatment beyond progression. This misspecification of the model leads to an underestimation of time on treatment beyond progression, reducing total QALYs accrued by crizotinib patients and also reducing total costs of treatment, with a net effect of underestimating the ICER.

To correct the model and accurately reflect the duration of treatment beyond progression it is necessary to substantially reprogram the model and to implement a full area under the curve model in which time on treatment is sourced from the observed time on treatment for patients in the PROFILE 1014 trial. The ERG were able to fix this issue and the results of the new ERG model are presented in Section 6. This fix, however, makes the assumption that time on treatment for patients in the PROFILE 1014 trial would reflect clinical practice and was not adjusted using the real world data in the way that PFS and OS have been. It is likely therefore that corrected model overestimates total time on treatment and as such overestimates the ICER, though it is unclear by how much. Further the ERG's corrections have a number of implications for other parts of the model relating to time on second-line therapy that the ERG were not able to fix. Further details on this issue are included in our discussion of duration of second-line treatments.

5.2.8.2 Duration of treatment with pemetrexed combination therapy

Duration of treatment with pemetrexed combination is based on the PROFILE 1014 study in which patients received a median of six cycles of therapy. The implementation of this in the model assumes

- Duration of time on crizotinib post progression was mis-specified; (note the ERG has only been able to partially rectify the mis-specification, due to lack of appropriate data);
- Duration of time on docetaxel mis-specified for both crizotinib and pemetrexed patients (note the ERG has not been able to rectify this error, due to lack of appropriate data);
- Duration of time on BSC mis-specified for both crizotinib and pemetrexed (note the ERG has only been able to partially rectify the mis-specification, due to lack of appropriate data).

Although the company appears to have undertaken a thorough approach to the internal and external validation of their results, the ERG is has serious concerns regarding the internal validity of the model, particularly as simple checks would have ensured that the many errors remaining in the model would have been identified. With regards to the external validity the ERG has some concerns regarding the (face-validity) of the projected survival gains observed in the model which appear to be inconsistent with data on survival rates in the UK presented in the background section of the CS. These data suggest that the 1 year survival rate of stage 3 patients would be 35%, this compares with a predicted survival rate on pemetrexed of 52% in the model which is assumed to include both stage 3 and 4 patients. The ERG would also have liked an examination of the model against the four non-UK economic evaluations identified in the cost-effectiveness review with a particular focus on drivers of cost-effectiveness.

5.3 Conclusions of the cost effectiveness section

A limited number of cost-effectiveness analyses of crizotinib were identified in the systematic review presented in CS, however none of these took UK perspective and were unlikely to generalizable to the UK NHS. Consequently, the manufacturer's model represents the most relevant source of existing evidence. The economic model described in the CS is considered by the ERG to meet the NICE reference case and is broadly in-line with the decision problem specified in the scope. The ICER presented in the CS was [redacted] per QALY; including a yet to be approved PAS the ICER was [redacted] per QALY.

The ERG identified that the electronic economic model submitted by the company contained a significant number of errors. Of these the most important was mis-specification duration of treatment with crizotinib post progression, which was significantly underestimated in the company model. As a consequence the ICER presented in the CS are incorrect and should not be relied upon. In addition to these interval validity issues the ERG also identified a number of uncertainties surrounding assumptions made in the company model. These are outlined in brief below:

The impact of these corrections on the resulting ICER is significant, increasing the ICER from [redacted] per QALY to [redacted] per QALY (See Table 3). The majority of the impact of the corrections on the model is to substantially increase the total costs associated with crizotinib. This is due a significant increase in total drug acquisition costs. This occurs because in the original company model the mean duration of crizotinib treatment was estimated at approximately [redacted] compared with [redacted] in the corrected model.

Table 3 Incremental cost-effectiveness ratios incorporating all corrections and adjustments to the manufacturer's base-case model

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's original base-case presented in the CS document	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 Additional ERG analyses

6.3.1 Exploration of the impact of alternative treatment strategies for pemetrexed patients

In the CS base-case analysis, up to 6 cycles of chemotherapy are assumed (pemetrexed plus cisplatin/carboplatin), based on the median number of cycles of pemetrexed plus cisplatin/carboplatin received in the PROFILE 1014 trial.[34] The SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy.[41] Discussions with the clinical advisors to the ERG suggest there is some variation practice as regards the typical number of cycles of therapy used. Therefore, ERG explored the impact of this assumption on the ICER.

Table 4 shows the results for alternative treatment strategies for pemetrexed patients. This analysis, however, only accounts for changes in costs and does not account for any effect on clinical benefits resulting from the use of fewer cycles of chemotherapy; this analysis should therefore be considered conservative with respect to the cost effectiveness of crizotinib. The impact of these alternative treatment strategies on the resulting ICER is small: an approximate £1,300 increase when patients had 5 cycles of pemetrexed plus cisplatin/carboplatin; and approximately £3,100 increase when patients had 4 cycles.

Table 4 impact of alternative treatment strategies for pemetrexed patients (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.2 Drug wastage for patients who die part way through a cycle of treatment

As noted in Section 5, the company base case assumes no drug wastage for either crizotinib of pemetrexed. The ERG consider it likely that for both treatment groups there would be some, albeit limited drug wastage when a patient discontinues treatment part was through a treatment cycle. The ERG therefore has undertaken an analysis including drug wastage in both arms. For crizotinib this was done by assuming that drug costs are based on the proportion of patients on treatment at the beginning of a model cycle rather than halfway through a cycle. For chemotherapy this was done by assuming drug costs are based on the proportion of patients eligible for treatment at the time of delivery of the next cycle of chemotherapy assuming a linear decline in treatment discontinuation within model cycles. The results of this analysis are presented in Table 5. This analysis shows that drug wastage has a modest impact on the resulting ICER, increasing it by approximately £2700 per QALY.

Table 5 Results of drug wastage (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st line crizotinib wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st line pemetrexed wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st line crizotinib and pemetrexed both wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.3 Removal of assumed transition utilities

In the CS base-case analysis, a 'transitional' utility was applied when moving between health states during the first cycle following progression. The CS presented a sensitivity analysis whereby the transitional utility was applied to patients receiving treatment beyond progression when they progressed. In this scenario it is assumed that utility drops immediately to the utility value for that health state.

The ERG has concerns about the use of such transitional utilities as this is likely to double count higher utility after progression. The ERG therefore considers the scenario analysis presented by the company in which no transitional utilities are included to be more plausible than the company base-case. The results of this analysis using the ERG corrected model are presented in Table 6. Excluding transitional utilities results in a small reduction in QALYs accrued in both treatment groups compared with the CS's corrected base-case and results in a slight reduction in the ICER (<£600).

Table 6 Results assuming no transitional utility (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No transitional utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.4 Exploration of alternative assumption regarding post progression utility for patients receiving crizotinib therapy beyond progression

The CS model assumed that the 73% of patients who receive treated beyond progression with crizotinib have a utility score of ([redacted]) based on the midpoint between pre progression utility ([redacted]) and post progression utility (0.66). While the ERG consider it is plausible that patients treated beyond progression may experience some utility benefit, it considers that the value chosen is probably too high, as it implies that progressed patients receiving crizotinib would have a higher utility than pre-progressed patients receiving pemetrexed patients. Given that symptom load for pre-progressed patients would likely be significantly lower, the ERG considers this unlikely. In the absence of appropriate data to populate this utility value the ERG presents an alternative analysis in which it is assumed that patients being treated beyond progression receive a utility value of [redacted] based on utility of pre-progressed patients receiving pemetrexed. The resulting ICERs with this assumption are presented in

Table 7. The results show that it has only a modest impact on the ICER.

Table 7 Results of alternative utility assumption for post progression patients receiving crizotinib therapy beyond progression (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative post progression utility for crizotinib patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.5 Exploration of alternative assumptions of utility regarding pre progressed patients who have completed chemotherapy treatment;

As noted in the section 5, chemotherapy is associated with frequent side effects and is therefore plausible that patients receiving treatment would have lower utility than those who have finished treatment. However, discussion with clinical advisors suggests that once treatment has been completed that patients who received first-line chemotherapy will experience a significant increase in HRQoL. Due to the way data was collected in PROFILE 1014 the ERG did not think this is adequately reflected in the HRQoL data used in the model. The ERG therefore present and alternative scenario which retains a differential utility between crizotinib and chemotherapy patients while the latter are on treatment, but once chemotherapy patients have discontinued treatment chemotherapy patients receive the higher utility of [redacted] currently assumed to be experienced by crizotinib patients. The results of this analysis are presented in Table 8. This analysis shows that there is a 0.01 of QALY gain in the pemetrexed + cisplatin/carboplatin patient group compared with the CS's base-case leading to modest increase in the estimated ICER.

Table 8 Results of alternative assumptions of utility regarding pre progressed patients after chemotherapy treatment completed (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progressed utility adjustment for chemotherapy patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.6 Impact of alternative assumptions regarding use of cisplatin and carboplatin

In the CS base-case, it is assumed that [redacted] of patients on pemetrexed combination therapy will receive cisplatin and [redacted] will receive carboplatin, which is based on the split observed in PROFILE 1014. The CS also presented a scenario analysis whereby 25% of patients receive

pemetrexed plus cisplatin and 75% receive pemetrexed plus carboplatin; this is based on clinical advice that some centres up to three quarters of patients may receive carboplatin instead of cisplatin. The clinical advisors to the ERG confirmed this scenario was more reflective of clinical practice in the UK suggesting that approximately 30% of patients would receive cisplatin and 70% carboplatin. Hence, ERG considered that the proportion of 25% of cisplatin and 75% of carboplatin are more plausible scenario. The ERG therefore present the results of this scenario analysis (Table 9) carried out by the company as the ERG include this in assumption in the ERG base-case analysis .The results show that it has minimal impact on the ICER.

Table 9 Results of alternative assumptions regarding use of cisplatin and carboplatin (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25% use of cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.7 Alternative costs for ALK testing

As described in section 5, the CS base-case testing strategy assumed that every non-squamous NSCLC patient receives an IHC test, and that those who score +1 or +2 go on to then receive a confirmatory FISH test. Based on this testing strategy the cost of identifying one ALK-positive patient is estimated to be [redacted]. The costs this is based on are however, subject to a degree of uncertainty as it is unclear whether laboratory and overhead costs are included. The ERG therefore sought to identify alternative source of costs and identified a survey of UK laboratories conducted by Cancer Research UK that suggested that the mean cost of ALK testing was £153 per patient. Given the incidence of ALK-positive patients, this would imply a cost of £4,500 to identifying one ALK-positive patient. The results of an analysis including this alternative cost of testing are presented in

Table 10. This analysis shows that the alternative cost of ALK testing has moderate impact on the resulting ICER increasing it by £3,500 compared with the CS's base-case.

Table 10 Results assuming alternative costs for ALK testing (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative costs for ALK testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.8 Addition of administration costs for crizotinib

The CS base-case analysis assumes no ongoing administration costs for crizotinib as it is an oral therapy and does not require hospital administration, and only includes a one-off cost to reflect where patients are given instructions on how to take the tablets by a nurse the first time they are prescribed the treatment. However, as noted in Section 5, in the previous appraisal of crizotinib as second-line treatment the committee (TA 296) the committee considered that there would be an administrative cost to the NHS associated with crizotinib therapy. The ERG therefore present an analysis in which an on-going per cycle administration costs is included. The results of this analysis are presented in Table 11.This analysis shows that addition of the per cycle administration costs of crizotinib has modest impact on the resulting ICER.

Table 11 Results assuming additional per cycle administration costs for crizotinib (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-going administration costs for crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 ERG's preferred base-case

Table 12 presents the ERG's preferred base-case this combines a number of the changes to the company base-case explored in Section 6.3. Specifically, the ERG base-case makes the following amendments to the CS's base-case:

1. Drug wastage for patients who die part way through a cycle of treatment in both crizotinib and chemotherapy group;
2. Removal of assumed transition utilities;
3. Alternative utility of [redacted] for the pre progressed patients who have completed chemotherapy treatment;
4. Alternative assumptions regarding use of 25% cisplatin and 75% carboplatin;
5. Alternative costs of £4,500 for ALK testing
6. Per cycle drug administration costs for crizotinib

The ERG considers this alternative base-case to be at least as plausible as the company's base-case. Combining these modifications to the company model leads to a substantial increase in the ICER from [redacted] in the corrected base-case to [redacted] in the ERG's alternative base-case.

Table 12 Incremental cost-effectiveness ratios of the CS's corrected base-case and ERG's preferred base-case (without PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 Exploratory analysis on PFS and OS

The base-case analysis in the CS makes use of the proportional hazards assumption, justifying this by inspecting the log-cumulative hazard plots for both PFS and OS. In the CS's base-case, the generalised gamma curve for PFS and the Weibull curve for OS were selected for both crizotinib and pemetrexed. However, the ERG believes that fitting separate parametric models is likely to produce more reliable estimates of PFS and OS (Sections 4.2.2.1 and 4.2.2.3). TThe ERG has therefore explored a range of scenarios where independent parametric survival curves are fitted to PFS and OS for crizotinib and pemetrexed patients.

The ERG conducted analyses uses the fully stratified model provided by company in its clarification response. The fully stratified model which comprises independent models for each treatment with separate covariates for prognostic factors, included the following assumptions

- Survival model parameters and baseline covariate parameters are estimated separately for each treatment arm
- The underlying shape and the impact of important prognostic factors are allowed to be different by treatment arm
- Uses two subsets of PROFILE 1014 data to fit the models for each treatment arm (smaller sample size)

6.5.1 Exploration of uncertainty around choice of parametric curves and estimated PFS

The AIC and BIC for the PFS curves (including covariates for treatment and prognostic factors) are provided in Table 46 (lower values are preferred for best fit). The PFS curve fits for crizotinib are shown in **Error! Reference source not found.** and the PFS curve fits for pemetrexed plus cisplatin/carboplatin are shown in **Error! Reference source not found.** along with their respective Kaplan-Meier curves, which have each been adjusted for separate covariates for prognostic factors.

- 1st assumption - including parametric curves of loglogistic for crizotinib and gamma for pemetrexed
- 2nd assumption - including parametric curves of lognormal for crizotinib and gamma for pemetrexed
- 3rd assumption - including parametric curves of gamma for crizotinib and gamma for pemetrexed
- 4th assumption - including parametric curves of loglogistic for crizotinib and Weibull for pemetrexed
- 5th assumption - including parametric curves of lognormal for crizotinib and Weibull for pemetrexed
- 6th assumption - including parametric curves of gamma for crizotinib and Weibull for pemetrexed

The results of the analysis are presented in Table 13. The results show that there is significant difference in QALYs. The QALYs are higher compared with the ERG's base-case in all assumptions in both treatments. The fully stratified model assumptions for PFS have moderate impact on resulting ICERs. The ICERs are lower than the ERG's base-case. The resulting ICERs vary between [redacted] and [redacted] per QALY.

Table 13 Incremental cost-effectiveness ratios of different combination of parametric curves for PFS (without PAS)

	PFS fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		ICERs
	Crizotinib	Pemetrexed	QALYs	Costs	QALYs	Costs	
ERG's preferred base-case (proportional hazard assumption)	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st assumption	Loglogistic	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd assumption	Lognormal	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd assumption	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th assumption	Loglogistic	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th assumption	Lognormal	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5.2 Uncertainty around choice of parametric curves and estimated OS

The AIC and BIC for the OS curves (including covariates for treatment and prognostic factors) are provided in **Error! Reference source not found.**; lower values are preferred for best fit. The OS curve fits for crizotinib are shown in **Error! Reference source not found.** and the OS curve fits for pemetrexed plus cisplatin/carboplatin are shown in

The ERG conducted analysis to explore impact on ICERs using the following selected combination of curves for OS:

- 1st assumption - including parametric curves of gamma for crizotinib and exponential for pemetrexed
- 2nd assumption - including parametric curves of gompertz for crizotinib and exponential for pemetrexed
- 3rd assumption - including parametric curves of weibull for crizotinib and exponential for pemetrexed
- 4th assumption - including parametric curves of gamma for crizotinib and weibull for pemetrexed
- 5th assumption - including parametric curves of gompertz for crizotinib and weibull for pemetrexed
- 6th assumption - including parametric curves of weibull for crizotinib and weibull for pemetrexed

Results of the analysis are presented in Table 14. The results show that the fully stratified model has significant impact on QALY gains. The QALY gains are lower for crizotinib patients and higher in pemetrexed compared with the ERG's preferred base-case. Therefore, the resulting ICERs are substantially higher than the ERG's preferred base-case.

Table 14 Incremental cost-effectiveness ratios of different combination of parametric curves for OS (without PAS)

	OS fitted curves		**Crizotinib**		**Pemetrexed + cisplatin/carboplatin**		
	Crizotinib	**Pemetrexed**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard assumption)	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st assumption	Gamma	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd assumption	Gompertz	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd assumption	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th assumption	Gompertz	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th assumption	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15 shows further illustration of uncertainty around the proportional hazard model vs. fully stratified model. There is approximately £27,000 increase in the ICER in the fully stratified model

compared with proportional hazard model keeping the fitted curves same for both treatments. The ICERs increases further to [redacted] when the fitted curves are selected based on lowest AIC. [redacted]

Table 15 Incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model (without PAS)

	Fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		
	PFS	**OS**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (fully stratified model and curves selected using lowest AIC)	Log-normal – crizotinib; and gamma - pemetrexed	Gamma – crizotinib; and exponential - pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.6 Conclusions from ERG analyses

In this Section the ERG has presented a number of additional analyses. These analyses were carried in a number of stages. The first stage address critically important errors in the electronic model submitted by the company which meant that total duration of treatment with crizotinib was significantly underestimated. The ICER from the correct base-case model was [redacted] per QALY which was significantly higher than the ICER in original model provide by the company [redacted]) due a substantial increase in total drug acquisition costs for crizotinib. Using the correct model the ERG then presented a number of sensitivity analyses to explore a number of issues raised in Section 5. This concluded with the presentation of an alternative ERG base-case which combined a number scenarios presented by the company and the alternative assumptions explored in this section. The ERG's base-case analysis suggests that the ICER for crizotinib compared with pemetrexed plus cisplatin/carboplatin is around [redacted] per QALY. This base-case is considered to be as plausible as the one presented by the company (corrected for calculation errors).

The final part of this section carried a further series of exploratory analyses that explored the impact of the proportional hazards assumption made in the analysis of PFS and OS. The results of this analysis show the ICER is generally robust to this assumption with regards to PFS, but is very sensitive with respect to this assumption with regards to OS producing significantly higher ICERs than when proportional hazards is assumed. This is part due to the immaturity of the OS data which

leads to considerable uncertainty around the extrapolation. Using the same parametric functions fitted in the company's base where proportional hazards is assumed this analysis gives a ICER of [redacted] per QALY (assuming ERG assumptions) and where the best statistically fitted curves are selected this analysis produces an ICER of [redacted].

10.3.1 Cost-effectiveness results (confidential PAS applied)

10.3.1 Results of CS's base case with PAS

Table 16: Deterministic results with PAS applied summarises the deterministic results with the PAS applied, and

Table 17 the probabilistic results. The PAS is yet to be approved and is therefore not included in the base-case results.

Table 16: Deterministic results with PAS applied

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£) *vs* baseline (QALYs)
Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	---	---	---	---
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,306

Table 17: Probabilistic results with PAS applied

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) *vs* baseline (QALYs)
Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	---	---	---
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	£45,488

10.3.2 Corrected model with PAS

Table 55 shows the results of corrections to the company's electronic model with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.2.

Table 18 Impact of model corrections to company's base-case (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	Costs	QALYs	Costs	ICER
CS's Base-case (Original model)	[redacted]	[redacted]	[redacted]	[redacted]	£46,306
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136

10.3.3 Results of sensitivity analyses with PAS

Table 19 shows the results of alternative treatment strategies for pemetrexed patients with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.1.

Table 19 impact of alternative treatment strategies for pemetrexed patients (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
5 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	£65,429
4 cycles of Pemetrexed + cisplatin/carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	£67,255

Table 20 shows the results of drug wastage analysis with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.2.

Table 20 Results of drug wastage analysis (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
1st line crizotinib wastage	[redacted]	[redacted]	[redacted]	[redacted]	£65,669
1st line pemetrexed wastage	[redacted]	[redacted]	[redacted]	[redacted]	£64,050
1st line crizotinib and pemetrexed both wastage	[redacted]	[redacted]	[redacted]	[redacted]	£65,582

Table 21 shows the results assuming no transitional utility with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.3.

Table 21 Results assuming no transitional utility (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
No transitional utility	[redacted]	[redacted]	[redacted]	[redacted]	£63,846

Table 59 shows results of alternative utility assumption for post progression patients receiving crizotinib therapy beyond progression with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.4.

Table 22 Results of alternative utility assumption for post progression patients receiving crizotinib therapy beyond progression (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
Alternative post progression utility for crizotinib patients	[redacted]	[redacted]	[redacted]	[redacted]	£65,215

Table 23 shows results of alternative assumptions of utility regarding pre progressed patients after chemotherapy treatment completed with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.5.

Table 23 Results of alternative assumptions of utility regarding pre progressed patients after chemotherapy treatment completed (With PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
Pre-progressed utility adjustment for chemotherapy patients	[redacted]	[redacted]	[redacted]	[redacted]	£65,679

Table 24 shows results of alternative assumptions of proportion used for cisplatin (25%) and carboplatin (75%) with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.6.

Table 24 Results of alternative assumptions regarding use of cisplatin and carboplatin (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
25% use of cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	£64,037

Table 25 shows results assuming alternative costs for ALK testing with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.7.

Table 25 Results assuming alternative costs for ALK testing (With PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative costs for ALK testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26 shows results additional per cycle administration costs for crizotinib with the CS'sproposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.3.8.

Table 26 Results assuming additional per cycle administration costs for crizotinib (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
On-going administration costs for crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	£68,477

Table 27 shows incremental cost-effectiveness ratios of the CS's corrected base-case and ERG's preferred base-case with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.4.

Table 27 Incremental cost-effectiveness ratios of the CS's corrected base-case and ERG's preferred base-case (with PAS)

	Crizotinib		Pemetrexed + cisplatin/carboplatin		
	QALYs	**Costs**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	£64,136
ERG's preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	£74,792

Table 28 shows incremental cost-effectiveness ratios of different combination of parametric curves incorporated to estimate PFS with the company‘s proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.5.1.

Table 28 Incremental cost-effectiveness ratios of different combination of parametric curves for PFS (with PAS)

	PFS fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		ICER
	Crizotinib	Pemetrexed	QALYs	Costs	QALYs	Costs	
ERG's preferred base-case (proportional hazard assumption)	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£74,792
1st assumption	Loglogistic	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£73,400
2nd assumption	Lognormal	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£73,256
3rd assumption	Gamma	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£73,936
4th assumption	Loglogistic	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£73,296
5th assumption	Lognormal	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£73,152
6th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£73,829

Table 29 shows incremental cost-effectiveness ratios of different combination of parametric curves incorporated to estimate OS (with the CS's proposed PAS applied). The results are equivalent to the without PAS results presented in Section 6.5.2.

Table 29 Incremental cost-effectiveness ratios of different combination of parametric curves for OS (with PAS)

	OS fitted curves		Crizotinib		Pemetrexed + cisplatin/carboplatin		
	Crizotinib	Pemetrexed	QALYs	Costs	QALYs	Costs	ICER
ERG's preferred base-case (proportional hazard assumption)	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£74,792
1st assumption	Gamma	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£132,436
2nd assumption	Gompertz	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£111,090
3rd assumption	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£96,048
4th assumption	Gamma	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£121,134
5th assumption	Gompertz	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£103,752
6th assumption	Weibull	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£91,001

Table 67 shows incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model with the company's proposed PAS applied. The results are equivalent to the without PAS results presented in Section 6.5.2.

Table 30 Incremental cost-effectiveness ratios of proportional hazard model vs. fully stratified model (with PAS)

	Fitted curves		**Crizotinib**		**Pemetrexed + cisplatin/carboplatin**		
	PFS	**OS**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
ERG's preferred base-case (proportional hazard model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	£74,792
ERG's preferred base-case (fully stratified model)	Gamma (same fitted curves for both treatments)	Weibull (same fitted curves for both treatments)	[redacted]	[redacted]	[redacted]	[redacted]	£89,754
ERG's preferred base-case (fully stratified model and curves selected using lowest AIC)	Log-normal – crizotinib; and gamma - pemetrexed	Gamma – crizotinib; and exponential - pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	£130,364

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from the CRD and CHE Technology Assessment Group, University of York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **6pm, 19 April 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

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

Issue 1 Number of errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report contains a multitude of typographical, potential calculation and citation errors present throughout all sections of the document. We are concerned that this large number of errors significantly limits the robustness of the report. Without access to the ERG economic model, the Company cannot explore the extent to which these errors extend to all calculations.	The report should be quality-checked, and this check extended to the ERG's model to ensure reliability of results.	The number of errors calls into question the confidence which can be placed in the ERG's critique and its associated results.	The ERG thanks the company for identifying the typographical errors within the ERG report. These errors were due to the ERG not being able to complete its usual quality assurance process due to the extensive work necessary in this submission. These errors, however, in no way impact on the overall robustness of the ERG's critique of the company submission or the additional analysis carried out by the ERG. The ERG has now made available the executable model for the company to inspect and welcome any feedback the company wishes to make.

Issue 2 Mis-characterisation of company's evaluation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
There are a number of points in the ERG report in which the Company Submission is described as containing critical calculation errors which impact the reliability of the submission.	The impact of error correction the ICER should be separated from the impact of alternative calculation approaches preferred by the ERG. Other issues which are not strict errors but are open to debate should be described as such.	Description of all points of disagreement as "errors" mischaracterises the robustness of the company submission. Pfizer accepts that the ERG disagrees with a number of	The ERG characterisation of the approach taken by the company as critical calculations error reflects the fact that the calculation of time on treatment on TBP was factually incorrect as

However, it is the case that many of the "errors" are in fact alternative approaches to those preferred by the ERG. Pfizer accepts that the ERG disagrees with some approaches or assumptions selected in the company submission, but to strictly define these as errors is misleading. This includes the calculation of treatment beyond progression (TBP), which the ERG defines as the most critical error in the submission. Indeed, Pfizer contend that there is an error in the ERG's preferred approach to the calculation of TBP, which is addressed in issue 3 below. The reference to errors which are in actual fact alternative approaches/assumptions, continuously repeated throughout the document, has the effect of making the report appear unbalanced. As such, the conclusions that can be drawn from the ERG's report are associated with uncertainty.	In instances where computational errors have been corrected, proposed wording is below: "However, the electronic model submitted by the company was subject to a number of calculation errors, but the impact to the ICER of these was less than £2,000/QALY." Additionally, owing to the minimal impact on the ICER, none of computational errors should be described as critical.	approaches taken, but does not consider the terminology used to describe them as accurate. The impact on the ICER at list price of error correction is: • Corrected base case following clarification questions – increase of £2,593/QALY • Corrected application of half-cycle correction (costs of treatment not using HC correction, QALYs calculated with HC correction applied from cycle 1; Time zero was included as a complete cycle in the model) – reduction of £1,471/QALY • Correction to number of patients at 8 cycles beyond progression - £0 impact in the base case The most significant "error" the ERG cite is the estimation of true treatment beyond progression time. The ERG propose a "correction" for this to the ICERs, however Pfizer contend that are indeed errors in the ERG's "correction". This is presented in Issue 3 below.	patients did not receive 4 cycles of therapy as suggested in the CS. The ERG was, however, not able to correct the model using the approach taken by the Company and was forced to take an alternative. This approach made different assumptions to those originally presented in the model, which were based on the restricted mean time on treatment, which the ERG considered to be clearly incorrect. The correction was therefore both a correction to calculation errors made in the company model and a change to assumptions made in the original CS. The ERG therefore stand by the wording in the original document that the original model presented in the CS contained critical calculation errors that substantially underestimated time on treatment.

Issue 3 Treatment beyond progression: impact on PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 82 the ERG present their "correction" for the calculation of treatment beyond progression. This is cited as the major weakness of the Company's estimates of cost-effectiveness: "Based on the exponential curve mean duration of treatment for all crizotinib a patient is estimated to be [redacted]*months. This compares with [redacted] using the truncated data reported in the CSR. Using this value and mean time to progression it is possible to calculate mean time on crizotinib post progression, which the ERG calculate to be [redacted] Firstly, as noted in Issue 2 above, Pfizer contend that the method put forward by the ERG is an alternative approach to that proposed in our submission, rather than a strict correction of an error. Secondly, although Pfizer have not had access to the ERG's model, it appears as though the calculations used in the ERG's "correction" of the Company's model (and therefore the subsequent analyses	As noted above, the impact of computational error correction the ICER should be separated from the impact of alternative calculation approaches preferred by the ERG (which includes the calculation of treatment beyond progression). Other issues which are not strict errors but are open to debate should be described as such. With respect to the correction of the ERG analyses, we cannot propose the exact figures to use without access to the ERG model. However, upon inspection of the ERG report, it appears there may be the following issues leading to an inaccurate calculation: PFS: The ERG's estimate of treatment beyond progression is calculated using the extrapolated total treatment duration (as the CSR dataset underestimates the mean due to crizotinib patients still on treatment), minus the mean PFS from the CSR dataset. However, when the ERG subtract the [redacted] mean PFS from the CSR, the calculations do not appear to account for proportion of crizotinib patients that are still pre-progression (i.e, the ERG's calculation on treatment beyond progression is not aligned to the calculation of PFS). Pfizer considers that PFS and treatment duration should be calculated using comparable approaches. In other words, if the ERG's extrapolation of treatment duration is to	With respect to the first point, description of all points of disagreement as "errors" mischaracterises the robustness of the company submission. With respect to the second point, changes to the ERG calculations may have a significant impact on the ICERs to be considered by the Committee. If it is the ERG's position that this is not a true error in their calculation, this at least confirms that the calculation of treatment beyond progression is a point of debate, and that their analyses are not ones which can be appropriately described as error correction.	The figures of [redacted] and [redacted] are both incorrect. These have been corrected in the ERG report. The mean time on treatment is calculated directly from the model which has now been provided to the company allowing them to verify our calculations. Note this error does not impact on the resulting ICERS.

run in Section 6) contain an error.	be adopted, PFS should likewise be extrapolated to establish the 'true' mean. This increased value for PFS would mean the ERG's estimation of treatment duration would be reduced by several months. It is proposed that the calculations are revisited and provided for Company review well in advance of the Committee meeting.		

Issue 4 Incorrect figure reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The information noted below in bold is incorrectly reported in the ERG report. ERG report states in Section 1 on page 13: "This is acceptable as the vast majority **(98.7%)** of ALK-positive patients are expected to be of non-squamous tumour histology" ERG report states in Section 3.1 on page 31: "However, the CS points out that the majority **(98.7%)** of ALK-positive patients are expected to be of non-squamous tumour histology."	Percentage to be corrected to the figure reported in the Company Submission: 97.7%	Correction of reporting inaccuracy See Company Submission on page 35.	Minor typographical error, changed as company suggests.

Issue 5 Incorrect figure reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The information noted below in bold is incorrectly reported in the ERG report. ERG report states in Section 1.1 on page 14: "This can be compared with the proportion patients who received cisplatin and carboplatin in the PROFILE 1014 trial: **53% and 47%** respectively, which therefore may not represent the clinical practice in the UK." And, ERG report states in Section 2.3.1 on page 28 that: "The proportion of patients who received cisplatin and carboplatin in the PROFILE 1014 trial presented in the CS was **53% and 47%,** respectively." And, ERG report states in Section 3.3.2.1 on page 32 that: "This can be compared with the proportion patients who received cisplatin and carboplatin in the PROFILE 1014 trial: **53% and 47%** respectively, which therefore may not represent the clinical practice in the UK."	Rounding of percentages corrected to: 54% cisplatin 46% carboplatin	Correction of reporting inaccuracy. The number of patients who received either pemetrexed plus cisplatin or pemetrexed plus carboplatin was 91 and 78, respectively, out of a total of 169 patients who received treatment in the chemotherapy group in PROFILE 1014 (Table 15 in the Company Submission and Solomon 2014)	Minor typographical error, changed as company suggests.

Issue 6 Incorrect figure reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The information noted below in bold is incorrectly reported in the ERG report. ERG report states in Section 1.2.2 on page 15: "…compared with 45% (95% CI 37%–53%) with chemotherapy (***P<0.0001***)."	P-value corrected to: "…compared with 45% (95% CI 37%–53%) with chemotherapy (P<0.001)."	Correction of reporting inaccuracy See Company Submission on page 76 and Solomon 2014.	Minor typographical error, changed as company suggests.

Issue 7 Omission of confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Data reported in Section 1.2.3 on page 15; in Section 4.2.1 (Table 4, final row) on page 37; and in Section 4.2.2 (Table 8) on page 41, row heading "Duration off follow-up" have not been appropriately marked as confidential.	To be highlighted as Academic in Confidence, as follows: "… (range [redacted] to [redacted]) in the crizotinib arm and 16.7 months (range [redacted] to [redacted]) in the chemotherapy arm."	Data presented have not yet been published and should thus be marked as Academic in Confidence.	Corrected as company suggest.

Issue 8 Incorrect reporting of PFS data

Description of problem	Description of proposed amendment	Justification for amendment	
Follow-up for PFS reported in the ERG report does not include	To add full details of progression events or death:	Reporting only progression events in the context of PFS follow-up is	Corrected as company suggest.

patients who died before disease progression, but rather only includes death. In PROFILE 1014, PFS was defined as time from randomisation to progression or death, whichever occurred first. ERG report states in Section 1.3.1 on page 16 that: "Follow-up was not complete for PFS: at the time of the data cut-off cancer had progressed in 51.7% of crizotinib patients and in 77.2% of chemotherapy patients…"	"Follow-up was not complete for PFS: at the time of the data cut-off, 58.1% and 80.1% of patients in the crizotinib and chemotherapy groups, respectively, had either experienced disease progressive or had died (without documented disease progression) …"	misleading as both progression and death (whichever occurred first) are included in the analysis of PFS.	

Issue 9 Omission of confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting incorrect or omitted. 1. ERG report states in Section 1.3.1 on page 16 that: "Follow-up was not complete for PFS: at the time of the data cut-off cancer had progressed in 51.7% of crizotinib patients and in 77.2% of chemotherapy patients and [redacted] of patients randomised to crizotinib were continuing in the trial at the data cut off." 2. And, in Section 4.4 on page 62 that:	To be highlighted as Academic in Confidence, as follows: 1. "… and in 77.2% of chemotherapy patients and [redacted] of patients randomised to crizotinib were continuing in the trial at the data cut off." 2. "However at the pre-specified data cut analysed not all patients had completed the trial, with [redacted] of patients randomised to crizotinib continuing in the trial."	Data presented have not yet been published but are not commercially sensitive and should thus be marked as Academic in Confidence.	Text changed as per Issue 8 therefore no longer relevant.

"However at the pre-specified data cut analysed not all patients had completed the trial, with 69.2% of patients randomised to crizotinib continuing in the trial."			

Issue 10 Query over accuracy of cited figure for patients still in crizotinib treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report states in Section 1.3.1 on page 16 that: "However at the pre-specified data cut analysed not all patients had completed the trial, with [redacted] of patients randomised to crizotinib continuing in the trial." This percentage was not explicitly stated in the original company submission; the spruce of this figure should be cited to ensure its accuracy.	Required citation for source of data	To ensure data is factually accurate, reference for this data is required.	Text changed as per Issue 8 therefore no longer relevant.

Issue 11 Clarification on methods used to estimate and extrapolate PFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Section 1.4, page 18, the following sentences are unclear, and could possibly be interpreted incorrectly: "A single parametric function was	Alternative wording: "Parametric survival models, including covariates for treatment and baseline patient characteristics were fit to patient level data for PFS and, separately, cross-over adjusted (two-	The amended wording clarifies how patient level data were used to estimate PFS and OS.	Changed as company suggest.

fitted to the Kaplan-Meier data on PFS with a covariate for treatment effect. OS was estimated by applying the crossover adjusted hazard ratio (Two stage model) to the parametric OS function calculated for crizotinib."	stage) counterfactual OS. The resulting parametric survival functions were then used to estimate PFS and, separately, OS for each treatment by varying the treatment parameter within survival equations."		

Issue 12 Omission of confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Commercial in Confidence highlighting omitted. ERG report states in Section 2.1 on page 25 the number of countries in which crizotinib has received regulatory approval.	To be highlighted as Commercial in Confidence, as follows: "… approved for use in ALK-positive NSCLC in [redacted] countries."	Number of countries in which crizotinib has received regulatory approval is considered Commercial in Confidence, as highlighted in the Company Submission on page 24.	Changed as company suggest.

Issue 13 Incorrect summary of data presented in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The data presented in the Company Submission are not accurately described in the ERG report. The ERG report states in Section 4.1.3 on page 35 that: "In addition, PFS data for Davies et al 2015 trial (Table 38 & Appendix 10 of the CS) and	Sentence to be amended as follows to include correction to the Table number and to include other data reported in the Company Submission: "In addition, PFS, OS and ORR data from Davies et al 2015 (Table **30** & Appendix 10 of the CS) and the number of adverse events for PROFILE 1001 trial were extracted (Appendix 11 of the CS). PFS and ORR data from PROFILE 1001 were only reported in text in the	The current wording in the ERG report does not accurately describe what data are presented in the Company Submission from the non-RCTs included.	Changed as company suggest.

number of adverse events for PROFILE 1001 trial were extracted (Appendix 11 of the CS). However, no further data was extracted for the two trials." However, the data referred to be the ERG as not being available were reported in the Company Submission, but only in the text.	Company Submission."		

Issue 14 Incorrect figure reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate information presented in the ERG report regarding the data cut-off date of PROFILE 1014. The ERG report states in Table 4 in Section 4.2.1 on page 36 that: Data cut-off: 18 months	Data cut-off: 23 months (January 2011 to 30th November 2013)	Correction of reporting inaccuracy	Minor typographical error, changed as company suggests.

Issue 15 Omission of confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Academic in Confidence highlighting omitted. ERG report presents median best percentage change in target lesions from baseline in Section	To be highlighted as Academic in Confidence, as follows: [redacted] *(for crizotinib group)* [redacted] *(for chemotherapy group)*	Data presented have not yet been published and should thus be marked as Academic in Confidence.	Changed as company suggest.

4.2.2 (Table 8) on page 41.			

Issue 16 Covariates included in Two-stage crossover adjustment method

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 4.2.2.3, page 48, it is stated. 'based on the CS evidence (page 82), the ERG understands that models were adjusted for baseline smoking status and ECOG, not for variables that were collected at the progression time point.' The inclusion of ECOG in this sentence is not strictly correct.	Remove reference to ECOG.	Three versions of the two-stage model were presented in Table 10, two of which were adjusted for baseline smoking status and ECOG at progressive disease (PD) by independent radiology review (IRR) and the third which was unadjusted for covariates. For the two adjusted models, if ECOG at PD by IRR was missing, ECOG was imputed using the two different methodologies described on page 223 of the submission document. This is correctly identified in the last paragraph on page 46 of the ERG report.	Text changed from: "the ERG understands that models were adjusted for baseline smoking status and ECOG status at progression time point. Thus, the ERG questions the appropriateness of this model for the PROFILE 1014 trial. This method also assumes that there is no time dependant confounding between the time of disease progression and time of switching." To "the ERG understands that models were adjusted for baseline smoking status and ECOG status at progression. This method assumes that there is no time dependant confounding between the time of disease progression and time of switching."

Issue 17 Inaccurate reporting of clinical data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Nausea and vomiting did worsen in the crizotinib group but this was significantly less severe than in the chemotherapy group. ERG states in Section 4.2.2.4 on page 55 that: "Crizotinib did cause significantly greater worsening of nausea and vomiting, diarrhoea and peripheral neuropathy."	Correct to: "Although, nausea and vomiting worsened in the crizotinib group compared to baseline, this was significantly less than the increase in symptom severity that was reported in the chemotherapy group. Crizotinib did however cause significantly greater worsening of diarrhoea and peripheral neuropathy compared to chemotherapy."	Correction of reporting inaccuracy. See Figure 13 in the Company Submission and Solomon 2014.	Text edited to reflect sentiment of company's proposed change.

Issue 18 Inaccurate figure reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The 95% confidence intervals of PFS from PROFILE 1001 reported in Section 4.2.3 on page 57 are incorrect. The report states: "The ORR for those who received first-line crizotinib was 63.6% (95% CI, 40.7 to **80.28**)."	Correct to: "The ORR for those who received first-line crizotinib was 63.6% (95% CI, 40.7 to **82.8**)"	Correction of reporting inaccuracy. Inaccuracy was also present in the Company Submission. See Camidge 2012 for correction.	Minor typographical error, changed as company suggests.

Issue 19 Incorrect reference citation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the ERG report Davis et al (2015) is incorrectly cited a number of times. On pages 43, 56, 58, 59, 70, 71 of the ERG report: Davis et al. (2015) is incorrectly referenced as Davis et al. (2005) or as Davis et al. (2014).	Correct to Davis et al. (2015)	Incorrect referencing of study.	Minor typographical error, changed as company suggests.

Issue 20 Reporting inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
PROFILE 1001 is described as including only first-line therapy. ERG report states in Section 4.3 on page 60 that: "… a pooled safety analysis from 1669 patients who received crizotinib across four clinical trials (PROFILE 1014 and 1001 which investigate crizotinib as a first-line therapy, and PROFILE 1005 and 1007 which investigate crizotinib as a second-line therapy)."	Suggested wording: "… a pooled safety analysis from 1669 patients who received crizotinib across four clinical trials (PROFILE 1014 which investigated crizotinib as a first-line therapy, PROFILE 1001 which included patients treated with crizotinib **as a first or later-line therapy**, and PROFILE 1005 and 1007 which investigated crizotinib as a second or later-line therapy)."	Correction of reporting inaccuracy Correction required as PROFILE 1001 also included patients treated at later lines of therapy.	Changed as company suggests.

Issue 21 Incorrect figure reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of data. ERG report states in Table 16 in Section 4.3.1 on page 61 that: "Treatment-related AEs with crizotinib" = [redacted]	Corrected to: [redacted]	Correction of reporting inaccuracy Inaccuracy was also present in the Company Submission.	Minor typographical error, changed as company suggests.

Issue 22 Incorrect figure reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of data. ERG report states in Section 9 on page 126 that: "PROFILE 1014 showed crizotinib to have a significant benefit in terms of median PFS compared to the pemetrexed group (HR 0.30, 95% CI 0.21 to 0.43)"	Corrected to: "… (HR 0.45; 95% CI, 0.35 to 0.60)."	Correction of reporting inaccuracy	We assume the company is referring to section 8. Text changed as suggested.

Issue 23 Un-specified abbreviation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The abbreviation PFC is used in the report (pages 68, 82, 100) however is not provided in the list of abbreviations.	Include the abbreviation PFC in the list of abbreviations and expand on first use in the document.	It is not clear what this abbreviation stands for.	Added to abbreviation list and expanded on first use.

Issue 24 Reporting of Non-UK evaluations for ALK-positive NSCLC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 69, the first sentence states "The most relevant of the 10 studies listed in Table 18 are the four economic evaluations of crizotinib from a non-UK perspective and an economic evaluation of certanib an alternative ALK-positive targeted therapy, also taking a non-UK perspective". This sentence implies that there should be 5 studies in Table 18 where there are only 4.	Update the text and/or table to accurately reflect the studies of interest.	This will improve understanding of the section.	Additional row added to Table 18.

Issue 25 Incorrect reference to sensitivity analysis in company's submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 19 on page 72 the ERG refers to sensitivity analyses being reported in Section 5.8.3 equal to pg. 178 to 181 in the company's submission. This section only describes probabilistic scenario analyses. The full section on sensitivity analyses (including probabilistic analysis and deterministic one-	Correct the section and page references in this row of Table 19.	The current section references may be misleading to the reader who may believe that probabilistic analysis and deterministic one-way sensitivity analyses were not conducted by the company.	Minor typographical error, changed as company suggests.

way sensitivity analysis) is presented in Section 5.8, on pages 175 to 181.			

Issue 26 Misleading description of additional utility for crizotinib patients receiving treatment beyond progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 73 there is a sentence which states "Crizotinib patients treated beyond progression are assumed to incur an additionality utility compared with untreated progressed patients." This is partially incorrect as it should focus on the utility difference with docetaxel patients which is the treatment patients have post-crizotinib. However, if the ERG is meaning to state that utility is greater than with no treatment at all, the Company agrees that this is a rationale assumption.	This sentence should likely read: Crizotinib patients treated beyond progression are assumed to incur an additionality utility compared with progressed patients treated with docetaxel.	The current sentence is misleading and may lead to misunderstanding.	Changed as company suggested

Issue 27 Description of treatments included in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 75 there is a sentence which states: "Patients initiating chemotherapy are assumed to have six lines of therapy (as per	Amend the sentence to the following: "Patients initiating chemotherapy are assumed to have a maximum of six cycles of therapy (as	The current sentence may be misleading and implies that prior to progression patients have six lines	Changed as company suggested

Profile 1014) and on progression are assumed to receive second-line therapy, consisting of docetaxel, which is in turn followed by BSC." This implies that patients have six lines of chemotherapy instead of six cycles. If the statement was meant to state "six cycles" rather than "six lines". If this is the case, the wording of the sentence is incorrect in context of the assumption, as the model assumes patients are allowed **up to a maximum** of six lines of therapy, not that all patients have six cycles. In the same sentence it is unclear why best supportive care is highlighted.	per PROFILE 1014) and on progression are assumed to receive second-line therapy, consisting of docetaxel, which is in turn followed by BSC."	of chemotherapy which is incorrect.	

Issue 28 Exclusion of crizotinib as a second-line treatment

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Inaccurate citing of the company's feedback on page 77 to an issue from the clarification stage. "The CS justifies the decision to exclude crizotinib as a second-line therapy on the grounds that crizotinib is currently only available via the CDF, and due to	The description of the justification should include the point made in the Company Submission that crizotinib is currently not standard of care in Wales in patients with relapsed ALK-positive NSCLC as it has not been approved by NICE.	The company's reasons for exclusion were uncertainty around the CDF but also issues with crizotinib not being standard of care in Wales, as cited in the response to question A8 at the clarification stage. The proposed amendment now accurately reflects this earlier	NICE justification does not extend to Wales. The ERG has, however, added a sentence to note that crizotinib is not available in Wales.

uncertainty over the future of the CDF."		text.	

Issue 29 Classification of discounting in the economic model as an error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In a number of places in the report (pages 79, 103), the ERG states that the company has incorrectly applied the discount rates by discounting on an annual basis rather than a per cycle basis. The company believes that the application of discount rates on an annual basis is not incorrect, but is an alternative approach to discounting. The company accepts that the ERG prefers to apply discounting on a per cycle basis, however disagrees with the ERG's conclusion that the company's application is incorrect.	Re-word these sections to state that the ERG prefers discounting by cycle rather than on an annual basis, and to remove the statements that this is an error in the company model.	The company believes that it is unfair to class this as an error when there are two alternative approaches which could be taken and the NICE methods guide does not specify which approach should be taken, only that an annual rate of 3.5% should be used for both costs and benefits (NICE 2013, p.49). The company believe this is a disagreement over the choice of methodology rather than an error in the company's calculations. The impact of these methods on the ICER is minimal (expected to be less than £200/QALY).	The ERG explains that this is non-typical approach and less accurate than discounting by cycle. Therefore while not strictly an error the model calculations are inconsistent with the typical approach to discounting taken. The ERG have edited the discounting section to make this clearer but stand by the classification as calculation error.

Issue 30 Clarification on data used in parametric models

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 5.2.7, page 80, for clarity, the use of the term 'patient level data' may be preferable to	Amend sentence to: "The ERG therefore presents an additional analysis in Section 6 where independent	The amended wording clarifies what data have been used for the parametric survival modelling.	The ERG disagrees: patient level data were not available to the ERG, but were derived

'Kaplan-Meier plots' in the following sentence: "The ERG therefore presents an additional analysis in Section 6 where independent parametric survival functions are fitted to the Kaplan-Meier plots of PFS for the crizotinib and pemetrexed arms of PROFILE 1014"	parametric survival functions are fitted to patient level PFS data for the crizotinib and pemetrexed arms of PROFILE 1014"		from the Kaplan-Meier plots. The alternative wording may be interpreted to suggest that the ERG did have patient level data. No change made

Issue 31 Incomplete sentence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 80 there is an incomplete sentence which simply states: "The ERG"	Remove or complete this sentence.	It is currently unclear if there is an additional point the ERG wishes to make in this section.	Deleted

Issue 32 ICERs in Table 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ICERs in Table 22 on page 80 do not match those presented in the company's submission, as the ICER's in the ERG's Table appear to deterministic ICERs extracted from the original model by the ERG. The ERG then state: "…there is significant uncertainty surrounding the presented base-case ICER not accounted for in the	Advised to either amend the ICERs in Table 22 to the probabilistic ones presented within the company's submission (rows 3, 4, 5 and 6 in Table 75 in the STA submission document, and Table 6 in the PAS template), or to explicitly state that these are the deterministic ICERs. Statement in the text should be corrected to read to: "…the uncertainty surrounding the presented base-case ICER was accounted for in the	Text is inaccurate and misleading.	The ERG was attempting to make the point that uncertainty over choice of treatment switching model was not accounted for in the PSA analysis. Text has been edited to make this clearer.

probabilistic analysis". This statement is false as this uncertainty was accounted for in the probabilistic analyses that were presented in the company's original submission, the PAS template, and the addendums to these sections provided at the clarification stage.	probabilistic analysis".		

Issue 33 Typographical error regarding duration of crizotinib therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81 there is a typographical error in the sentence "The ERG considers the approach taken by the company to be reasonable with regards to patients who discontinue treatment to progression, but has identified a number of issues regarding the assumptions made for patients treated beyond progression and the way 'time on treatment' is implemented in the electronic model for these patients." Instead of stating "patients who discontinue treatment to progression" this should state "patients who discontinue treatment at progression".	Amend the wording from "patients who discontinue treatment to progression" to "patients who discontinue treatment at progression".	The current wording changes the meaning of the sentence.	Minor typographical error, changed as company suggests.

Issue 34 Unclear how the mean duration of treatment beyond progression is calculated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81 a mean duration of treatment beyond progression with crizotinib of 4.76 months is stated by the ERG. It is not clear how this value has been calculated, as our calculation is as follows: CSR Table 14.4.1.1.6.1 states a mean of 20.2 weeks of treatment beyond progression = 4.66 months.	Double check the value and either correct it to 4.66 months or provide clarification as to how the value of 4.76 was calculated.	It is currently unclear how this value was calculated and if incorrect the ERG is overestimating the duration of treatment beyond progression. This may have a small impact on the results of the analysis.	Text was altered to make clearer. This has no impact on the model as this value was not used in the ERG's corrected model.

Issue 35 Unreferenced figure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81 the ERG states that "47.6% of crizotinib patient were still on therapy at the time of the analysed data cut of 30th November 2013". As the percentage figure of 47.6% is not explicitly cited in the Company's original submission, it is not clear the source of this data and clarification is requested.	Include further clarification on the source of this figure.	The current sentence may be misleading. This could impact the results of the ERG's analysis into treatment beyond progression.	Text added to clarify source as the company PFC response.

Issue 36 Unclear calculation of mean number of cycles of treatment received beyond progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 83 the ERG states that the economic model produces a mean number of cycles of treatment beyond progression of 2.2. The company is unable to replicate this number and using the following formula gets a mean number of cycles of treatment beyond progression of 2.42 =SUMIF($C$15:$C$258,"<="&Time_horizon,AG15:AG258)/TBP_prop_criz	Double check the value and either correct it to 2.42 cycles or provide clarification as to how the value of 2.2 was calculated.	It is currently unclear how this value was calculated. This does not impact the results of the analysis.	Minor typographical error, changed as company suggests. This value was not used in the ERG's modelling.

Issue 37 Incorrect proportion of patients receiving no further treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 85 the ERG state that "74% and 26% of crizotinib and pemetrexed patients respectively received no further treatment." Based on Table 21, the value for pemetrexed should be 100% - 72.5% = 27.5%, which rounds to 28% not 26%.	Amend the value of 26% to 28%.	The current proportion is incorrect. This does not impact the results of the analysis.	Figures were based on older version of Table 21 and have been corrected as suggested

Issue 38 Quantification of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81, when discussing the methods of crossover adjustment	"As such, whilst the ERG consider there to be issue with the methodological models	The text contradicts the Table above the paragraph.	The suggested correction misses the point that all

and how these impact the ICER, the ERG state: "As such, the ERG consider there to be significant and unquantifiable uncertainty surrounding the estimated OS benefits and by extension to the estimated ICER." The declaration that this uncertainty is "unquantifiable" is an inaccurate assertion considering the ERG in fact quantify this uncertainty in table 22 on the previous page.	recommended in NICE DSU 16, the uncertainty surrounding the estimated OS benefits and by extension to the estimated ICER is quantified in Table 22."		models are potential subject to bias which the ERG cannot quantify. The ERG has edited the section to make this clearer.

Issue 39 Potentially inaccurate figure provided

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81: "…the mean duration of treatment beyond progression is 4.76 months, conservatively equivalent to 5 cycles." No reference is provided for this figure of 4.76 months. Data from the CSR suggests that it may be an incorrect calculation.	Provide reference, or adjust figure.	Data needs to be referenced, or adjusted to reflect CSR table 14.4.1.1.6.1 which states 20.2 weeks (=4.66 months). Without full information of the ERG's calculations of treatment beyond progression, it is not known if this will impact the ERG's analyses.	Details of the calculation have now been added. This figure was not used in the economic analysis.

Issue 40 Exponential curve not visible

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Figure 6 – does not show exponential curve.	If exponential curve is hidden behind other curve, please bring to front as this is the chosen curve for the analyses. If it is missing, please add.	Exponential curve not visible.	Exponential curve was hidden behind Weibull curve. Figure altered so this is reversed and a note added to state Weibull curve is hidden behind the Exponential curve.

Issue 41 Incorrect author name

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 24 on page 87 the ERG refers to a study by Doyal et al. (2008). The correct author for this study is Doyle.	Correct the author name from Doyal to Doyle.	The current referenced author is incorrect.	Minor typographical error, changed as company suggests.

Issue 42 Drug wastage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 93 it is stated that for both crizotinib and pemetrexed no drug wastage was assumed for either treatment. This is incorrect. Wastage for both was considered in the modelled base case.	Adjust wording to reflect that wastage was in fact included in the base-case, but that it was incorrectly adjusted for half-cycle correction.	There was a computational change required to account for half-cycle correction, but the statement that "no" drug wastage was considered is false as wastage was included in the original model. This statement is misleading and inaccurate unless the wording is changed. A scenario where wastage was	The ERG was not able to identify the series of analysis referred to, but assumes the Company is referring to the scenario in which vial wastage for pemetrexed combination therapy excluded. The ERG have edited text to clarify that no drug wastage due to discontinuation was allowed for

		excluded is presented in rows 3, 4, 5 and 6 in Table 75 in the STA submission document, and Table 6 in the PAS template.	in the company model.

Issue 43 Rounding

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 94 the ERG state the cost of oral chemotherapy SB11Z was £163. The actual cost used in the economic model was £163.85 which rounds to £164.	Correct the cost to £164.	The current cost is incorrectly rounded. This does not impact the results of the analysis.	Minor typographical error, changed as company suggests.

Issue 44 Incorrect reference to PAS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 28 on page 95 the words "with PAS" should be removed from the final row of the table as the values in the table reflect the list price for crizotinib. This is a typographical error which has been carried across from the company submission.	Remove the words "with PAS" from the table.	The inclusion of this text may be misleading to readers. This does not impact the results of the analysis.	Text deleted

Issue 45 Uncorrected figures reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Table 31 on page 97 the cost	Remove the second row containing district	The inclusion of district nurse twice	Changed as company

for district nurse is included twice, and the total costs are based on those reported in the company submission which were identified as incorrect in the response to clarification question B4c. The correct values should be £7,318 (£5,954, £8,820).	nurse and update the total costs.	may be misleading. The total costs do not reflect the costs used in the economic model.	suggests.

Issue 46 Uncorrected figures reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 98 the total cost of treating adverse events due to pemetrexed are stated to be £163.20. This is incorrect and should be £82.04 as discussed in the company response to clarification question B4b.	Update the cost of adverse events due to pemetrexed.	The current total cost reported does not reflect the cost used in the economic model.	Changed as company suggests.

Issue 47 Uncorrected figures reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 99 the cost of treating thrombocytopenia stated to be £758.50. This is incorrect and should be £750.09 as discussed in the company response to clarification question B4a.	Update the cost of treating thrombocytopenia.	The current cost reported does not reflect the cost used in the economic model.	Changed as company suggest.

Issue 48 Incorrect figures reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Table 33 on page 99 the ERG states that the tests used are "IHC followed by ALK". This should state IHC followed by FISH. Additionally, the cost of identifying one ALK-positive patient for IHC followed by FISH for all positive scores is incorrectly reported as £1,754.23. This cost should be £[redacted].	Replace ALK with FISH in the test column of the table. Correct the cost of cost of identifying one ALK-positive patient for IHC followed by FISH for all positive scores.	The current wording is misleading. The current cost reported does not reflect the cost used in the economic model. These updates do not impact the results of the analysis.	Changed as company suggest.

Issue 49 Omission of confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 99, the cost of IHC should be marked as CIC as per the company submission, but is not.	Mark this cost as CIC.	This cost is data on file and is therefore CIC. This does not impact the results of the analysis.	Changed as company suggest.

Issue 50 Incorrect figure reported in base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 100 the incremental cost is reported incorrectly as £58,046 in the text. The value of £58,406 in Table 34 is correct.	Amend the incremental costs in the text to reflect the results in Table 34.	The value in the text is incorrect and may be misleading. This does not impact the results of the analysis.	Changed as company suggest.

Issue 51 Misleading presentation of scenario analysis results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 102, the ERG discusses the results of the analyses pertaining to the non-squamous population alongside the analyses pertaining to the squamous population. This creates confusion, as it is not clear that the results presented for scenario analyses of patient characteristics, crossover method and parametric curve functions for PFS and OS are for the non-squamous population and not the squamous population.	Suggest this paragraph is split into two, one with squamous population results and one with non-squamous population results and that the scenario analysis reviewing the squamous population be presented last.	The current presentation may be misleading.	Text edited to highlight key sensitivity analyses

Issue 52 Incorrect statement regarding the cost of administration for crizotinib in the company base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 94 the ERG incorrectly states that "The company base-case instead includes a one-off cost of oral administration during the first model cycle." This is incorrect as the Company base case assumes no administration cost for crizotinib; however a scenario analysis was presented whereby a one-off cost of oral administration was	Revise the text to describe clearly that the company's base case was to assume no administration cost for crizotinib, but that a scenario analysis was presented which included a one-off cost of oral administration.	The current description of the company's base case is incorrect. This does not impact the results of the analysis.	Text revised to state no administration costs included for crizotinib.

included. This was additionally clarified in the company's response to clarification question B6.			

Issue 53 Characterisation of the exclusion of administration costs for crizotinib as an error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 103 the ERG state the errors they identified in the company's model. This includes the statement that "One-off administration cost for crizotinib were not included". To describe this as an error is not correct, as a scenario analysis was provided which included this cost. The response to clarification question B16 described how this is applied in the model. Pfizer accept that the ERG disagrees with its exclusion, but to describe the exclusion of the cost in the base case as an error misrepresents the results in the submission.	Remove this statement from the list of errors and instead describe it as an assumption which the ERG disagrees with.	The company believes that it is not correct to class this as an error when there are a number of alternative approaches which could be taken and have been taken in previous technology appraisals of oral treatments, as discussed by the ERG in their report. The company therefore believe this is a disagreement over the choice of methodology rather than an error in the company's model. Table 75 (row 16) in the original Company Submission explores this assumption and presents the probabilistic ICER of including the cost.	The option to include these did not work in the original model. Text has been changed to make it clear the ERG are referring to model controls.

Issue 54 Characterisation of the duration of time on docetaxel and BSC post progression as an error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 103-4, the ERG state	Remove this statement from the list of errors	The company believes that it is	As stated in the response to

the errors they identified in the company's model. This includes "Duration of time on docetaxel mis-specified for both crizotinib and pemetrexed patients" and "Duration of time on BSC mis-specified for both crizotinib and pemetrexed". Pfizer does not believe this to be an error in the model, but instead that the ERG disagrees with the assumptions made to simplify the application of the costs of treatment post-progression. The company therefore believes that it is inappropriate for the ERG to classify this as an error. Instead it is more appropriate to categorise this as assumption with which the ERG disagrees.	and instead describe it as an assumption which the ERG disagrees with.	inappropriate to class this as an error when there are a number of alternative approaches which could be taken and have been taken in previous technology appraisals of oncology treatments. Some examples of previous technology appraisals in NSCLC whereby the costs of second-line treatment were applied in a simplified manner include: • TA181 (pemetrexed), whereby the costs of second-line treatment were incurred as a lump sum calculated based on the mean number of cycles per patient as patients entered the health state. This was not queried by the ERG or committee. • TA258 (erlotinib), whereby the costs of second-line treatment were excluded. This was not criticised by the ERG or committee. The company therefore believe this is a disagreement over the choice of methodology rather than an error in the company's model.	issue 2 the approach taken by the company did not generate the values implied in their CS and were therefore considered erroneous calculations by the ERG.

Issue 55 Incomplete reflection of company's justification

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 114 the ERG cites the justification for the company's use of proportional hazards was the inspecting the log-cumulative hazard plots for both PFS and OS. The ERG failed to cite the clinical expert opinion that was sought into the plausibility of this assumption, as detailed in responses to clarification questions B11 and B13.	In order to accurately reflect the company's justification and not mislead the reader, the expert validation should also be cited here.	The omission of important rationale can lead to misinterpretation.	The ERG have altered the text to reflect the justification was also based on expert clinical opinion, but have also added text to highlight that no details of the clinical justification were actually provided to the ERG in the company's response.

Issue 56 Lack of clarity over choice of crossover adjustment method used in ERG exploratory analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In section 6.5.2 (pages 117-121) the ERG present additional analyses using alternative OS curves; however it is not stated that the method of crossover adjustment used in the ERG base case, and whether it is consistent with the company base case.	Add a statement that the method of crossover adjustment used is TSA, consistent with the company base case.	It is not clear from the current text, without cross-referencing to the response to clarification questions, that the crossover adjustment method used by the ERG is consistent with the company base case. This does not impact the results of the analysis.	Additional text added to make clear TSA method of crossover adjustment is being used.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from the CRD and CHE Technology Assessment Group, University of York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **6pm, 19 April 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

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

Addendum to Issue 3 from the Company's response to the ERG Report Factual Accuracy Check (19Apr16)

Since the ERG's model has been made available, the Company wishes to clarify a comment made in *Issue 3* from our original response, which was made prior to the ERG's model being made available for review.

- The ERG's report (page 82) suggests the calculation of treatment beyond progression is made by subtracting the mean PFS taken directly from the truncated data reported in the CSR from the mean treatment duration which is derived from the ERG's extrapolation of the discontinuation curve.
- The Company stated that this would lead to an inaccurate calculation of mean treatment beyond progression, for reasons stated in *Issue 3* around not using a comparable approach.
- However, the ERG's model may actually calculate treatment beyond progression in the way the Company suggested and in contrast to how the ERG explains the calculation in its report.
- The Company asks the ERG to clarify the methodology used to calculate mean treatment beyond progression, whether this is as stated in their report which includes using the mean PFS taken from the truncated CSR (which the Company highlighted as incorrect), or if in fact the ERG calculate mean treatment beyond progression using the extrapolated PFS curve instead.
- The ERG report should be amended to further clarify this point.

ERG response to addendum

The ERG calculated mean time on treatment post progression by subtracting mean time to progression from mean duration of treatment i.e. the way the company suggested. Note this will be subject to issue 1 and will therefore overestimate mean time on treatment post progression. A further erratum page has been prepared to make the calculation of the duration of post progression treatment clear. The ERG have further added additional text to highlight the implication of issue 1, see below.

Issue 1 Error in estimation of treatment beyond progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG's model adjusts the PROFILE 1014 PFS and OS based on real-world patient characteristics. This is in line with the approach used in the Company's base case, and has the effect of reducing the QALYs in each arm. However, the ERG's preferred base case and their "correction" of the Company's base case includes an unadjusted cost of treatment (based on an extrapolation of the discontinuation curve from PROFILE 1014, pertinent to the patients in the trial). As such, the ERG's model reduces the QALYs in the crizotinib arm to reflect real-world patients, but uses the costs pertinent to the trial population,	If the discontinuation curve is to be used to estimate crizotinib treatment beyond progression, a real-world data adjustment as applied to the PFS and OS data should similarly be applied to the discontinuation curve. If this error is not fixed, it should be made clear in the ERG report that the real-world data adjustment has not been applied to the discontinuation curve in the ERG model and thus leads to a considerable overestimation of the ICER.	The Company proposed a model adjusted for real-world patient characteristics, and the ERG also presented their modelled base case and sensitivity analyses with this adjustment. These adjustments affect the shape/scale/magnitude of the parametric curves for both PFS and OS in both the crizotinib and the comparator arm, in all analyses. These adjustments have a significant impact on the ICER. As this significantly impacts the ICER it should be made clear in the ERG report that the necessary real-world adjustment to the treatment duration has not been conducted and this leads to a considerable over estimation of the ICER.	The company raises a valid point that there is an inconsistency in our approach. However, the ERG cannot implement the proposed change as it does not have access to this data. The ERG has alter the text on page 84 to make it clear that his may lead to overestimation of the ICER. Additionally, the text on page 105 has been altered to make clear the error was not fully fixed. However, the ERG can only speculate as to the magnitude of the impact of this issue and it would be inappropriate to suggest that this would lead to considerable overestimation of the ICER without appropriate

without adjusting these down for a real-world population. This error leads to a considerable over estimation the ICER.			data to back up such an assertion. The ERG recommends that the company carries out its proposed analysis and raises this issue at the committee.

Issue 2 Treatment beyond progression for crizotinib is not bounded by 0% in the ERG economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When calculating the number of patients with treatment beyond progression (TBP) for crizotinib within the economic model (column AI in sheet Calc Tx1), the ERG has used the calculation TBP = minimum of treatment duration – PFS and progressed. In rows 16 and 17, treatment duration is lower than PFS resulting in negative patients in the TBP column. This has a knock on effect and results in negative life years, QALYs and costs being attributed to TBP during these cycles.	Amend the formulae in column AI to the following: =MIN(MAX(S[row]-P[row],0),Q[row])	The current calculation is incorrect and results in a negative proportion of patients in TBP which is infeasible; this should be bounded by 0%.	This correction is valid and has a small impact on the estimated ICER.

Issue 3 Pemetrexed treatment beyond progression not explicitly accounted for but is present

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pemetrexed treatment duration has been modelled using	Change the formulae in column AN to the following:	The current calculation is incorrect and results in negative	The change suggested to column AN is valid and

Kaplan-Meier data. This results in treatment duration > PFS in some cycles, which in turn leads to negative “off treatment” QALYs being incurred during these cycles (cells AN17 and AN18 in sheet Calc Tx2). This is due to QALYs for pemetrexed patients being split into “on treatment”, “off treatment” and “BSC” (as docetaxel is excluded) rather than by pre/post progression. The “off treatment” QALY calculation includes the calculation of the proportion of patients off treatment and in PFS, which is not bounded by 0. This also results in double-counting of QALYs for patients in progressed disease receiving BSC, as the proportion of patients receiving BSC (column AH) is assumed equal to the proportion of patients in progressed disease (as Docetaxel is set to 0), but in rows 17 and 18 treatment duration is > PFS, resulting in double-counting of the patients who are receiving treatment with pemetrexed but who have progressed in the QALY calculations.	=MAX(0,(P[row]-S[row]))*(cycle_length/365.25)*$G[row]*IF('ERG Controls'!$T$22=1,Utilities!$C$32,Utilities!$C$31) Change the formulae in column AH to the following: =ROUND(Q[row]-MAX(0,(S[row]-P[row]))-AE[row],10)	QALYs incurred and double counting of some QALYs.	appropriate. This has a small impact on the estimated ICER. The change to column AH is unnecessary and has no impact on the ICER.

Issue 4 Pemetrexed cost adjustment applied incorrectly

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The adjustment to the cost of pemetrexed treatment in column AQ of sheet Calc Tx2 is incorrect. More cycles of pemetrexed are being costed than should be, based on the selection in sheet Tx acquisition cost, cells E98:E106. These cells are referred to within the formulae in column AQ of sheet Calc Tx2 however the placement of the brackets means that in model cycle 5 there is a cost for pemetrexed where there should not be, based on the maximum number	Change the formula in cell AQ20 to =IF('ERG Controls'!X32=1,H20*'Calc Tx2'!S20*VLOOKUP(E20,'Tx acquisition cost'!B109:D113,3),('Tx acquisition cost'!E104*(O19*(24/cycle_length)+O20*(6/cycle_length))+'Tx acquisition cost'!E105*(O19*(3/cycle_length)+O20*(27/cycle_length)))*p_c_cost_pem_ciscarbo*H20) i.e. add open brackets following the references to Tx acquisition cost cell E104 and E105, and close brackets after the sum of weighted patients in column O. The formulae in all cells in this column are inconsistently applied and some have the same errors, however correcting these does not change the values calculated as the multiplier is 1.	The current calculation is incorrect and results in additional costs for pemetrexed.	Correction is appropriate, but only impacts on some analyses. Impact on the ICER is small..

of treatments selected being 6.			

Issue 5 Incorrect figure from model stated in the report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Sheet: Discontinuation, Cell H80 Value says 4.71 cycles of crizotinib beyond progression. This equates to 4.66 months, however the ERG reports this as 4.76 months. This pertains to *Issue 34* that the company has already fed back on.	Change figure in report from 4.76 to 4.66.	Incorrect figure in report.	This has already been addressed in the original factual error report.

Issue 6 Incorrect figure for crizotinib treatment duration from model stated in the report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Sheet: Discontinuation, Cell F83 Value says 23.37 months of mean crizotinib treatment, however the ERG report (p82) states this as 23.73 months.	Change figure in report, or clarify if figure in model is incorrect.	Inconsistency in figures across report and model.	This has already been addressed in the original factual error report.