NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

Contents:

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

Pre-meeting briefing

Ceritinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer [ID1117]

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

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

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

Please note that when the company checked the ERG report and model for factual inaccuracies it identified some errors in the ERG exploratory analyses (see issues 1, 2 and 3 of the company response). The ERG produced an erratum to address these errors, and the corrected results have been included in this document.

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

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Key issues (1)

Key clinical issues

- How reliable are results from the matched adjusted indirect comparison (MAIC)?
  - Which is more relevant: MAIC1 (PROFILE-1014) or MAIC2 (ALEX)?
  - Is PROFILE-1014 generalisable to clinical practice in the UK?
- How does the tolerability profile of ceritinib compare with crizotinib?
- Does ceritinib improve response rate and duration compared with crizotinib?

Key cost-effectiveness issues

- **Survival:** In practice, approximately what proportion of people receiving a 1st line ALK inhibitor would live for 5 years or more?
- **Treatment duration**: When would it be clinically appropriate to stop treatment with 1st line ALK inhibitor in practice? How long is 1st line crizotinib taken in practice?

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Key issues (2)

Key cost-effectiveness issues continued

- **Costs**: Should the model account for drug wastage? Would pharmacists be responsible for monitoring and dose adjustments?
- **Utilities**: Consider a patient with RECIST-defined disease progression, who is still receiving 1st line ALK inhibitor treatment because they continue to demonstrate clinical benefit. Would their quality of life be:
  - better than someone with disease progression who switched to 2nd line treatment? (and who may or may not still be receiving 2nd line treatment)
  - worse than someone who had a 1st line ALK inhibitor and is progression-free? (and who may or may not still be receiving 1st line treatment)
- **Costs and QALYs of subsequent treatment after 1st line ALK inhibitor:**
  - What proportion of ALK +ve NSCLC patients in UK clinical practice receive active 2nd/3rd/4th line treatments? (30–40%? 60%? 80%?)
  - Should the % of people on subsequent treatments be based on trial data or real world prescribing? Should costs and utilities of 2nd line treatments use the distribution of treatments from the trial or real world prescribing?
- **Innovation:** Is ceritinib innovative? Are any benefits not captured in the model?

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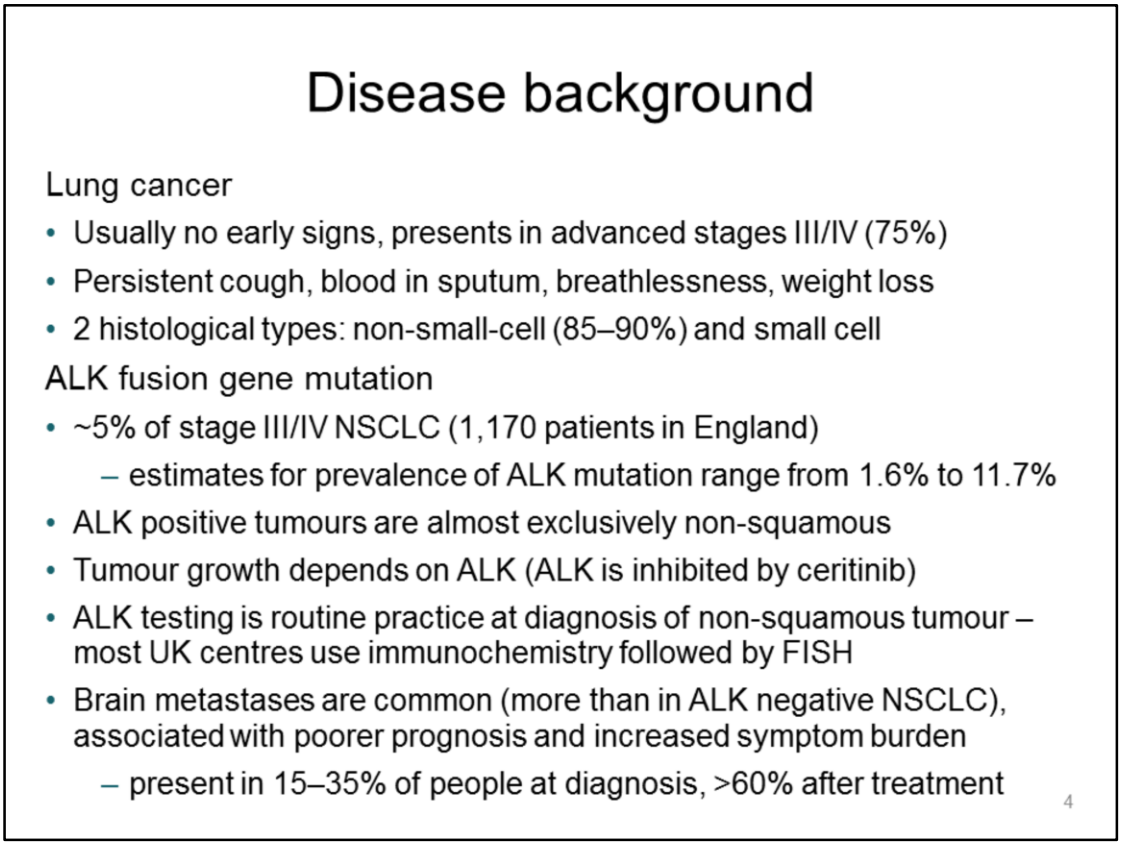
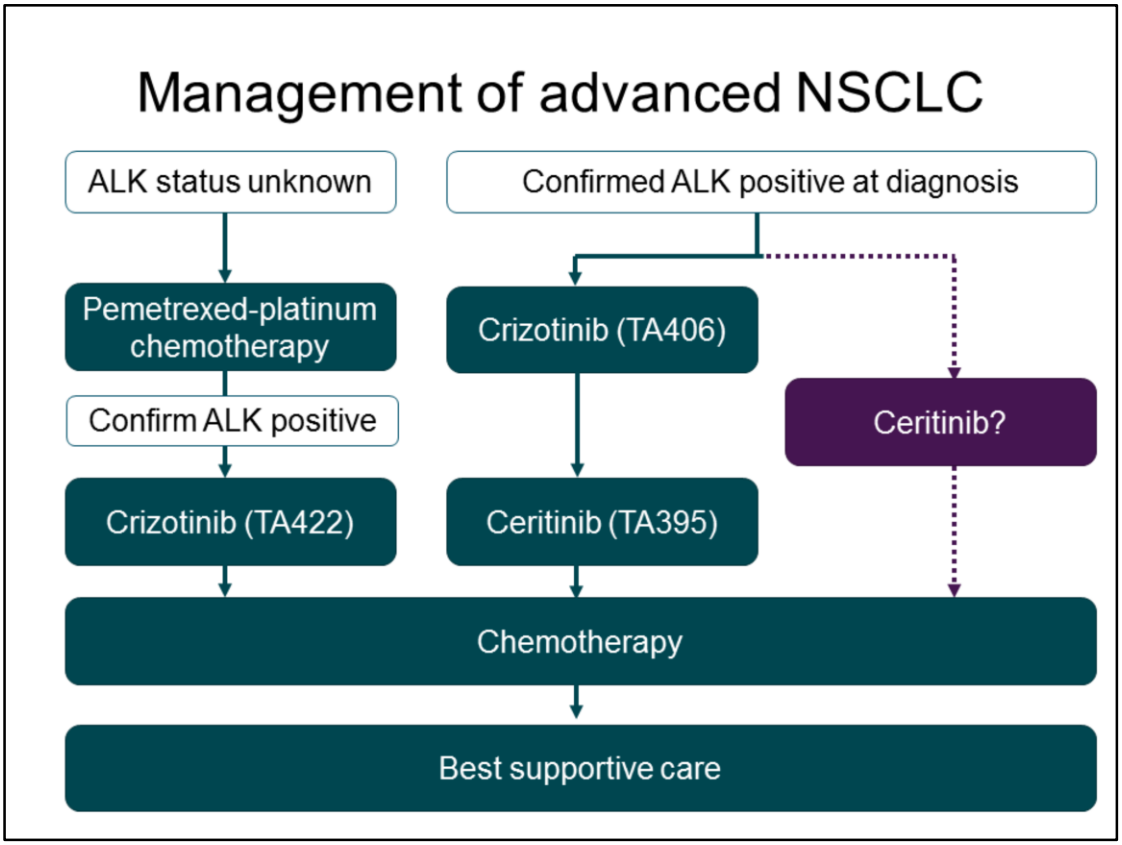


The company submission suggested that crizotinib provides poor control of intracranial disease, but the ERG did not entirely agree. The data from the Phase III trial of crizotinib (PROFILE-1014), that included patients with treated and neurologically stable brain metastases, found that intracranial lesions progressed, or new intracranial lesions developed, in 25 patients in the crizotinib group and in 26 patients in the chemotherapy group (15% each). However, crizotinib was associated with statistically significant improvements in the intracranial-disease control rate in patients with brain metastases, and non-statistically significant improvements in intracranial time to progression, in patients with and without brain metastases at baseline, compared with treatment with chemotherapy. The ERG's clinical advisor suggested that the additional survival provided by crizotinib allows time for the appearance of brain metastases (which are common in NSCLC), which would not have been seen with chemotherapy.



People whose cancer tests positive for the ALK mutation receive first line treatment with crizotinib. When the disease relapses, patients are offered second line systemic treatment with ceritinib if progression has occurred on crizotinib, or crizotinib if it was not used in the first line setting. Entry into clinical trials may be considered in the first, second, third and fourth line settings. Patients with poor performance status may be offered best supportive care (which may include radiotherapy).

ESMO guidelines recommend that brain metastases are treated with local radiotherapy. However the company's clinical advisers suggest that radiotherapy may only be given to approximately 15% of patients with brain metastases. The company noted results from a in the UK and Australia (QUARTZ) which suggest radiotherapy does not improve outcomes.

If recommended, ceritinib would displace crizotinib in the first line setting and the second line treatment would change to chemotherapy, or the patient could be considered for a clinical trial of an alternative second generation, or a third generation, ALK inhibitor (lorlatinib, brigatinib and alectinib). Clinical experts suggest it would not be appropriate to follow ceritinib treatment with crizotinib treatment because mutations that lead to resistance to second-generation ALK inhibitors (ceritinib) confer an increased risk of resistance to crizotinib as a first-generation ALK inhibitor. The clinical expert statement for this appraisal

suggests that there are case reports of response to crizotinib after ceritinib, but notes that the third generation ALK inhibitors in development would be more effective in this setting.

Patient perspectives

- Treatment not curative, therefore patients value:
  - improved quality of life
  - symptom control
  - even small extensions in survival
- Advanced NSCLC has multiple debilitating and distressing symptoms
  - some are very difficult to manage clinically eg breathlessness
  - therapies with anti-tumour activity provide best option for symptom relief
- Anecdotally, ceritinib has been well tolerated, especially compared with chemotherapy

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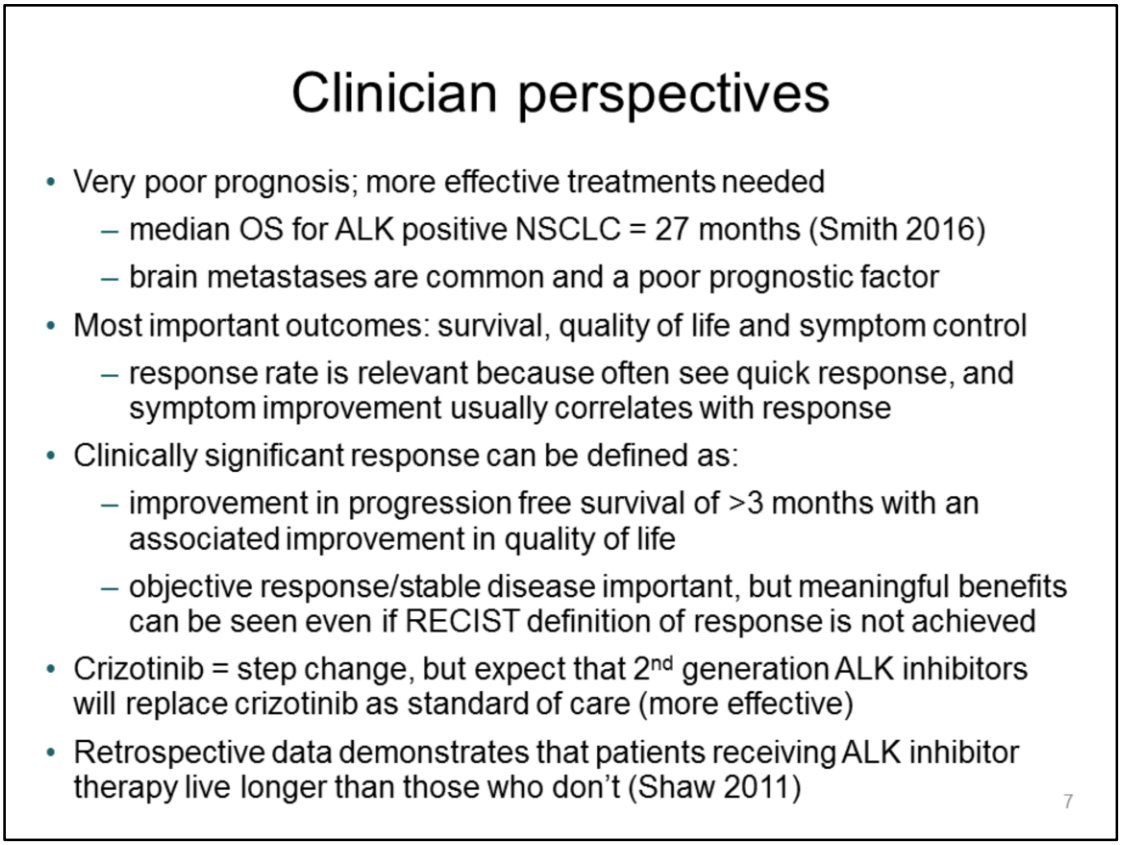

References from clinical expert statements

- Smith M, Yip K, Doherty G et al 2016 NCRI conference abstracts (recent UK audit data)
- Shaw A, Yeap BY, Solomon B, et al Lancet Oncology 2011; doi.org/10.1016/s1470-2045(11)70232-7

Decision problem

Population	People with untreated, anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer
Intervention	Ceritinib
Comparators	• Crizotinib • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) ○ with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only)
Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.

The company did not include:
- Pemetrexed as a comparator because it is only relevant for people who have not had (results of) ALK test therefore not eligible for ceritinib.
- Cost of testing for ALK mutations because it is already part of routine clinical practice at diagnosis

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The company's rationale for deviating from the scope (excluding a comparator and the cost of ALK testing) is supported by statements from clinical experts for this appraisal.

The trials of ceritinib and crizotinib used different tests for the ALK mutation:
- Ceritinib trial: Ventana anti-ALK (D5F3) immunohistochemistry (IHC) test
- Crizotinib trial: Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular)

Testing for the ALK mutation using immunohistochemistry, as in the ceritinib trial, is the more common method used in current UK practice. With respect to the difference between the trials - the company explained that at least 12 studies have compared the D5F3 ICH test with FISH testing and reported an excellent correlation between the results of the 2 tests. One of the clinical experts for this appraisals agreed that results from both tests are fairly concordant. The ERG did not see any reason to suspect that using different ALK testing methods would have any significant implications regarding the patient populations or the results reported from these studies.

	Intervention	Comparator
	Ceritinib	Crizotinib
Marketing authorisation	First-line treatment of adults with anaplastic lymphoma kinase-positive advanced NSCLC	
Mechanism of action	2nd generation ALK inhibitor	1st generation ALK inhibitor
Half maximal inhibitory concentration (IC50)	0.15 nM (lower IC50 = greater binding affinity)	3 nM
Administration & dosage	Oral, 750 mg once daily (without food)	Oral, 250 mg twice daily (with/without food)
Duration of treatment	"As long as clinical benefit is observed" (SmPC)	Not stated in SmPC
Cost	Both technologies have a confidential patient access scheme (PAS), agreed by the Department of Health, which provides a simple discount to the list price	
PIII trial	ASCEND-4	PROFILE-1014 ALEX *(published after company submission; not included in base case)*

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Treating for "as long as clinical benefit is observed": the clinical expert statements explain how clinical benefit is defined in practice and when the decision to stop treatment would be made. One expert gave examples of when it would be appropriate to continue treatment after disease progression as defined by the RECIST criteria, which might not be clinically meaningful.

Clinical effectiveness

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ASCEND-4 (ongoing trial)	
Study design	Multicentre, randomised, open-label study with 7 UK sites
Population	Adults with untreated stage IIIB/IV ALK positive NSCLC Majority non-squamous, 96.5% had non-adenocarcinoma Asymptomatic/neurologically stable brain metastases (≥2 wks)
Randomisation stratified by	• WHO performance status (0 versus 1–2) • prior adjuvant therapy (yes versus no) • brain metastases at screening (yes versus no)
Technologies	Intervention: ceritinib 750 mg/day (n=189), continued as long as clinical benefit observed (beyond RECIST-defined progression)
	Comparator: platinum-based chemotherapy (n=187): cisplatin or carboplatin (investigator choice) with pemetrexed, followed by pemetrexed maintenance for those with un-progressed disease
Cross over permitted after progression	Chemo arm: 105 (72% of pts who stopped) had an ALK inhibitor • 80 patients crossed over to ceritinib, 23 had crizotinib Ceritinib arm: 34 (18%) had subsequent anti-cancer therapy • 24 had platinum-based chemo, 6 had an ALK inhibitor
Primary endpoint	Progression-free survival (RECIST), central assessment
Median follow up	19.7 months (data cut off June 2016)
HRQoL	EQ-5D-5L, EORTC QLQ-C30, LCSS, QLQ-LC13 11

Abbreviations: EORTC-QLQX, European Organisation for Research and Treatment of Cancer's core QoL questionnaire; HRQoL, health-related quality of life; LCSS, lung cancer symptom scale; QLQ-LC13, lung cancer specific questionnaire

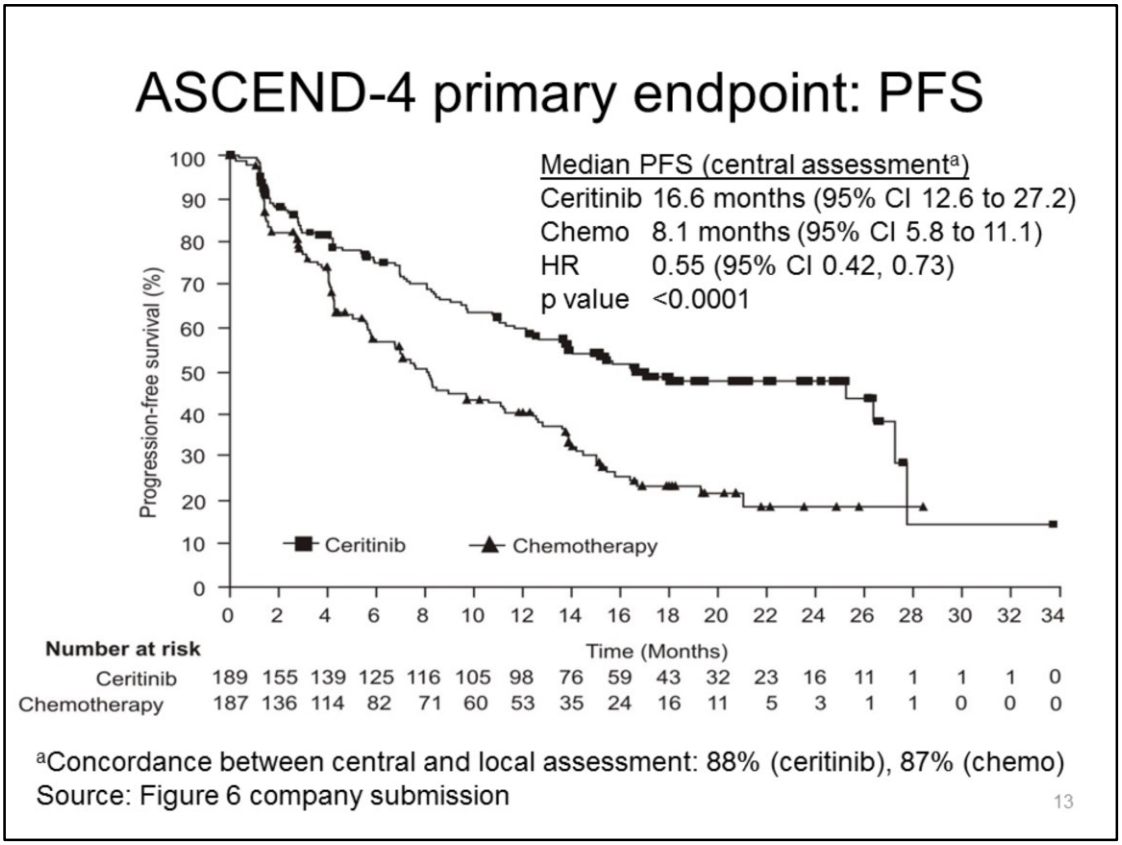
See table 5 of the company submission for a summary of the ASCEND-4 trial methodology.

The company mapped the EQ-5D-5L data to the EQ-5D-3L using NICE-recommended methods. The NICE position statement on the EQ-5D-5L valuation set is here: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf

ASCEND-4: baseline characteristics

	Ceritinib (n=189)	Chemotherapy (n=187)
Age, median years (range)	55 (22–81)	54 (22–80)
Female, n (%)	102 (54)	114 (61)
WHO performance status, n (%)		
0	69 (37)	70 (37)
1	107 (57)	105 (56)
2	13 (7)	11 (6)
Missing	0 (0)	1 (1)
Current smoker, n (%)	15 (8)	15 (8)
Histology or cytology, n (%)		
Adenocarcinoma	180 (95)	183 (98)
Stage at time of study entry, n (%)		
Locally advanced (stage IIIb)	9 (5)	5 (3)
Metastatic (stage IV)	180 (95)	182 (97)
Metastatic site of cancer, n (%)		
Bone	77 (41)	80 (43)
Brain	59 (31)	62 (33)
Liver	34 (18)	39 (21)

Source: table 6 company submission



The difference between arms in progression-free survival (PFS) was apparent from approximately 3 months onwards in the Kaplan–Meier plots.

Ceritinib did not have a statistically significant PFS benefit in people with brain metastases

Central assessment	Patients with brain metastases		Patients without brain metastases	
	Ceritinib (n=58)	Chemo (n=57)	Ceritinib (n=131)	Chemo (n=130)
Median PFS, months (95% CI)	10.7 (8.1 to 16.4)	7.0 (4.2 to 11.1)	26.3 (15.4 to 27.7)	8.2 (5.8 to 12.8)
HR (95% CI)	0.80 (0.50 to 1.28) p=NS		0.45 (0.32 to 0.64) p<0.05	
Source: table 12 company submission				

- Local assessment also showed no significant difference between treatment arms for people with brain metastases

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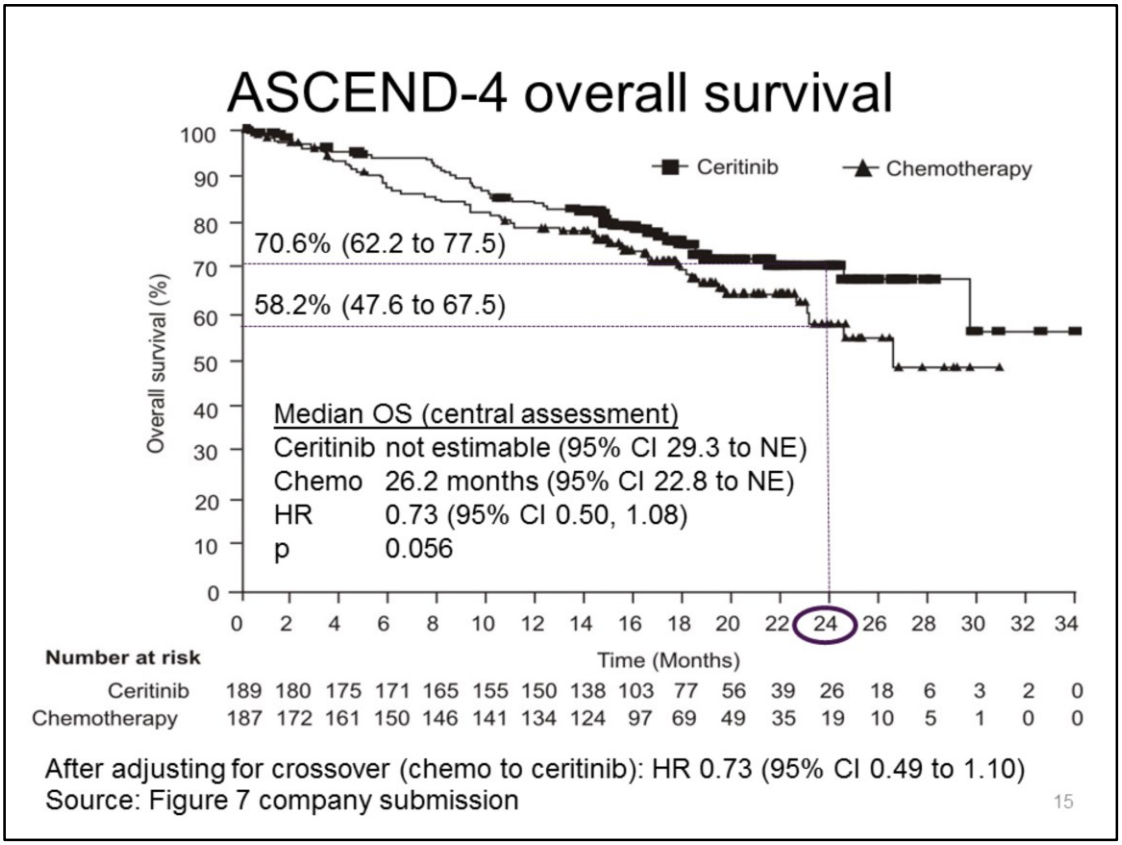
In ASCEND-4, 121 patients (61 patients in the ceritinib group and 60 patients in the chemotherapy group) had brain metastases (measurable or non-measurable) at baseline.

PFS results are presented on the slide above, and response rates below.

Of the 121 patients with brain metastases at baseline, intracranial response was assessed only 22 patients in each group. These results provide evidence for the intracranial activity of ceritinib, but are necessarily limited by the small size of the patient population in each treatment group.

- overall intracranial response rate: 72.7% in the ceritinib group (95% CI 49.8 to 89.3) and 27.3% in the chemotherapy group (95% CI 10.7 to 50.2)
- median duration of intracranial response: 16.6 months in the ceritinib group, and not estimable in the chemotherapy group



At the time of the analysis, the overall survival (OS) data were immature: only 107 events (42% of the required OS events) had occurred. At the data cut-off in June 2016 (19.7 months), 48 (25.4%) patients in the ceritinib group had died. Ceritinib reduced the risk of death by 27%. Two further OS analyses of ASCEND-4 are planned: one after observing 215 deaths, and a final analysis for OS after observing 253 deaths.

The company did a sensitivity analysis using rank-preserving structural failure time (RPSFT) to correct for the confounding introduced by patients crossing over from chemotherapy to ceritinib after disease progression. in the chemotherapy arm, 105 (72%) of 145 patients received an ALK inhibitor after stopping chemotherapy. This included 80 patients who crossed over to receive ceritinib and 23 who received crizotinib. In the ceritinib arm 34 (18%) of 189 patients received subsequent anti-cancer therapy: 24 received platinum-based doublet chemotherapy, and 6 received an ALK inhibitor (ceritinib, n=1; crizotinib, n=3; or lorlatinib, n=2).

The hazard ratio after adjusting for crossover was similar to that from the primary analysis, suggesting that cross-over did not affect the difference in OS between the treatment groups for this data-cut. The company noted that the duration of follow-up is currently insufficient to conclude whether there is a difference in OS according to the RPSFT analysis.

ASCEND-4 secondary endpoints (central assessment)

	Ceritinib (n=189)	Chemotherapy (n=187)
Overall response rate, % (95% CI)	72.5 (65.5 to 78.7)	26.7 (20.5 to 33.7)
Median time to response, weeks (range)	6.1 (5.1 to 61.7)	13.4 (5.1 to 90.1)
Median duration of response, months (95% CI)	23.9 (16.6 to not estimable)	11.1 (7.8 to 16.4)
EQ-5D utility (during treatment)	0.81	0.77

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Other health-related quality of life outcomes are detailed in section 2.6.6 (pages 46–51) of the company submission.

The company did not include response rates in its matched-adjusted indirect comparison of ceritinib with crizotinib because the definitions of response were different in each trial (see subsequent slides). The response rates with crizotinib in PROFILE-1014, as reported in the NICE appraisal (TA406) were as follows:

- Overall response rate: 74% (95% CI, 67% to 81%)
- Median time to response: 1.4 months (range 0.6 to 9.5 months)
- Median duration of response: 11.3 months (95% CI. 8.1 to 13.8 months)

A medical chart review of patients who received crizotinib in the first-line setting (Davis et al. 2015) reported an overall response rate of 69% with crizotinib.

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Match-adjusted indirect comparison 1 (PROFILE-1014): baseline characteristics

% of patients	Before Matching			After Matching to PROFILE-1014		
	ASCEND-4 (n=376)	PROFILE 1014 (n=343)	p-value	ASCEND-4 (n=376) (ESS=340)	PROFILE 1014 (n=343)	p-value
Age <65 years	78.5	84.0	[redacted]	[redacted]	[redacted]	[redacted]
Female	57.4	61.8	[redacted]	[redacted]	[redacted]	[redacted]
Race – White	53.7	51.3	[redacted]	[redacted]	[redacted]	[redacted]
Race – Asian	42.0	45.8	[redacted]	[redacted]	[redacted]	[redacted]
Current smoker	8.0	4.4	[redacted]	[redacted]	[redacted]	[redacted]
Former smoker	30.9	32.1	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma	96.5	93.9	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance score 0 or 1	93.6	94.8	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic disease	96.3	98.0	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases	32.2	26.8	[redacted]	[redacted]	[redacted]	[redacted]

*p-values <0.05 were considered significant
ESS, effective sample size
Source: table 19 company submission

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In the absence of head-to-head trial data for ceritinib and crizotinib, the company conducted a matching-adjusted indirect comparison (MAIC) using ASCEND-4 (ceritinib) and PROFILE-1014 (crizotinib). The MAIC approach indirectly compares 2 treatments while adjusting for cross-trial differences in patient characteristics. The company applied weights to patients enrolled in ASCEND-4 to match all of the reported baseline characteristics with those of the PROFILE 1014 trial population, as the latter was considered to reflect the characteristics of the UK patient population. Although both trials included chemotherapy as a comparator, the company considered that the chemotherapy regimens used in each trial were not comparable (for example, PROFILE-1014 did not include pemetrexed maintenance therapy, which is known to improve survival), and therefore the MAIC was unanchored (that is, the treatment network was disconnected because there was no common comparator across the trials).

Prior to matching, the only statistically significant difference between trial populations was number of current smokers. After applying weights, all baseline characteristics were exactly balanced. The effective sample size in ASCEND-4 was reduced by 10% after weighting to 340 (compared to the actual sample size of 376). The company concluded that the extent of weighting required in the MAIC was mild and there was no evidence of extreme weights. The company noted that this is consistent with good overlap between the populations.

The MAIC did not adjust for potential differences in adverse event rates between subgroups, or the differences in inclusion criteria with respect to presence of brain metastases at baseline (in PROFILE-1014 only patients with brain metastases were only eligible if they had received radiotherapy, whereas in ASCEND-4 all patients with brain metastases were included provided that metastases were asymptomatic or neurologically stable, and any previous radiotherapy to the brain had been completed at least 2 weeks before study treatment initiation). The company gave the following rationale for not adjusting for these differences:

- Adverse events (AEs): subgroup analyses showed that AE rates were similar across subgroups. In addition, the ICER was not sensitive to the cost of AEs (see clarification question B7 and the results of sensitivity analyses on the model in table 51 of the company submission).
- Presence of brain metastases at baseline: the MAIC adjusted for the baseline presence of brain metastases in the PROFILE 1014 population, but the difference in the inclusion criteria for patients with brain metastases between the 2 trials was not adjusted for. All patients with brain metastases in PROFILE-1014 had received brain radiotherapy prior to study entry, compared with only 39% of patients with brain metastases in the ceritinib arm of ASCEND-4. The company suggested that this difference in inclusion criteria is likely to favour crizotinib, and that not adjusting for the difference was conservative; if prior radiation treatment is associated with long-term benefit, this would have contributed to the response observed in PROFILE-1014 and created a bias against ceritinib in the MAIC of PFS and OS outcomes (see clarification question A8).

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MAIC1 (PROFILE-1014): results used in company's base case model

	Before matching		After matching	
	Ceritinib (ASCEND-4) n=189	Crizotinib (PROFILE-1014) n=172	Ceritinib (ASCEND-4) n=189 (ESS=171)	Crizotinib (PROFILE-1014) n=172
Progression-free survival (PFS)				
Median, months (95% CI)	16.6 (12.6 to 27.2)	10.8 (8.5 to 13.8)	[redacted]	10.8 (8.5 to 13.8)
HR (95% CI)	[redacted] p=[redacted]		[redacted] p=[redacted]	
1-year PFS rate	59.9%	47.8%	[redacted]	47.8%
p value	[redacted]		[redacted]	
Overall survival (OS) *(median OS not reached)*				
HR (95% CI)	[redacted] p=[redacted]		[redacted] p=[redacted]	
1-year OS rate	83.6%	83.3%	[redacted]	83.3%
p value	[redacted]		[redacted]	

CI, confidence interval; ESS, effective sample size; HR, hazard ratio; NR, not reached
Source: table 20 company submission

The outcomes included in the MAIC were progression-free survival (PFS) and overall survival (OS). The company did not formally compare:

- response rates because the definitions of response were different in each trial
- PFS in subgroups with/without brain metastases because of the difference in inclusion criteria with respect to brain metastases.

Without matching, the indirect comparison between the ASCEND-4 and PROFILE-1014 trials showed that ceritinib was associated with a significantly longer PFS than crizotinib. After matching to PROFILE-1014, the MAIC generated a slightly improved hazard ratio and a much higher median PFS with ceritinib. Before matching, the 95% confidence intervals (CIs) for median PFS of crizotinib and ceritinib had a slight overlap, whereas after adjustment the 95% CIs were no longer overlapping, which the company noted is consistent with a statistically significant difference in median PFS between ceritinib and crizotinib.

Before and after matching, ceritinib was associated with numerically longer OS compared to crizotinib (this was not statistically significant). The matched hazard ratio for OS was lower than the unmatched estimate.

MAIC2 (ALEX): baseline characteristics

% of patients	Before Matching			After Matching to ALEX		
	ASCEND-4 (ceritinib arm n=189)	ALEX (crizotinib arm n=151)	p-value	ASCEND-4 (ceritinib arm n=189) (ESS=174)	ALEX (crizotinib arm n=151)	p-value
Age <54 years	46.6	50.0	0.528	50.0	50.0	1.00
Female	54.0	57.6	0.501	57.6	57.6	1.00
Race – Asian	40.2	45.7	0.310	45.7	45.7	1.00
Current smoker	7.9	3.3	0.072	3.3	3.3	1.00
Former smoker	34.9	31.8	0.543	31.8	31.8	1.00
Adenocarcinoma	95.2	94.0	0.624	94.0	94.0	1.00
ECOG performance score 0 or 1	93.1	93.4	0.926	93.4	93.4	1.00
Metastatic disease	95.2	96.0	0.725	96.0	96.0	1.00
Brain metastases	31.2	38.4	0.165	38.4	38.4	1.00

*p-values <0.05 were considered significant
ESS, effective sample size
Source: table B2.1 company response to clarification

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The ALEX trial comparing crizotinib with alectinib had not been published at the time of the company submission and therefore was not included in its base case MAIC or base case cost-effectiveness analysis. The company provided the results of a second MAIC (MAIC2) in response to clarification question B2, in which the data for crizotinib came from the ALEX trial instead of PROFILE-1014. Because there was no common comparator between all 3 studies (ASCEND-4, PROFILE-1014 and ALEX), they could not all be combined in one indirect analysis.

The main differences between ALEX and the 2 other trials were:

- The primary outcome in ALEX was investigator-determined, rather than centrally determined, PFS. However, independent review committee PFS was a secondary outcome.
- Treatment with crizotinib continued until disease progression, and it was not clear if some patients continued to receive treatment post-progression. This difference is only relevant to the comparison of overall survival.

Prior to matching, there were no statistically significant differences between the trial populations; the ceritinib patients had a numerically higher proportion of current smokers compared to the crizotinib patients (7.9% vs. 3.3%). After applying weights, all baseline

characteristics were exactly balanced. The effective sample size in the ceritinib arm of ASCEND-4 was reduced by 8% after weighting to 174 (compared to the actual sample size of 189).

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MAIC2 (ALEX): results used in scenario analyses

	Before matching		After matching	
	Ceritinib (ASCEND-4) n=189	Crizotinib (ALEX) n=151	Ceritinib (ASCEND-4) n=189 (ESS=174)	Crizotinib (ALEX) n=151
Progression-free survival (PFS)				
Median, months (95% CI)	16.6 (12.7 to 27.2)	10.4 (7.6 to 14.5)	[redacted]	[redacted]
HR (95% CI)	[redacted] p=[redacted]		[redacted] p=[redacted]	
Overall survival (OS) *(median OS not reached)*				
HR (95% CI)	[redacted] p=[redacted]		[redacted] p=[redacted]	
1-year OS rate	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; ESS, effective sample size; hazard ratio (HR); NR, not reached
Source: response to clarification question B2a

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Without matching, the indirect comparison between the ASCEND-4 and ALEX trials showed that ceritinib was associated with a significantly longer PFS than crizotinib, with the same hazard ratio as in the unmatched comparison with the PROFILE-1014 trial. After matching to ALEX, the median PFS with ceritinib remained similar but the 95% confidence interval widened, and the compared with crizotinib increased slightly. The unmatched and matched hazard ratios for OS were similar to the estimates from the first MAIC. The matched hazard ratio for OS was lower than the unmatched estimate.

Treatment-related AEs in ASCEND-4

Ceritinib trial arm	All grades	Grade 3 or 4
Total treatment-related AEs	97.4%	65.1%
Total treatment-related serious AEs	15.9%	12.2%
Diarrhoea	80.4%	4.2%
Nausea	64.0%	2.6%
Alanine aminotransferase (ALT) increased	59.3%	29.6%
Vomiting	57.1%	4.8%
Aspartate aminotransferase (AST) increased	50.8%	15.9%
Gamma-glutamyltransferase (GGT) increased	34.9%	26.5%
Decreased appetite	25.4%	0.5%
Alkaline phosphatase increased	24.9%	6.3%
Fatigue	22.2%	2.6%
Abdominal pain	20.6%	2.1%
Creatinine increased	19.6%	1.6%
Upper abdominal pain	17.5%	1.1%
Weight decreased	15.3%	2.1%
Asthenia	11.1%	2.6%
Rash	11.1%	0.5%
Electrocardiogram QT prolonged	10.1%	1.6%
Withdrawal due to treatment-related AEs	5%	
Dose reductions	68%	

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The most common adverse events (AEs) were gastrointestinal: diarrhoea, nausea and vomiting, followed by elevation in the serum levels of liver enzymes and alkaline phosphatase. Nausea, vomiting and elevated AST were the only serious Aes considered related to treatment, and they were reported in ≥2% of patients. Dose reductions and treatment interruptions occurred throughout the treatment period, but their frequency was highest during weeks 3 to 6, and these were primarily due to GI toxicity and liver function abnormalities, respectively.

The company compared the safety results from ASCEND-4 with the results from PROFILE-1014 and concluded that ceritinib offers clinically meaningful improvements over crizotinib:

- treatment-related grade 3/4 serious AEs were reported in 12.2% of patients receiving ceritinib compared with 35.1% receiving crizotinib, which the company suggest is clinically meaningful, especially in the context of the longer duration of treatment (~16 months for ceritinib and 10.3 months for crizotinib)
- grade 3/4 neutropenia was observed in only 1% of patients receiving ceritinib compared with 11% receiving crizotinib
- any-grade vision disorders (70%), constipation (43%) and oedema (49%) were reported in ≥40% of patients receiving crizotinib but only 19% (constipation) or <15% (vision disorders and oedema) of patients receiving ceritinib.

- rates of discontinuation due to treatment-related AEs were 5% for both ceritinib and crizotinib
- grade 1/2 GI toxicities were the most frequently reported AEs in both ASCEND-4 and PROFILE-1014

See sections 2.10 and 2.13.2 of the company submission.

ERG critique of ASCEND-4

- Good quality trial, population generalisable to UK clinical practice
- 2nd line treatments do not reflect practice; face validity of OS results uncertain
- OS results confounded because patients
  - remained on treatment beyond disease progression
  - could switch from chemotherapy to ceritinib
  - company's adjustment for crossover does not adjust for the post-ceritinib treatments received in those randomised to ceritinib, nor does it account for patients who remained on ceritinib beyond disease progression
- No evidence for a specific intracranial benefit with ceritinib
  - ASCEND-4 did not assess intracranial outcomes in people without metastases at baseline, so the impact of ceritinib in preventing the development of new brain metastases is unknown
  - ASCEND-4 subgroup results for median PFS with ceritinib show a bigger difference between patients with and without brain metastases at baseline (10.7 months versus 26.3 months) than subgroup analysis of crizotinib in PROFILE-1014 (9 months versus 11.1 months)
- No clear difference between rate of AEs in ceritinib and crizotinib trials

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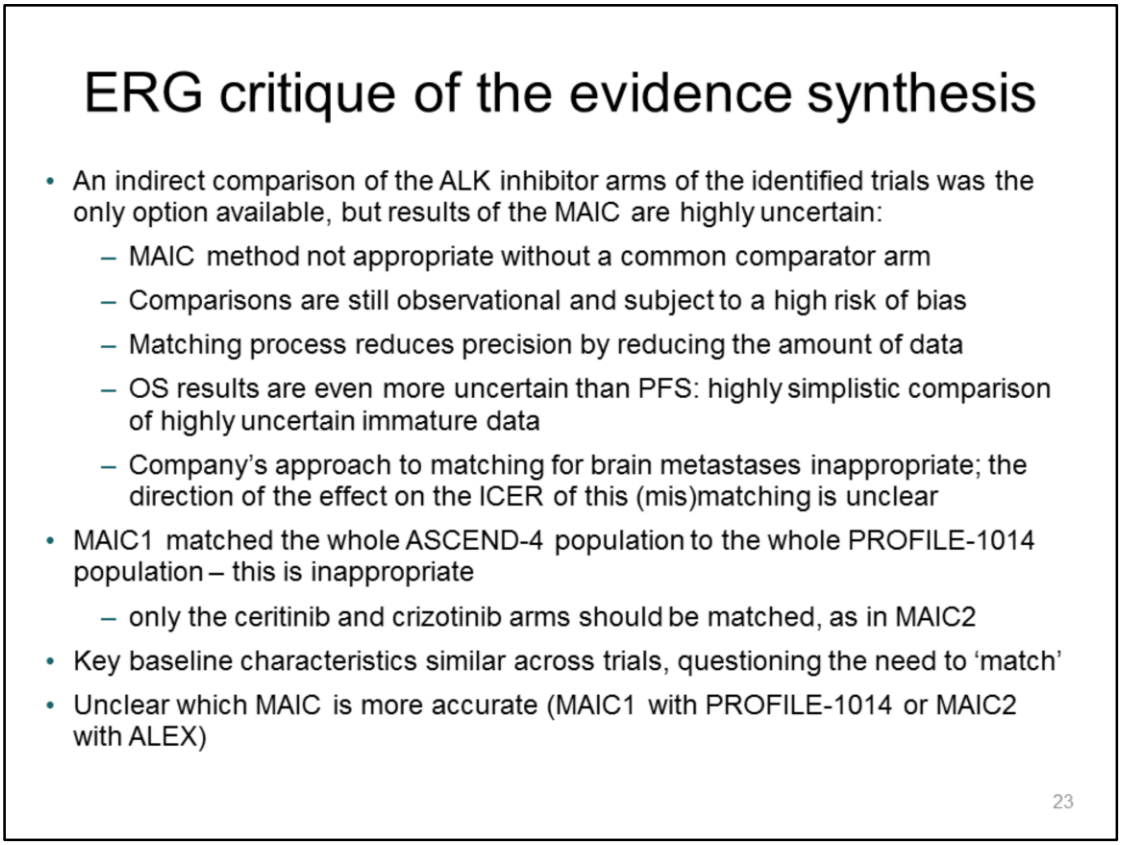
The ERG noted that compared to a real world cohort from the UK and Europe, the patients in all the relevant trials are slightly younger, have a higher proportion of females and a lower proportion of former of current smokers and a higher proportion of trial patients are ECOG status 0 or 1. The ERG's clinical adviser commented that, except that a higher proportion of men might be expected in clinical practice, the ASCEND-4 trial population can be considered generalisable to NHS practice.



The ERG acknowledged that an indirect comparison of individual trial arms was the only option available to compare ceritinib and crizotinib, but cannot be certain whether the results derived from the MAIC are any more reliable than that from a naïve comparison of the unadjusted data. The ERG explained that the MAIC method was developed as an improvement on standard indirect comparison methods, which use aggregate data only; it was not developed as a method to be used without a common comparator arm. An unanchored comparison assumes that all effect modifiers and prognostic factors are accounted for and this assumption is largely considered impossible to meet (see Decision Support Unit Technical Support Document 18). The ERG explained that without a common comparator there is nothing to use as a measure of the success of the matching to reduce confounding, and therefore the results are still observational and subject to a high risk of bias. Despite matching, the analysis can be subject to the effects of residual confounding due to unobserved differences between trials. In addition, the matching process reduces the precision of results by reducing the amount of data (the 'effective sample size').

The ERG noted that HR generated by MAIC is an important parameter in the model because it directly informs the quality-adjusted life year gains on treatment, and was therefore concerned about the reliability of the company's base case model results.

Cost effectiveness

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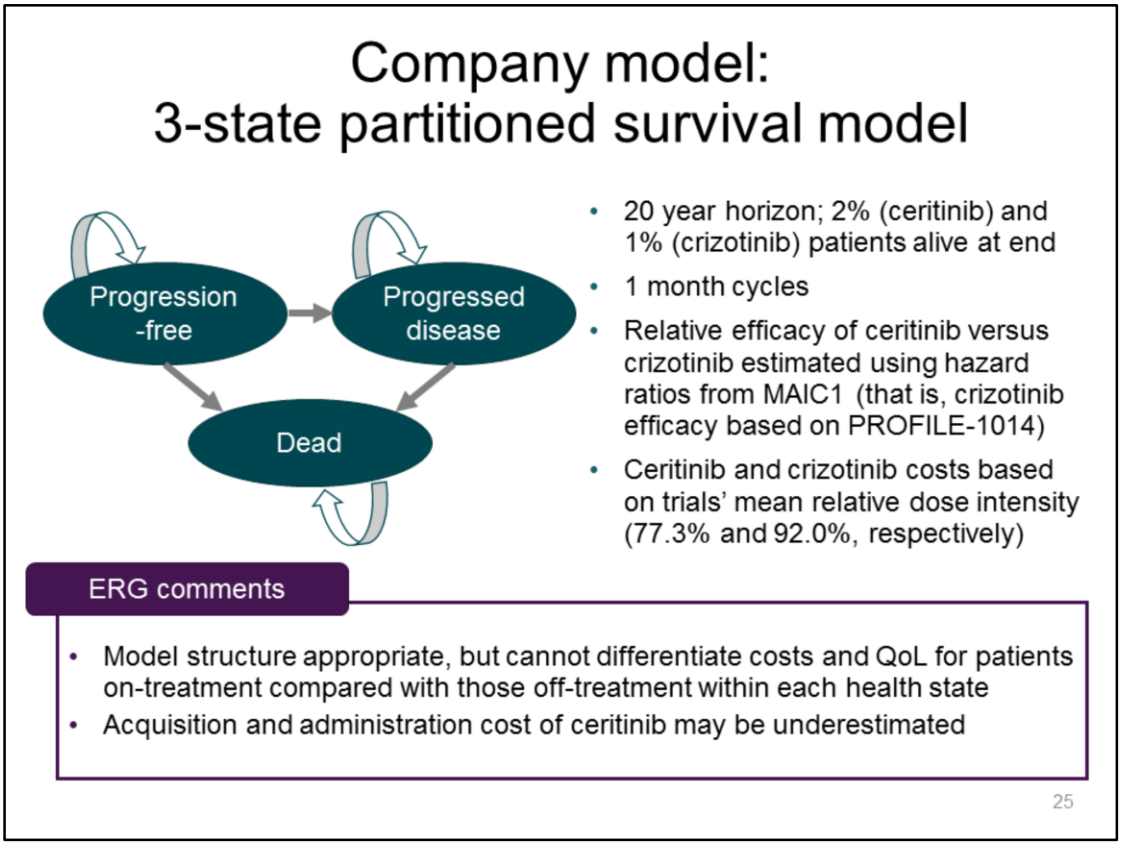
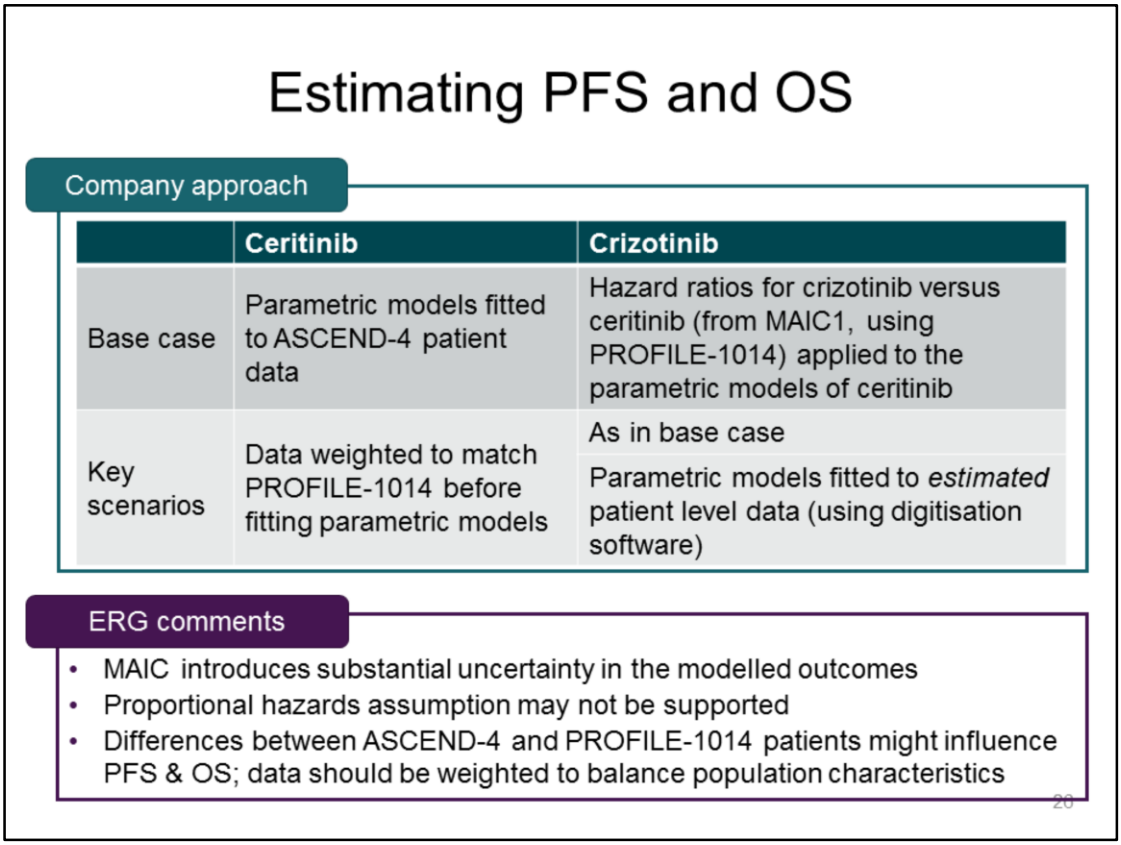


In a partitioned survival model (also known as 'area under the curve' analysis) the proportion of patients in the progression-free state is based on estimates of PFS, while the proportion of patients in the death state is 1 minus the estimate of OS. The proportion of patients in the pre-progression state is calculated as the difference between OS and PFS. The PFS and OS curves for ceritinib were derived from the ASCEND-4 trial by fitting parametric functions to patient-level time-to-event data (Kaplan-Meier curves). The relative efficacy of ceritinib compared with crizotinib was estimated using indirect comparison; hazard ratios from the company MAIC were applied to the PFS and OS curves for ceritinib. The ERG considered the model structure was largely appropriate. However, it noted that it was difficult for the model to distinguish between costs and quality of life in patients who are on- and off-treatment in the progression-free and post-progression health states. The ERG explained that the current model would require re-structuring to properly implement these analyses, by including health states for patients being on- and off-treatment. But the ERG performed exploratory scenario analyses to distinguish quality of life between patients on- and off-treatment within health states (see subsequent slides on utility values).

The ERG was concerned that ceritinib costs were underestimated:

- Acquisition costs: the ERG noted that the dose intensity in ASCEND-4 is low and may be unrealistic in real-world setting eg due to drug wastage.

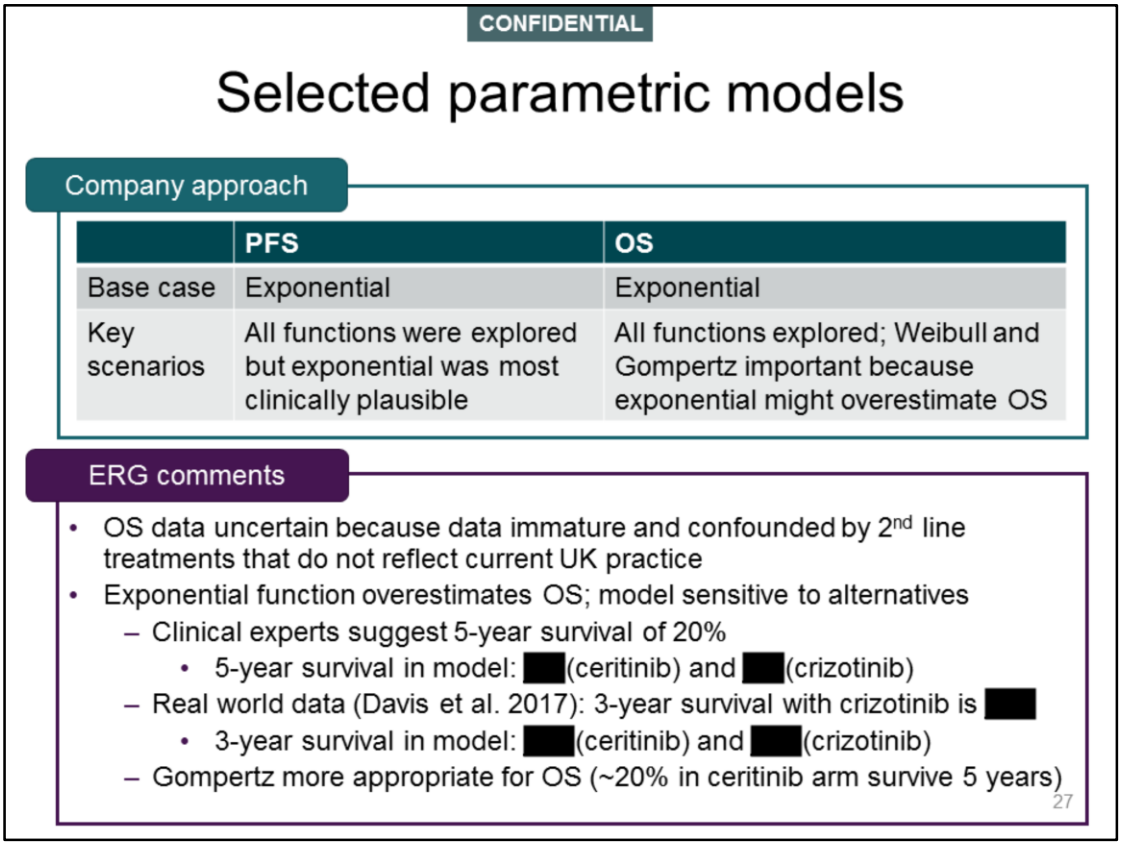
- Administration costs: the company assumed that treatment was administered by a pharmacist alone, which the ERG considered implausible.



ERG comment on proportional hazards:
The ERG was not fully satisfied with the company's rationale for assuming proportional hazards (that is, the hazard for disease progression, death or treatment discontinuation with crizotinib remains constant over the model duration). The ERG explored the impact of relaxing the proportional hazards assumption in scenario analyses, by fitting parametric models to the patient level data for ceritinib and crizotinib independently. Patient level data from the PROFILE-1014 trial of crizotinib was not available, so the ERG used the Kaplan-Meier curves estimated by the company using digitisation software (in response to clarification question B1b).

ERG comments on population used to model survival:
The ERG noted that differences between populations in ASCEND-4 and PROFILE-1014 might influence PFS and OS. It was therefore concerned that the efficacy data in the base case model was based on the ASCEND-4 population (that is, the relative efficacy of crizotinib used the ASCEND-4 patient level data as a starting point). The ERG requested a scenario analysis from the company in which the ASCEND-4 data was weighted to the PROFILE-1014 trial to balance population characteristics, before extrapolating using a parametric function (clarification question B1a). Weighting the data caused a slight upward shift in the parametric functions of PFS and OS compared to the base case but the

company used the same parametric function to extrapolate the data (see next slide for details) because the shape of the different parametric functions, and their relative ranking in terms of fit with the observed data, was similar to the base-case.



Progression-free survival (PFS)
The company explained that although the Gompertz function had the best fit with the observed trial data for PFS, it gave implausible long-term results: 23.1% of patients treated with ceritinib were progression-free after 5 years using the Gompertz function. By contrast, the exponential function predicted that 8.8% of patients treated with first-line ceritinib would remain progression-free at five years. The ERG was satisfied with the choice of curve for PFS.

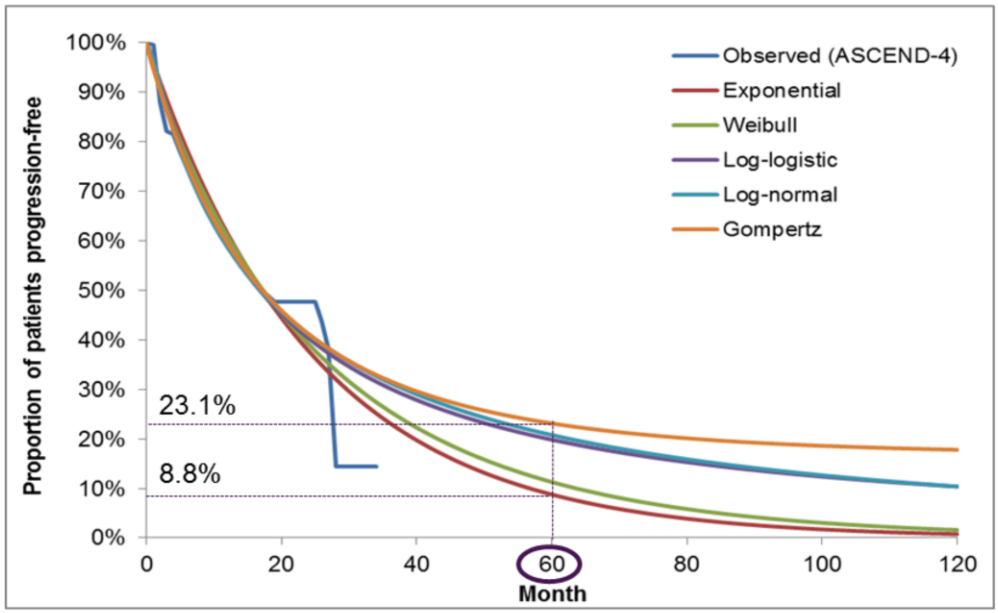
Overall survival (OS)
The company noted that clinical experts supported using the exponential function to model overall survival, but that they considered that it overestimated long-term survival compared with clinical practice. The company defended its choice of the exponential function to extrapolate PFS and OS because the estimates of post-progression survival in the model were nearly equivalent to the first-line ceritinib and crizotinib treatment arms in ASCEND-4 and PROFILE 1014, respectively. However, the ERG considered that the estimates of long term survival produced with the exponential curve were inconsistent with clinical experience of ALK inhibitors and real world data on the survival of patients who had received crizotinib.

In the company's response to the factual accuracy check, it noted that recently published

OS data from PROFILE-1014 support using the exponential function to extrapolate OS; PROFILE-1014 predicted that 56.6% of patients will be alive at 4 years. Median OS for crizotinib in PROFILE-1014 has not be reached at a median follow-up of 46 months, median OS for chemotherapy was 47.5 months.

The ERG used the Gompertz curve to model overall survival in its alternative base case. As mentioned on the previous page, the ERG explored the impact of relaxing the proportional hazards assumption in additional scenario analyses.

Observed and predicted PFS for ceritinib using different parametric functions



Source: figure 17 company submission

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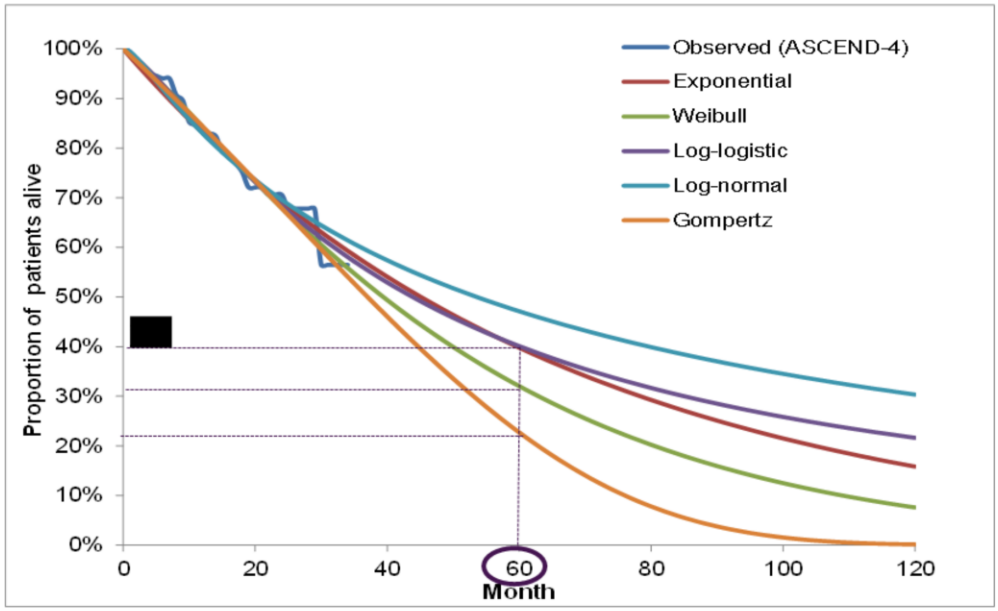
Observed and predicted OS for ceritinib using different parametric functions



Source: figure 18 company submission

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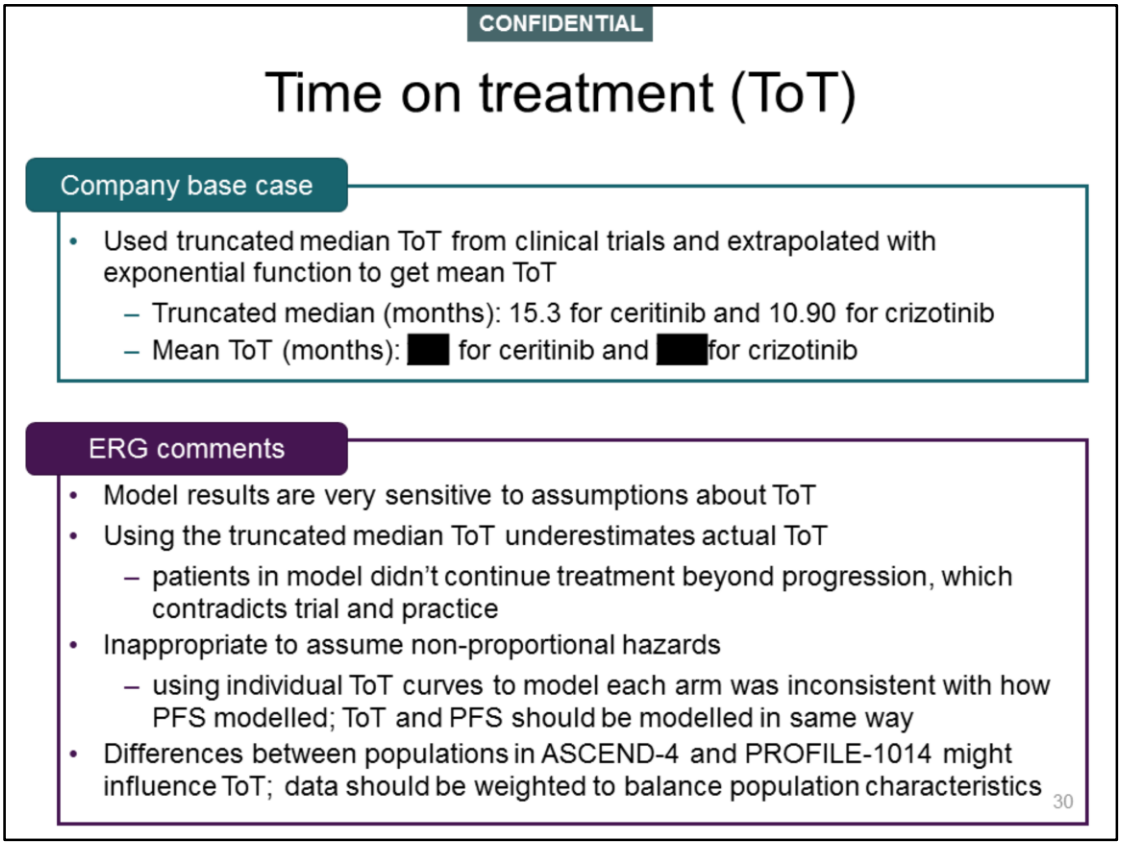


The ERG noted that the duration of therapy has a significant impact on total drug acquisition costs, which are the key driver of the incremental costs in the model. Sensitivity and scenario analyses showed that the model results are very sensitive to assumptions about time on treatment. The ERG's concerns with the company's base case assumptions are expanded below.

Using the truncated median time on treatment underestimates treatment duration

- The mean duration of treatment with ceritinib in the company's base case model (estimate academic-in-confidence, see slide) is lower that the mean time on treatment calculated using the individual patient data from the ASCEND-4 trial, indicating that the company's method for estimating time on treatment is not appropriate. The company and ERG did not have access to patient-level data for crizotinib so could not comment on its true treatment duration, but the ERG suggest that it is reasonable to expect that the company's estimate for duration of crizotinib therapy is also inaccurate.
- The ERG also noted that the time on treatment curves in the company base case model are below the progression-free survival curves, implying that patients do not remain on treatment after disease progression. This contradicts the protocol for ASCEND-4, and ceritinib's marketing authorisation, which state that treatment can continue beyond RECIST-defined progression, for as long as clinical benefit is

observed.

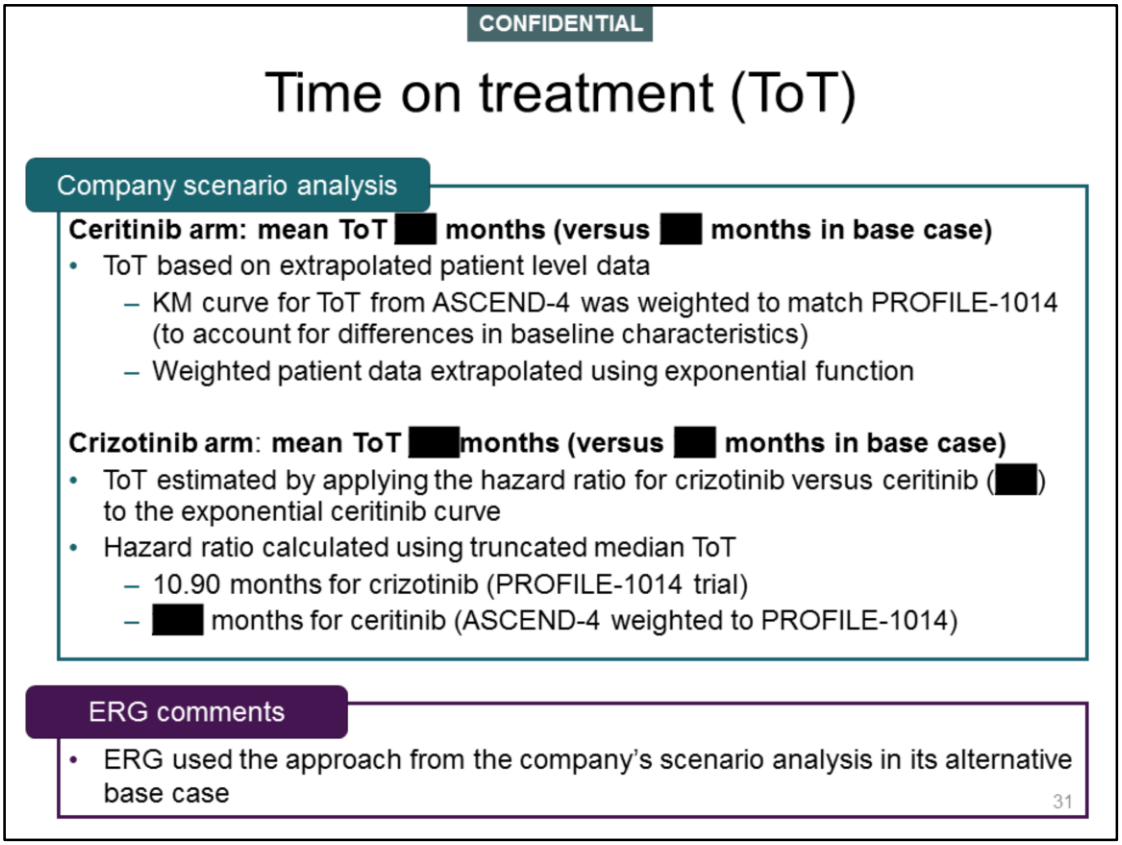
- In ASCEND-4: of the ceritinib patients who had RECIST-confirmed disease progression, 84% received at least 1 dose of ceritinib after disease progression and 49% continued ceritinib for at least 2 cycles after progression. This resulted in a median additional exposure of 9.6 weeks.
- In the NICE technology appraisal of crizotinib (TA406), 73% of patients received treatment beyond progression for a median of 3.1 months.

Using individual curves to model each arm (non-proportional hazards) was inconsistent with modelling PFS

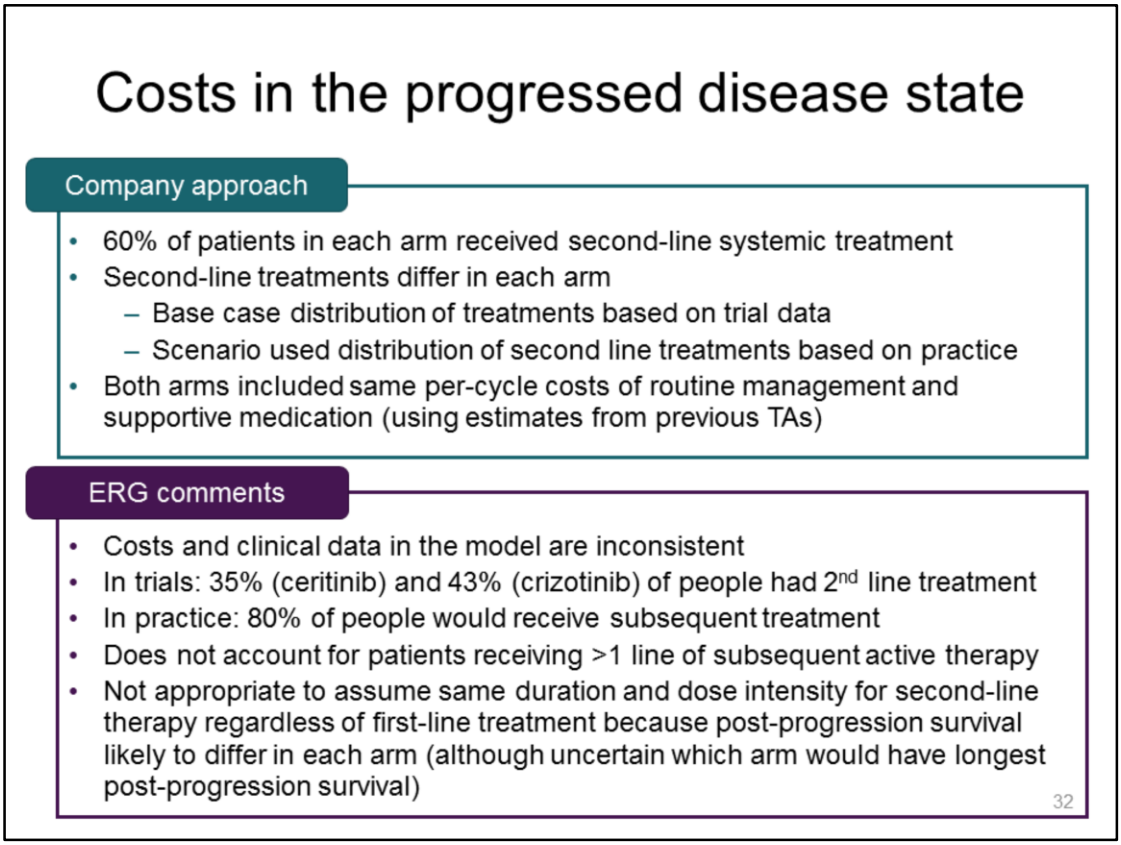
- The ERG assert that time on treatment and progression-free survival (PFS) should be modelled in same way, because the 2 outcomes are likely to be correlated. That is, if proportional hazards are assumed for PFS then they should also be assumed for treatment duration. The ERG requested this as a scenario analysis from the company at clarification (see next slide). The ERG considered that using patient level data from ASCEND-4 should produce more accurate estimates.

Differences between trial populations might influence ToT

- The ERG suggested that the patient level data from ASCEND-4 should be adjusted to the crizotinib population in PROFILE-1014 before extrapolating (see next slide).



The company performed the scenario described above in response to a clarification request from the ERG (question B6). The ERG used the approach from the company's scenario analysis in its alternative base case (described in the ERG report as 'proportional hazards of treatment duration' and 'clinical data matched to the PROFILE-1014 population').



The company's base case assumed that 60% of patients received second line systemic treatment, based on feedback from clinical experts. The company's justification for assuming more people received second line active treatment than reported in the clinical trials of ceritinib (where 35% of patients had second line treatment) and crizotinib (where 43% of patients had second line treatment) was that the trials have limited post-progression follow up time. The company expect that more patients would have started second line treatment after the data cut off for the trials.

The distributions of second line treatment differed according to the first line treatment, and in the base case were informed by distributions in the clinical trials of ceritinib and crizotinib. A scenario analysis used distributions based on clinical advice, because the distributions of treatments used in the clinical trials did not reflect current prescribing.

The ERG was concerned that, in both the company base case and the scenario analysis, second line treatments were inconsistent with the clinical data used in the model:

- In the base case, more people received subsequent treatment than in the trials, but efficacy was based on trial data.
- In the scenario analysis which reflected real world prescribing of subsequent treatments, the company did not account for how the different distribution of subsequent therapies

might affect post-progression survival.

Furthermore, the ERG was concerned that the inconsistency between the second-line treatments used in the trials (and therefore in the model) and in UK clinical practice suggests that the clinical data used in the model is unlikely to fully reflect the relative benefits of ceritinib and crizotinib in practice. The ERG considered this to be a major source of uncertainty that will impact the ICER substantially.

Distribution of second-line treatment according to first-line treatment arm

	Base case (based on trial)		Scenario (based on real world)	
Second-line treatment	1st line ceritinib (%)	1st line crizotinib (%)	1st line ceritinib (%)	1st line crizotinib (%)
Ceritinib	1.9	10.8	0.0	60.0
Crizotinib	9.4	1.5	0.0	0.0
Docetaxel	3.8	4.6	0.0	0.0
Pemetrexed	0.0	0.0	0.0	0.0
Platinum doublet	45.0	43.1	60.0	0.0
pemetrexed +	45.0	43.1	60.0	0.0
cisplatin, or	22.5	20.0	30.0	0.0
carboplatin	22.5	23.1	30.0	0.0
No active treatment	40.0	40.0	40.0	40.0
Cost of PD treatment, £	8,135.41	8,645.67	3,957.08	28,083.54

ERG comments

- Distribution in base case does not reflect clinical practice (eg wouldn't have crizotinib after ceritinib)
- Scenario analysis more realistic, but inconsistent with clinical data in model

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In the company's base case, nearly half of patients received second-line platinum doublet therapy (45% in the first-line ceritinib arm and 43.1% of patients in the first-line crizotinib arm), approximately 10% of patients in each arm received ceritinib or crizotinib (whichever drug they have not received first line), and the remaining patients received docetaxel.

In the company's scenario analysis it assumed that **all** patients who received subsequent treatment would receive:

- platinum doublet therapy after first line ceritinib
- or ceritinib after first line crizotinib.

As in the base case, the remaining 40% of patients in both arms received no further systemic treatment.

Utilities

Company approach

Health state	Utility value	Source
Ceritinib		
Progression-free[a]	0.810	ASCEND-4
Progressed disease	0.641	Chouaid et al. 2013
Crizotinib		
Progression-free[a]	0.810	PROFILE-1014
Progressed disease	0.641	Chouaid et al. 2013

[a] because these are treatment-specific, company did not separately apply AE-related disutilities or make adjustments for different treatment response rates

ERG comments

- Model structure can't distinguish between patients on- and off-treatment
- Progression-free utilities appropriate, concerns about progressed disease:
  - Inappropriate to apply same utility for progressed disease in both arms
  - Chouaid most appropriate source, but issues with generalisability
  - QoL for people on 1st line therapy beyond progression is underestimated
  - Company method for calculating weighted average not appropriate

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Neither ASCEND-4 nor PROFILE-1014 provided data that could be used to derive utility values for the progressed disease health state. The company identified Chouaid et al. (2013) in a systematic literature review. Chouaid et al. (2013) reports the results from a multi-national cross-sectional study among patients receiving any treatment for advanced NSCLC in real-world settings. The study collected EQ-5D from 263 patients receiving any treatment for advanced NSCLC and reported utility scores according to progression status and line of therapy. The company derived the progressed disease utility value of 0.641 using a weighted average of the utilities reported by Chouaid et al. (2013) among patients in the following disease states:

- first-line progressed disease (that is, patients who continue first-line treatment beyond progression) (0.67; n=26)
- second-line progression-free (0.74; n=44) or progressed disease (0.59; n=17)
- and third-/fourth-line progression-free (0.62; n=24) or progressed disease (0.46; n=21).

The company used the sample size for each state as the weight for the post-progression utility estimate.

The ERG was satisfied with the company's calculation and application of progression-free utilities in both arms, but had the following concerns about the utility for progressed

disease:

- It might be inappropriate to apply the same utility for progressed disease in each arm given that patients would receive a different mix of therapy in each arm (regardless of whether trial-based second line treatments or the real world prescribing is used).
- The study by Chouaid et al. (2013) was not generalisable to this decision problem and might have underestimated the utility value for progressed disease (that is, predicted a worse quality of life than would be expected):
    - Chouaid et al. (2013) was not specific to people with ALK positive NSCLC (who are thought to be younger, fitter and with a better quality of life than ALK-negative NSCLC patients)
    - Chouaid et al. (2013) was conducted before ALK inhibitors were in routine use; targeted ALK therapy is associated with a better quality of life than other second line chemotherapy options.
- Chouaid et al. (2013) reported a utility value specific to people who continued first-line treatment beyond disease progression (0.67), which was included in the company's weighted average utility for progressed disease. The ERG considered that Chouaid's estimate of 0.67 was too low, because it was based on patients receiving chemotherapy instead of an ALK inhibitor, as well as the issues with the generalisability of the study population. The ERG concluded that the utility for progressed disease would not represent patients who remained on first-line therapy after progression (that is, it would underestimate the utility for these patients, possibly to a different extent in each treatment arm).
- The ERG did not agree with the company's approach to calculating the weighted average value for progressed disease - the company include the Chouaid et al. (2013) estimate for people on second-line treatment who are progression-free (0.74), however this value correspond to patients within the progression-free health state and should not be used to inform the utility for progressed disease.

Adverse events

Company approach

- Treatment-related grade 3/4 AEs included if they affected ≥5% of patients receiving ceritinib or crizotinib in ASCEND-4 and PROFILE 1014, respectively

Adverse events, %	Ceritinib	Crizotinib
Neutropenia	0.5	11.1
Diarrhoea	5.3	2.3
Pulmonary embolism	0.0	6.4
Vomiting	5.3	1.8
Hyperglycaemia	6.3	0.0
ALT elevation	30.7	14.0
AST elevation	16.9	0.0
GGT increased	28.6	0.0
Alkaline phosphatase increased	7.4	0.0

ERG comments

- Safety was not a key model driver and the ERG did not explore uncertainty

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Summary of ERG critique

Main areas of uncertainty relate to the clinical evidence available to populate the model:

- relative treatment effect is based on the highly uncertain MAIC analysis
- hazard ratios from MAIC were applied to unadjusted survival curves from ASCEND-4 (instead of weighting data to PROFILE-1014)
- OS data are immature
- extrapolation of OS is optimistic

Also uncertainty regarding the:

- assumption of proportional hazards for PFS and OS
- methods used to estimate of duration of first-line treatment
- distribution of second-line therapies (in both treatment arms)
- duration of post-progression treatment (in both treatment arms)
- utility values in the post-progression health state
- acquisition and administration costs of ceritinib and crizotinib

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ERG alternative base case

	ERG base case	Company base case
Time on treatment	Assumed proportional hazards • Ceritinib: patient-level data • Crizotinib: hazard ratio from MAIC1 (PROFILE-1014)	Used trial-derived truncated medians for both arms
Overall survival	Gompertz curve	Exponential curve
Clinical data (OS, PFS, ToT)	Adjusted ceritinib data to match PROFILE-1014 population	Unadjusted ceritinib data
% of patients on 2nd-line treatment	Based on ASCEND-4 (35%) and PROFILE 1014 (40%)	60% of patients have 2nd line treatment
	distribution of treatments was based on trials in both base cases	
Post-progression utility	• Recalculated post-progression utility • Added a health state: 'sustained utility on progression'	On-treatment post-progression utility not differentiated
Acquisition cost	Included drug wastage	Assumed no wastage
Administration cost	Additional cost for to reflect need to monitor tolerance to dose	Included only the cost of a pharmacist's time to dispense

After correcting minor calculation errors in the company's model, the ERG applied 7 changes to produce its alternative base case (see table above). The first 2 changes (to time on treatment calculation and overall survival extrapolation) had the biggest impact on the model results.

The ERG's alternative base case could not account for all of the limitations in the company's model, such as the:

- highly uncertain results of the MAIC analysis
- uncertain survival benefit
- uncertain assumption of proportional hazards for PFS and OS (see later for exploratory analyses)
- inconsistency between the modelled second line treatments and those used in practice, and the underestimation of the number of people receiving second line treatment; although the ERG considered this a serious limitation, it concluded it was preferable for the costs in the model to reflect those of the trial on which the survival benefit was modelled
- uncertainty in the duration of post-progression treatment.

ERG alternative base case: changes to post-progression utility

- ERG made 2 changes to the modelled utility values in its alternative base case:
  1. recalculated post-progression utility
  2. added a health state: 'sustained utility on progression' to reflect patients who continued receiving first-line treatment beyond disease progression
- The updated utility values are tabulated below

Health state*	Company utility	ERG utility
Progression-free	**0.810**	**0.81**
Source	*ASCEND-4 and PROFILE-1014*	*Company base case*
Progressed disease	**0.641**	**0.56**
Source	*Weighted average from Chouaid (2013)*	*Amended weighted average from Chouaid (2013)*
Sustained utility on progression	**N/A**	**0.68**
Source	*N/A*	*Midpoint of utilities in other 2 health states*
**the same utilities were used in the ceritinib and crizotinib arm*		

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The ERG made 2 changes to the calculation of utility values in the model. First, it recalculated the utility value in the progressed disease health state. The ERG's progressed disease utility was, as in the company base case, based on a weighted average of the utilities reported by Chouaid et al. (2013), however the ERG amended the calculation by removing 2 of the utility estimates:

- the estimate for people who continue first-line treatment beyond progression (0.67); these people were represented by a new health state (see below)
- the estimate for people on second-line treatment who are progression-free (0.74); this value correspond to patients within the progression-free health state and should not be used to inform the utility for progressed disease.

The ERG's second change was to differentiate quality of life in people receiving first-line treatment beyond progression. To do this, the ERG created an additional health state ('sustained utility on progression') using the difference between the time on treatment curve and the PFS curve. The utility value in this health state (0.68) was the midpoint of the progression-free utility (estimated by the company as 0.81) and the ERG's updated utility for the progressed disease health state (0.56).

The revised utility analysis reduced the total QALYS gained in each arm of the model, and

the ICER for ceritinib increased. Because the same utility values were used in each treatment am, the ICER was not substantially impacted.

Base case results (using list prices)

	Total cost, £	Total QALYs	Δ cost, £	Δ QALYs	ICER, £/QALY
Company base case					
Crizotinib	91,970	2.68			
Ceritinib	106,954	3.22	14,985	0.54	27,936
ERG alternative base case (with Gompertz OS)					
Crizotinib	119,687	2.03			
Ceritinib	139,573	2.40	19,887	0.37	58,808
ERG alternative base case (with exponential OS)					
Crizotinib	123,005	2.67			
Ceritinib	143,792	3.22	20,787	0.56	37,410

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Source: table 47 company submission, table 54 ERG erratum (corrected in response to issues 1, 2 and 3 of the company's factual accuracy check), table 6 ERG addendum
Results using the confidential patients access schemes for both drugs are presented in the confidential appendix to the PMB.

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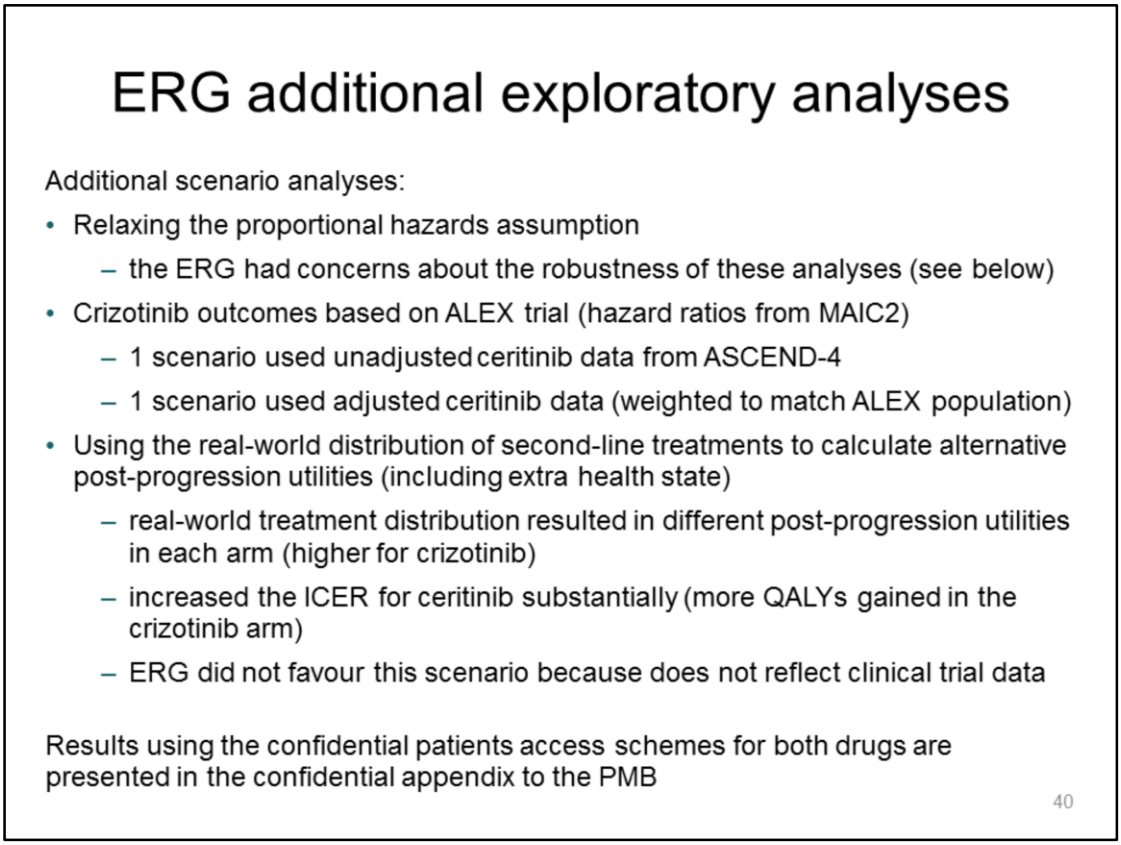
Disaggregated costs and QALYs are presented on table 49 of the company submission.

The main differences in costs and QALYs in the company base case model were as follows:

- First-line drug and drug administration costs were the largest component of the total costs for both ceritinib (75.1% without PAS) and crizotinib (71.87% without PAS). Ceritinib patients spent a longer time on treatment, hence the higher cost; although the difference was reduced due to the relative dose intensity adjustments made, where ceritinib was associated with a lower dose intensity compared with crizotinib.
- Pre-progression medical costs were noticeably higher for ceritinib, compared with crizotinib (34.35%). This was due to ceritinib patients spending longer on treatment (longer PFS with ceritinib than crizotinib).
- Ceritinib generated higher QALYs and higher life-years than crizotinib.
    - Ceritinib generated nearly all of its additional QALYs and life-years in the progression-free health state; post-progression QALYs and life-years were approximately equal to those with crizotinib



Relaxing the proportional hazards assumption

To explore the impact of relaxing the proportional hazards assumption, the ERG fitted parametric models to the patient level data for ceritinib and crizotinib independently (using the same parametric function for each treatment arm). Time on treatment was estimated as per the company base-case using the truncated median time on treatment. The ERG presented the results of 2 scenarios:

- Exponential function for PFS and OS (as in the company base case), fitted independently to ceritinib and crizotinib data
- Weibull function for OS (because it is more clinically plausible than the exponential function) and exponential function for PFS, fitted independently to ceritinib and crizotinib data.

The results of the ERG's exploratory analyses indicated that the assumptions of proportional hazards may be inappropriate. However, the ERG noted several limitations with these analyses:

- the immaturity of the OS data means that fitting independent parametric curves is subject to significant uncertainty and extrapolations may be unreliable
- the alternative method of estimating treatment duration in the ERG's alternative base case cannot be implemented because it relies on the proportional hazard assumption
- the alternative set of utility values in the ERG's alternative base case cannot be used.

See section 6.5 of the ERG report and section 1.9 of its confidential appendix for more information on the methods and results of these analyses.

Innovation (comments from the company)

- Promising Innovative Medicine designation for previously treated NSCLC
- Unmet need in untreated ALK-positive NSCLC: crizotinib is the only option
  - primary resistance to crizotinib in 5% of patients
  - median time to disease progression on crizotinib is 12 months
- Greater potency, specificity and penetration of blood-brain barrier than crizotinib
  - allows once daily dosing
  - translates into clinically meaningful improvement in PFS
- Benefits not captured in the QALY:
  - better tolerability than crizotinib: less grade 3/4 neutropenia and any-grade constipation, oedema and vision disorders (of these, the model costs included only grade 3/4 neutropenia)
  - reduced productivity loss, carer burden, impact on patient's family
  - psychological impact of prolonging the duration of remission and reducing the number of disease progressions a patient experiences

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The company did not make a case for considering ceritinib as an end-of-life treatment because the criterion for short life expectancy is not met.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ceritinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer [ID1117]

Document A

Company evidence submission summary for committee

Novartis Pharmaceuticals UK Ltd confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

22nd September 2017

File name	Version	Contains confidential information	Date
ID1117 ceritinib untreated ALK NSCLC Document A	Final	Yes	22/09/2017

Contents

Tables and figures

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List of figures

Submission summary

A.1 Health condition (see section B1.3)

Anaplastic lymphoma kinase-positive non-small cell lung cancer (ALK+ NSCLC) is a unique subpopulation of patients with NSCLC having a specific mutation in the gene encoding ALK, a receptor tyrosine kinase involved in the regulation of the RAS and JAK/STAT signalling pathways. Mutations in the ALK gene result in constitutive activation of ALK which in turn leads to activation of downstream regulator proteins, promoting cell growth and proliferation, angiogenesis and decreased apoptosis.[1,2]

Patients with ALK+ NSCLC represent 2-7% of all patients with NSCLC[3-5] and they are generally younger, often being diagnosed in their 50s, rather than their mid-60s.[6,7] Most present with advanced disease,[8] so their prognosis is poor. Estimated 5-year overall survival (OS) for NSCLC is 7%–24% for stage III disease and 2%–13% for stage IV disease,[9] and, prior to the introduction of ALK inhibitors, outcomes were generally worse in patients with ALK+ versus ALK-negative disease.[10]

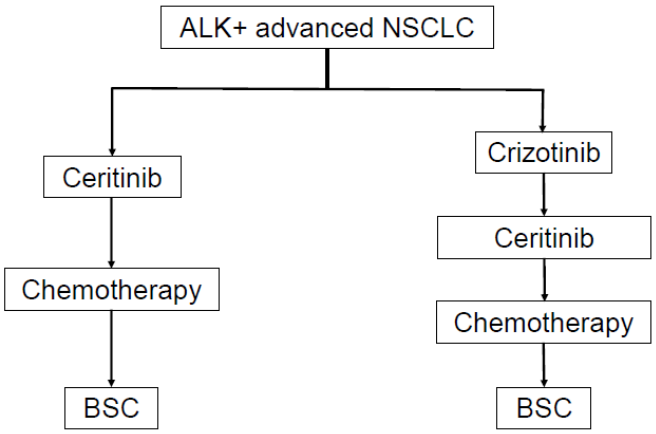
Advanced NSCLC is associated with a high symptom burden, including chest-related symptoms, fatigue, appetite loss and psychological distress.[11-14] Metastases further add to this symptom burden. In particular, 15–35% of patients with ALK+ tumours have brain metastases at initial diagnosis[15-17] and the incidence can increase to 60% over the course of first-line therapy.[18] Patients with brain metastases can experience seizures, numbness, altered sensations, motor weakness, visual disturbances and speech difficulties[19] and may be prohibited from driving.[20]

A.2 Clinical pathway of care (see section B1.3)

The management of patients with advanced NSCLC in clinical practice in the UK follows the guidelines and recommendations of NICE and European Society for Medical Oncology (ESMO).[21,22] For untreated ALK+ advanced NSCLC the NICE Clinical Guideline 121 recommends crizotinib, and options for previously treated ALK+ advanced NSCLC are: crizotinib, or ceritinib for adults who have previously received crizotinib. Current ESMO guidelines broadly concur with NICE guidance. [21]

Ceritinib is a next-generation ALK inhibitor therapy which extends the armamentarium available for treating ALK+ NSCLC,[23] by providing a new first-line therapeutic option.[24] Thus it is envisaged that ceritinib would be an alternative first-line option to crizotinib. Following disease progression, patients receiving first-line ceritinib would then progress to chemotherapy (CT), followed by best supportive care (BSC). Of note, crizotinib is not appropriate following ceritinib, as confirmed by clinical experts, as mutations that lead to resistance to second-generation ALK inhibitors confer an increased risk of resistance to crizotinib as a first-generation ALK inhibitor.[25] Currently, patients receiving crizotinib as first-line therapy receive ceritinib as second-line therapy, followed by CT and then BSC.

Figure 1 Place of ceritinib in the treatment of ALK+ NSCLC



BSC, best supportive care

A.3 The technology (see section B1.2)

Table 1 summarises the mechanism of action, method of administration and status of the marketing authorisation for ceritinib as a first-line treatment for adult patients with ALK+ advanced NSCLC.

Table 1 Ceritinib for first-line treatment of ALK+ advanced NSCLC

UK approved name and brand name	Zykadia®; ceritinib[2]
Mechanism of action	Ceritinib is a highly selective, potent, second-generation TK inhibitor of ALK, a protein involved in regulation of the RAS and JAK/STAT signalling pathways. ALK is a TK receptor protein. Under normal conditions, ALK is only activated in response to ligand binding, which induces dimerisation and, in turn, autophosphorylation. Activated ALK phosphorylates downstream signalling proteins in the RAS and JAK/STAT signalling pathways, leading to cell growth and proliferation, promoting angiogenesis and decreasing apoptosis. [1,2] ALK+ tumours have rearrangements of the *ALK* gene, which result in constitutive activation of the ALK protein.[26,27] In the majority of ALK+ NSCLCs, a somatic gene rearrangement generates an EML4-ALK fusion protein that contains the N-terminal domain of EML4 fused to the C-terminal domain of ALK.[2,27-31] Constitutive activation of the ALK protein results in aberrant downstream signalling of the RAS and JAK/STAT pathways, leading to uncontrolled proliferation. Ceritinib specifically targets the ALK protein, competing with adenosine triphosphate for binding to the active site. Ceritinib thus directly inhibits autophosphorylation of ALK and its subsequent activation thus, in turn, inhibiting ALK-mediated phosphorylation and activation of the downstream regulatory proteins in the signalling pathways. In this way, in ALK+ NSCLC, ceritinib inhibits signalling pathways that would otherwise promote cell proliferation.[28,32,33]

	Ceritinib is a second-generation ALK inhibitor that has greater affinity and specificity for ALK than the first-generation ALK inhibitor, crizotinib. Ceritinib has been shown to overcome resistance to crizotinib in preclinical and clinical (phase 1) studies,[2,23,34] and has demonstrated superior efficacy to crizotinib as a first-line therapy for ALK+ NSCLC
Marketing authorisation/CE mark status	Marketing authorisation for ceritinib as a first-line treatment option for adult patients with ALK+ advanced NSCLC was received on 26 June 2017. Ceritinib received marketing authorisation on 6 May 2015 as a second-line treatment for adult patients with ALK+ advanced NSCLC previously treated with crizotinib.
Indications	The indication (in relation to this submission) is the first-line treatment of adult patients with ALK+ advanced NSCLC.
Method of administration and dosage	Ceritinib is an oral therapy, taken once daily continuously. The capsules must be taken on an empty stomach and no food should be eaten for at least 2 hours before and 2 hours after the dose is taken.[2] The recommended dose of ceritinib is 750 mg (5 x 150 mg capsules) and therapy should be continued for as long as clinical benefit is observed.[2] Dose reductions may be required due to adverse reactions, and should be achieved using decrements of 150 mg daily. Approximately 68% of patients initiating treatment at the recommended dose of 750 mg required at least one dose adjustment due to adverse reactions, with a median time to first dose reduction of approximately 9 weeks.[35]
Additional tests or investigations	Identification of the specific ALK+ NSCLC patient population in whom first-line ceritinib is indicated requires genetic testing. This testing is currently recommended for all patients with advanced NSCLC to determine eligibility for therapy with an ALK inhibitor.[21] Thus, no additional tests over and above current clinical practice are required for selection of patients to receive first-line therapy with ceritinib. Recommended monitoring during treatment with ceritinib is largely the same as that recommended for first-line crizotinib in this patient population, and includes:[2] • Liver laboratory tests (including ALT, AST and total bilirubin) prior to the start of treatment, every 2 weeks for the first month and monthly thereafter • Monitoring for gastrointestinal toxicity and for pulmonary symptoms indicative of pneumonitis • Periodic monitoring of ECG and electrolytes, heart rate and blood pressure • Monitoring fasting plasma glucose prior to treatment and periodically thereafter • Monitoring of lipase and/or amylase prior to treatment and thereafter as clinically indicated Use of ceritinib in the first-line treatment of adult patients with ALK+ advanced NSCLC will not adversely impact or alter the current infrastructure and service provision requirements, and is not expected to increase resource use. This reflects the fact that: • Currently, the majority of patients with ALK+ advanced NSCLC receive crizotinib. The tests for identifying these eligible patients and the monitoring required during therapy are largely the same as for ceritinib (although full blood counts and monitoring for renal function are additionally recommended during therapy with crizotinib[36])

	• Interventions for the management of gastrointestinal adverse events (e.g. anti-emetics and anti-diarrhoeals) are likely to be comparable for ceritinib and crizotinib
List price and average cost of a course of treatment	The list price is £4,923.45 for a 30-day supply, and this is the price agreed with the Department of Health for 3 packs of 50 x 150 mg capsules each.
Patient access scheme (if applicable)	A confidential simple discount PAS of [redacted] is currently in place.

ALK, anaplastic lymphoma kinase; ALK+, anaplastic lymphoma kinase-positive; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHMP, Committee for Medicinal Products for Human Use; ECG, electrocardiogram; EML4, echinoderm microtubule-associated protein-like 4; JAK/STAT, janus kinase/signal transducer and activator of transcription; NSCLC, non-small cell lung cancer; PAS, patient access scheme; RAS, rat sarcoma; TK, tyrosine kinase

A.4 Decision problem (see section B1.1)

Ceritinib is currently approved and recommended by NICE for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib.[2,37] This submission relates to the extension of the indication for ceritinib to include first-line treatment of adult patients with ALK+ advanced NSCLC and covers the full marketing authorisation for this first-line indication.

Table 2 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated ALK+ advanced NSCLC	People with untreated ALK+ advanced NSCLC	
Intervention	Ceritinib	Ceritinib	
Comparator(s)	• Crizotinib • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) and with or without pemetrexed maintenance treatment	Crizotinib	Crizotinib is now the standard of care for first-line treatment of ALK+ advanced NSCLC. Clinical expert opinion suggests that > 90% of these patients would be treated with crizotinib in England and Wales.[38]
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	

Economic analysis		Cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year gained. The time horizon of the model is 20 years, which is sufficient for this patient population to reflect any differences in costs or outcomes between the technologies being compared. Costs have been considered from an NHS and Personal Social Services perspective.	
Special considerations including issues related to equity or equality		ALK testing will not be included in the analysis.	ALK testing is currently performed routinely in this group of patients due to the availability of crizotinib as a first-line ALK inhibitor.

ALK+, anaplastic lymphoma kinase-positive; NSCLC, non-small cell lung cancer

A.5 Clinical effectiveness evidence (See section B2.6)

Evidence for the efficacy and safety of ceritinib as first-line therapy in patients with ALK+ NSCLC is provided by the phase 3 RCT, ASCEND-4, as described in Table 3, and data from this study are used in the economic model. This multicentre, randomised, open-label study conducted in 134 sites across 28 countries assessed the efficacy and safety of ceritinib versus platinum-based chemotherapy (CT) in patients with ALK+ advanced non-squamous NSCLC, untreated with any systemic anti-cancer therapy (except neoadjuvant or adjuvant therapy). Results have been reported for the first planned interim analysis, performed after a median follow up of 19.7 months (data cut off, June 2016) and include the primary endpoint – progression-free survival (PFS) – the key secondary endpoint – overall survival (OS) – and a number of other secondary endpoints including response rates and patient reported outcomes (PROs).[24,35] Safety data have also been reported. No further studies were identified that investigated ceritinib in this patient population. However, three non-RCTs (ASCEND-1,[39] ASCEND-2,[40] ASCEND-3[41]) and an RCT comparing ceritinib versus CT (ASCEND-5[42]) have investigated ceritinib in patients with ALK+ advanced NSCLC who had received prior therapy (CT and/or an ALK inhibitor) for advanced disease. These studies provide supporting evidence for the safety profile of ceritinib; data from these studies are not used in the economic model, as they relate to a different patient population to that which is relevant in this submission. Preliminary safety data have also been reported for two further ongoing studies, ASCEND-6[43] and ASCEND-8.[44]

In ASCEND-4, patients untreated with systemic therapy were randomised 1:1 to receive ceritinib or CT (cisplatin or carboplatin plus pemetrexed). If present, brain metastases were required to be asymptomatic or neurologically stable. Randomisation was stratified according to World Health Organization (WHO) performance status (0 vs. 1–2), prior adjuvant therapy (yes vs. no) and the presence or absence of brain metastases at screening. Ceritinib was administered orally once daily (in the fasted state, i.e. at least one hour before or two hours after food), at a dose of 750 mg (5 x 150

mg capsules) continuously for the 21-day treatment cycle. CT was administered intravenously, comprising cisplatin (75 mg/m²) or carboplatin (area under the concentration time curve 5–6 mg/mL.min) plus pemetrexed (500 mg/m²) given every 21 days for four cycles, and patients who completed the four cycles of CT without disease progression subsequently received pemetrexed maintenance therapy (500 mg/m²) every 21 days. In both treatment groups, patients continued to receive therapy until disease progression (according to Response Evaluation Criteria In Solid Tumours [RECIST] 1.1 criteria, central assessment) or unacceptable toxicity. Patients could continue therapy beyond disease progression if the investigator judged that they were experiencing clinical benefit, but they were not followed for efficacy or PROs beyond progression. Patients could undergo dose reductions or treatment interruptions for management of AEs. A maximum of three dose reductions were allowed for patients treated with ceritinib (150 mg per reduction, to a minimum dose of 300 mg/day). Patients randomly assigned to CT were allowed to cross over to ceritinib after centrally confirmed, RECIST-defined progressive disease.

Efficacy outcomes were based on determination of tumour response according to RECIST 1.1 criteria and were performed both locally and centrally, based on computed tomography scans or MRI of the chest and abdomen. Assessments were completed at baseline, every 6 weeks from cycle 1 day 1 to month 33 and then every 9 weeks thereafter and at the end of treatment. Intracranial responses were assessed in patients with brain metastases by computed tomography scan or MRI performed at each tumour assessment time point. PROs were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30),[45] the corresponding lung cancer module (QLQ-LC13), [46] the Lung Cancer Symptom Scale (LCSS),[47] and the EuroQol Group 5-Dimension (EQ-5D-5L) self-report questionnaire.[48] The primary endpoint was PFS, assessed centrally according to RECIST 1.1, and the key secondary endpoint was OS. The investigators and patients were not masked to treatment assignment, but the study sponsor personnel remained blinded until data lock for the primary analysis.

Table 3 Clinical effectiveness evidence (B2.2 table 4)

Study	**ASCEND 4, NCT01828099, CLDK378A2301, Soria *et al*., 2017**				
Study design	Phase 3 open-label RCT				
Population	Untreated adult patients with stage IIIB/IV ALK+ NSCLC				
Intervention(s)	Ceritinib				
Comparator(s)	Platinum-based chemotherapy, i.e. cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance therapy				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	Efficacy data for ceritinib from ASCEND-4 are used in the model, as this study provides relevant data for ceritinib in the patient population of interest.				
Reported outcomes specified in the decision problem	Primary outcome: PFS Key secondary outcome: OS Other outcomes: response rate, safety and HRQoL				
All other reported outcomes	Other secondary outcomes: PFS (local assessment), ORR, DOR, DCR, TTR, OIRR, IDCR, DOIR, PRO: EORTC QLQ-C30, QLQ-LC13, LCSS, EQ-5D and safety				

Soria *et al.,* 2017[24]

ALK+, anaplastic lymphoma kinase-positive; DCR, disease control rate; DOIR, duration of intracranial response; DOR, duration of response; EORTC-QLQ, European Organisation for Research and Treatment of Cancer core Quality of Life questionnaire; HRQoL, health-related quality of life; IDCR, intracranial disease control rate; LCSS, lung cancer symptom scale; NSCLC, non-small cell lung cancer; OIRR, overall intracranial response rate; ORR,

objective overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcomes; QLQ-LC13, lung cancer specific questionnaire; TTR, time to response

A.6 Key results of the clinical effectiveness evidence

Table 4 summarises the key efficacy data for ASCEND-4 (see Section B2.6.1).

Table 4 Summary of efficacy data for the phase III trial ASCEND-4

Endpoints	Central assessment			Local assessment		
	Ceritinib (n=189)	Chemotherapy (n=187)	p-value or HR	Ceritinib (n=189)	Chemotherapy (n=187)	p-value or HR
Median PFS, months (95% CI)	16.6 (12.6–27.2)	8.1 (5.8–11.1)	HR 0.55 p <0.001	16.8 (13.5–25.2)	7.2 (5.8–9.7)	HR 0.49 p <0.001a
Median OS, months (95% CI)	NE (29.3–NE)	26.2 (22.8–NE)	HR 0.73 p = 0.056	-	-	-
2-year OS, % (95% CI)	70.6 (62.2–77.5)	58.2 (47.6–67.5)	NA	-	-	-
ORR,[b] % (95% CI)	72.5 (65.5–78.7)	26.7 (20.5–33.7)	-	73.5 (66.7–79.7)	32.1 (25.5–39.3)	-
Median TTR, weeks[c](range)	6.1 (5.1–61.7)	13.4 (5.1–90.1)	-	6.3 (5.1–71.9)	12.6 (4.7–84.0)	-
Median DOR,[c] months (95% CI)	23.9 (16.6–NE)	11.1 (7.8–16.4)	-	23.3 (17.6–NE)	8.0 (5.8–13.4)	-
EFS, % (95% CI)			-			-
At 21 months	59.0 (49.3–67.4)	NEd		53.9 (42.9–63.6)	13.8 (1.6–39.1)	
At 24 months	48.2 (32.3–62.4)	NE[d]		41.5 (26.6–55.8)	NE[d]	

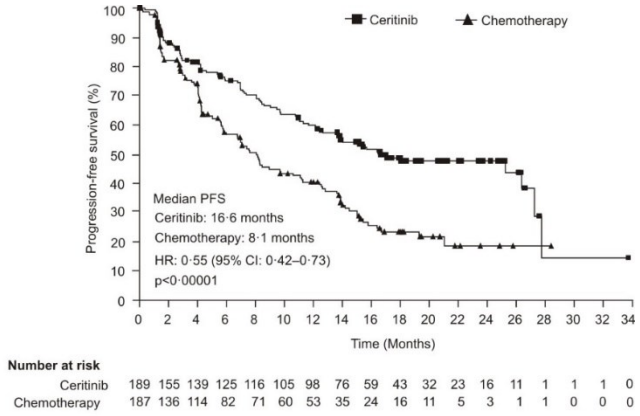
Soria *et al.*, 2017[24], Soria et al Supplementary appendix[49], ASCEND-4 CSR[35]
[a]Nominal p-value
[b]ORR = CR+PR
[c]Patients with a best overall response of CR or PR
[d]Not estimable as no responders were at risk at the time point
CI, confidence interval; CR, complete response; CSR, clinical study report; DOR, duration of response; EFS, event-free survival; HR, hazard ratio; NA, not applicable; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response

A.6.1 Primary efficacy outcome – PFS (Section B2.6.2)

Ceritinib provided a median PFS of 16.6 months in the overall population

The ASCEND-4 study met its primary objective, demonstrating a statistically significant and clinically meaningful improvement in PFS for ceritinib over CT. The median PFS was 16.6 months for ceritinib compared with 8.1 months for CT (central assessment) (HR, 0.55; p<0.00001). The PFS advantage was apparent from approximately three months onwards in the Kaplan–Meier plots, and the event-free probability estimates remained higher throughout the study period for ceritinib compared with CT. At 24 months, the Kaplan–Meier-estimated PFS was 47.6% for ceritinib compared with 18.6% for CT. Results for local assessment corroborated those reported for central assessment, with median PFS being 16.8 months for ceritinib (Table 4). Concordance rates between central and local review were high, being 88% for ceritinib, and 87% for CT.

Figure 2 Kaplan–Meier plots of PFS in ASCEND-4 (central assessment)



Soria *et al.,* 2017[24]
CI, confidence interval; HR, hazard ratio

Ceritinib prolonged PFS compared with CT in patients both with and without brain metastases.[24,35] Median PFS achieved with ceritinib was 26.3 months in patients without brain metastases (vs 8.2 months for CT) and 10.7 months (vs 7.0 months) in patients with brain metastases according to central assessment, and similar results were reported for local assessment.

A.6.2 Key secondary efficacy outcome – OS (Section B2.6.3)

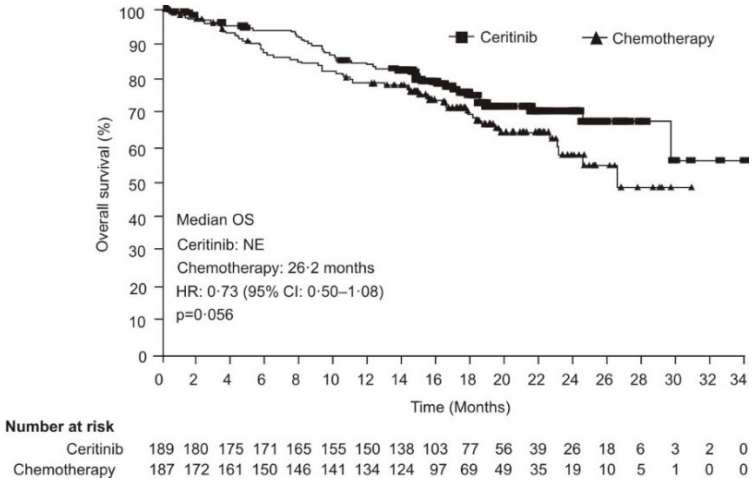
The interim analysis reported a 2-year OS of 71% for ceritinib

At the time of the analysis, the OS data were immature; only 107 events (42% of the required OS events) had occurred. The study did not cross the efficacy stopping boundary for OS (–3.2546 [Z-scale], corresponding to p=0.0006 on the p-value scale), and is therefore ongoing.

At the data cut-off, 48 (25.4%) patients in the ceritinib group had died, resulting in an estimated 24-month OS rate of 70.6%. This compares with a 24-month OS of 58.2% for CT. Median OS was 'not reached' in the ceritinib group and was estimated as 26.2 months in the CT group (HR, 0.73; p=0.056). Thus, ceritinib reduced the risk of death by 27% compared with CT. The OS Kaplan–Meier plots for the two treatment groups diverged from four months onwards, indicating a positive trend in favour of ceritinib (Figure 3).

At the time of the OS analysis, 105 (72%) of 145 patients initially randomised to CT had received an ALK inhibitor after CT discontinuation; this included 80 patients who crossed over to receive ceritinib. Of the other 25 patients, 23 received crizotinib. Conversely, in the ceritinib group, 34 (18%) of 189 patients had received subsequent anti-cancer therapy, of whom 24 received platinum-based doublet CT, and six received an ALK inhibitor (ceritinib, n=1; crizotinib, n=3; lorlatinib, n=2). A sensitivity analysis using rank-preserving structural failure time (RPSFT) methodology was performed to correct for the confounding introduced by patients crossing over from CT to ceritinib. The resulting HR estimate was similar to that from the primary OS analysis, suggesting that cross-over from CT to ceritinib on disease progression did not affect the difference in OS between the treatment groups for this data-cut (HR 0.73; 95% CI, 0.49–1.10). The duration of follow-up is currently insufficient to conclude whether there is a difference in OS according to the RPSFT analysis.

Figure 3 Kaplan–Meier plot of OS in ASCEND-4



Soria *et al*., 2017[24]
CI, Confidence interval; HR, Hazard ratio

A.6.3 Whole-body tumour response rates (Section B2.6.4)

Almost three-quarters of patients achieved a tumour response to ceritinib and responses were sustained for a median of two years

Overall, 72.5% of patients receiving ceritinib achieved a tumour response, with most being classified as a partial response (PR, 72.0%) (Table 5). The median time to response was 6.1 weeks. Among patients with a confirmed CR or PR, the median duration of response (DOR) was 23.9 months. These results compare favourably with those for the CT group, where the ORR was 26.7%, time to response was 13.4 weeks and median DOR was only 11.1 weeks. Similar results were reported for local assessment, with concordance rates between central and local assessment for best overall response being 79.9% for ceritinib and 73.3% for CT.

Table 5 Summary of whole-body tumour response rates in ASCEND-4

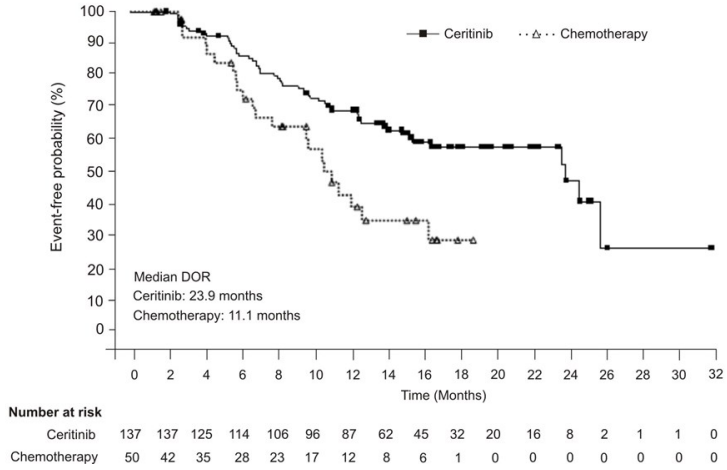
Response	Central assessment		Local assessment	
	Ceritinib (n=189)	Chemotherapy (n=187)	Ceritinib (n=189)	Chemotherapy (n=187)
ORR, n (%) (95% CI)	137 (72.5) (65.5–78.7)	50 (26.7) (20.5–33.7)	139 (73.5) (66.7–79.7)	60 (32.1) (25.5–39.3)
CR, n (%)	1 (0.5)	0	5 (2.6)	0
PR, n (%)	136 (72.0)	50 (26.7)	134 (70.9)	60 (32.1)
SD, n (%)	23 (12.2)[a]	88 (47.1)[b]	30 (15.9)	82 (43.9)
PD, n (%)	19 (10.1)	26 (13.9)	11 (5.8)	21 (11.2)
Unknown, n (%)	10 (5.3)	23 (12.3)	9 (4.8)	24 (12.8)
Median time to first response (in responders), weeks (range)	6.14 (5.1–61.7)	13.36 (5.1–90.1)	6.29 (5.1–71.9)	12.64 (4.7–84.0)
Median DOR (in responders), months (95% CI)	23.9 (16.6–NE)	11.1 (7.8–16.4)	23.3 (17.6–NE)	8.0 (5.8–13.4)

Estimated 21-month event-free rate, % (95% CI)	59.0 (49.3–67.4)	NE	53.9 (42.9, 63.6)	13.8 (1.6–39.1)

Soria et al Supplementary appendix[49]
[a]Three NCRNPD cases are based on patients with non-measurable disease.
[b]Nine NCRNPD cases are based on patients with non-measurable disease,
CI, confidence interval; CR, complete response; DOR, duration of response; NCRNPD, non-CR/non-PD; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

In the Kaplan–Meier plots for duration of response, the curves separated from approximately three months onwards and the event-free probability remained higher in the ceritinib arm, indicating a longer duration of response with ceritinib. The estimated event-free rate at 24 months was 48.2% for patients in the ceritinib arm (Figure 4).

Figure 4 Kaplan–Meier plot of duration of response per central assessment by treatment arm in ASCEND-4 (FAS – patients with confirmed CR or PR)



ASCEND-4 CSR.[35]
CSR, clinical study report; NE, not estimable

A.6.4 HRQoL (Section B2.6.6)

Symptom severity and HRQoL were assessed while patients were receiving treatment using the QLQ-C30, QLQ-LC13, LCSS and EQ-5D instruments. Results clearly demonstrated that patients in general experience less severe symptoms (including both those related to lung cancer and to the side effects of treatment), together with better functioning and HRQoL, during therapy with ceritinib compared with CT. The only exception was GI symptoms, which were more severe with ceritinib compared with CT. Furthermore, median time to a definitive deterioration in lung cancer symptoms was 24 months according to scores obtained with the QLQ-LC13, indicating that ceritinib provides patients with a prolonged period with minimal worsening of disease-specific symptoms. This is supported by the EQ-5D score (0.81) and EQ-VAS score (77.0) reported for patients receiving ceritinib, which are indicative of a good HRQoL. These data suggest that the clinical benefits reported for ceritinib therapy translate into meaningful improvements in symptoms and HRQoL, and that the effects of AEs are mitigated by the impact of treatment on disease-related symptoms.

A.6.5 Safety profile (Section B2.10)

In ASCEND-4, while most (97%) patients reported AEs related to treatment with ceritinib, and 65% of patients experienced grade 3/4 treatment-related AEs, only 5% of patients discontinued therapy due to treatment-related AEs. Thus AEs due to ceritinib were generally manageable and reversible with dose adjustments, dose interruptions, and with supportive medication. Importantly, no new safety information emerged that would substantially alter the safety profile of ceritinib demonstrated in earlier studies in ALK+ NSCLC. The most common AEs (any grade, ≥35% of patients) were GI (i.e. diarrhoea, nausea and vomiting), followed by elevation in the serum levels of liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT)]. Elevated liver enzymes were also the most frequently reported grade 3/4 AEs (reported in ≥15% of patients); most other grade 3/4 AEs related to treatment were reported in less than 5% of patients.

A.7 Evidence synthesis (Section 2.9)

A systematic review identified that there are no direct head-to-head trials of ceritinib versus crizotinib in ALK+ advanced NSCLC but identified the pivotal phase III trial for crizotinib in the relevant indication, PROFILE 1014.[50] Comparing the design and patient populations involved in the pivotal phase III trials for ceritinib (ASCEND-4) and crizotinib (PROFILE 1014) indicated that a matching-adjusted indirect comparison (MAIC) would be feasible, and the most appropriate approach for comparing key efficacy outcomes for ceritinib and crizotinib in the relevant patient population.

In the MAIC, weights were applied to patients enrolled in ASCEND-4 to exactly balance all baseline characteristics between the two trial populations. The extent of weighting required to achieve this was mild, with the effective sample size (ESS) in ASCEND-4 being reduced by 10% after weighting, and there was no evidence of extreme weights.

After weighting, ceritinib was found to reduce the risk of disease progression or death compared with crizotinib by [redacted] ([redacted]). Median PFS was [redacted] months for ceritinib versus 10.8 months for crizotinib, and 1-year PFS increased from 47.8% for crizotinib to [redacted] for ceritinib ([redacted]) Comparison of OS data from both studies showed that, after weighting, ceritinib provided a greater reduction in the risk of death compared with crizotinib of [redacted], but the difference was not statistically significant ([redacted]). These results suggest that ceritinib offers significant clinical benefits over crizotinib for the management of adults with ALK+ advanced NSCLC untreated with prior systemic therapy.

A.8 Key clinical issues

The following assumptions should be considered when interpreting the available clinical data regarding the efficacy and safety of ceritinib and the comparison versus crizotinib:

- There are no direct head-to-head comparative data for ceritinib and crizotinib in the relevant indication. However, the pivotal phase III trials for both agents involved similar patient populations that closely correspond to the anticipated patient population and both used a similar trial design. Thus a MAIC was considered an appropriate approach to compare the efficacy for both agents.
- OS data for ceritinib and crizotinib are currently immature. Thus the impact of treatment on OS cannot be conclusively deduced from the available evidence.
- Both pivotal trials assessed the efficacy and safety of ceritinib and crizotinib given according to the licensed indication and in the relevant patient population, and eligible patients were

identified through ALK+ testing as would be used in routine clinical practice. Thus the results for both studies can be considered to be representative of the expected outcomes achieved in routine clinical practice.

- Both trials included PRO assessments performed while patients continued to receive study treatment. They thus provide a valuable assessment of the impact of ceritinib and crizotinib on disease-specific symptoms and HRQoL during treatment.

A.9 Overview of the economic analysis

Figure 5 summarises the model structure and the key features of the cost-effectiveness analysis are summarised in Table 6

Figure 5 Partitioned survival model structure – B.3.2.3

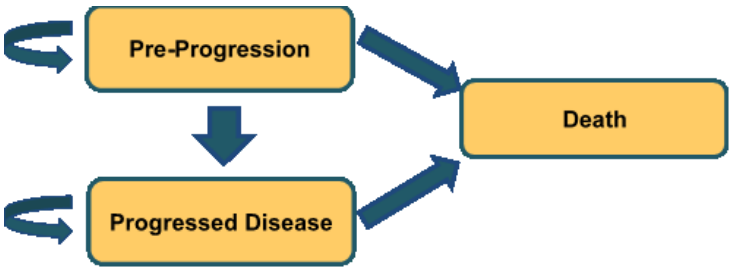


Table 6 Features of the economic analysis (Section B3.2, table 29)

	Current appraisal	
	Chosen values	**Justification**
Time horizon	20 years	Sufficiently long that the majority of patients in the model have died by the end of the modelled time horizon
Health states	Progression free, progressed disease, death	Reflects the aim of treatment: to maintain patients in progression-free state
Comparator	Crizotinib	Current standard of care
Treatment discontinuation	Treatment continued beyond progression based on data from the pivotal trial	Reflects the data source used for efficacy estimates
Transition through the model	Based on the pivotal trial, ASCEND-4 for ceritinib, the MAIC for crizotinib, and extrapolation using parametric survival models	Reflects the expected clinical outcomes
Source of utilities	ASCEND-4 data for PF, published data from PROFILE 1014 for crizotinib, and published literature for PD	ASCEND-4 collected EQ-5D utilities for ceritinib during treatment and PROFILE 1014 collected equivalent data for crizotinib. Patients could continue on treatment beyond disease progression. However, data post-progression were not collected consistently in all patients in either study
Source of costs	Drug acquisition costs were from the Monthly Index of Medical Specialities (MIMS) for branded products, and the electronic market information tool (eMit) for generic products.	

	Drug administration costs were from PSSRU 2016 for the hourly rate of a hospital pharmacist. Administration costs and health state costs were from NHS reference costs 2015-16. Palliative care costs were from Georghiou & Bardsley, 2014[51]	

EQ-5D, EuroQol Group 5-Dimension questionnaire ; MAIC, matching-adjusted indirect comparison; PF, progression free; PF, progressed disease

A.10 Incorporating clinical evidence into the model

A.10.1 Progression-free survival and overall survival (Section B3.3.2)

PFS and OS inputs for ceritinib were based on ASCEND-4,[35] PFS and OS curves were derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, and log-normal distributions) to patient-level data from the ASCEND-4 trial to extrapolate efficacy outcomes beyond the trial period.[35] Based on AIC/BIC fit statistics and expert opinion, the exponential function was selected as the most appropriate base-case parametric model for PFS and OS. PFS and OS inputs for crizotinib were based on estimates of the relative efficacy of ceritinib versus crizotinib were obtained from the MAIC that adjusted for observed differences between the two trial populations, as described in section **Error! Reference source not found.**. In this MAIC, all the baseline haracteristics of the reweighted ASCEND-4 trial population were exactly matched to the characteristics of the PROFILE 1014 trial population, as the latter was considered to reflect the characteristics of the UK patient population (see also section **Error! Reference source not found.**).[52] se of exponential PFS and OS functions for ceritinib yielded estimates of post-progression survival that were nearly equivalent to the first-line ceritinib and crizotinib treatment arms in ASCEND-4 and PROFILE 1014, respectively.

A.10.2 Adverse events (Section B3.3.3)

Treatment-related grade 3/4 AEs were included in the model if they affected ≥5% of patients receiving ceritinib or crizotinib in ASCEND-4 and PROFILE 1014, respectively, as summarised in Table 7.

Table 7 Treatment-related grade 3/4 adverse events included in the economic model

Adverse events, %	Ceritinib	Crizotinib
Neutropenia	0.5	11.1
Diarrhoea	5.3	2.3
Pulmonary embolism	0.0	6.4
Vomiting	5.3	1.8
Hyperglycaemia	6.3	0.0
Alanine transaminase (ALT) elevation	30.7	14.0
Aspartate aminotransferase (AST) elevation	16.9	0.0
Gamma-glutamyltransferase increased	28.6	0.0
Blood alkaline phosphatase increased	7.4	0.0

ASCEND-4 CSR[35]; Solomon *et al.,* 2014[50]

A.10.3 Treatment duration (Section B3.3.4)

In the base case, patients were assumed to continue first-line treatment until discontinuation, based on treatment duration data reported from the ASCEND-4 and PROFILE 1014 trials. The proportion of patients on treatment in each cycle was estimated using an exponential survival function for each treatment. In the base case, the rate parameter (λ) of the exponential functions for ceritinib and crizotinib was estimated using the truncated median treatment durations reported in their respective clinical trials. This data approach was selected due to the unavailability of time-to-event data for crizotinib treatment discontinuation.

For ceritinib, the exponential rate of treatment discontinuation was estimated based on the truncated median duration of 15.3 months reported in the ASCEND-4 trial CSR, in which treatment duration was counted from the first ceritinib dosing date until the last ceritinib dosing date prior to the data cut-off. For crizotinib, the exponential rate of treatment discontinuation was estimated using the truncated median treatment duration of 10.9 months reported in the PROFILE-1014 trial. In sensitivity analyses, several alternative treatment duration scenarios (see Table 8).

Table 8 Summary of mean treatment duration by treatment arm: base case and scenario analyses

Treatment duration assumption	Mean treatment duration (months)*	
	Ceritinib	Crizotinib
Base case: Treatment until discontinuation (based on truncated median duration for both ceritinib and crizotinib)	[redacted]	[redacted]
Scenario 1a: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on ASCEND-4)	[redacted]	[redacted]
Scenario 1b: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on PROFILE 1014)	[redacted]	[redacted]
Scenario 2: Treatment until progression	[redacted]	[redacted]
Scenario 3: Treatment until discontinuation or progression, whichever occurs first	[redacted]	[redacted]

*After applying a half-cycle correction

A.10.4 Utility inputs (Section B3.4)

Utility values for the progression free (PF) health state were obtained for each treatment arm based on EQ-5D data reported from the ASCEND-4 and PROFILE 1014 trials. In the ASCEND-4 trial, mean utility values were compared for ceritinib and CT using a repeated-measures regression model of EQ-5D index scores (based on the EQ-5D crosswalk value set for the UK using the time trade-off method).[35] The PF utility value for crizotinib was taken from a repeated measures regression model comparing overall EQ-5D index scores for the treatment arms of PROFILE 1014, as reported by Felip et al. (2015).[53]

Because EQ-5D scores were not collected systematically after disease progression in ASCEND-4 or PROFILE 1014, trial-based estimates of PD utility do not accurately reflect the health status of patients during the entire PD period before death. Thus the base-case utility value for the progressed disease (PD) health state for both treatment arms was estimated based on the utility study by Chouaid *et al.,* (2013), a multi-national cross-sectional study among patients receiving any treatment for advanced NSCLC in real-world settings.[54] Table 9 summarises the utility values used in the base case.

Table 9 Base case health state utilities

Health state	Utility value	Source
Ceritinib		
Progression free (stable disease or objective response)	0.81	ASCEND-4 CSR
Progressed disease	0.64	Chouaid *et al.,* 2013
Crizotinib		
Progression free (stable disease or objective response)	0.81	PROFILE 1014 (Felip *et al.,* 2015)
Progressed disease	0.64	Chouaid *et al.,* 2013

ASCEND-4 CSR[35]; Chouaid *et al.,* 2013[54]; Felip *et al.,* 2015[41]

A.11 Key model assumptions and inputs (Section B3.6)

Table 10 and Table 11 summarise the key model assumptions and inputs into the model (see section B3.6).

Table 10 Key assumptions of the model

Parameter	Assumption
Treatment discontinuation rules (Section B3.3.4)	• Patients receive first-line treatment according to the following treatment discontinuation rules: o Base case: Treatment until discontinuation, based on reported median treatment duration (right-truncated at the data cut-off) for ceritinib in ASCEND-4 and crizotinib in PROFILE 1014 o Alternatives to the above scenario were tested as part of the sensitivity analysis, including: ▪ Based on patient-level time-to-event data in ASCEND-4 for ceritinib and reported truncated median treatment duration in PROFILE 1014 for crizotinib ▪ Assuming equivalent time on treatment for ceritinib and crizotinib, with both based on ASCEND-4 ▪ Assuming equivalent time on treatment for ceritinib and crizotinib, with both based on PROFILE 1014 o Other sensitivity analyses included: ▪ Treatment until progression ▪ Treatment until discontinuation or progression, whichever occurs first
Treatment costs: First-line treatment (Section B3.5.1)	• Patients incur costs for first-line drug acquisition and administration during the period of time that they remain on treatment
Treatment costs: second-line treatments (Section 3.5.4)	• Patients incur costs of second-line treatments upon discontinuation of the first-line treatment. In the base case, the second-line treatments reflected those observed in the respective trials (i.e., ASCEND-4 and PROFILE 1014). In a scenario analysis, second-line treatments instead reflected current real-world practice based on input from medical experts
Health state costs and AE costs (Sections B3.5.2, 3.5.3 and 3.5.5)	• Medical costs in the PF health state include monthly monitoring and other medical costs. In addition, the cost of treatment-associated AEs was applied as a one-time cost in the first model cycle • Medical costs in the PD health state include monthly monitoring and outpatient costs • All patients incur one-time terminal care costs before death

Parameter	Assumption
ALK testing costs (Section 3.5.7)	• ALK testing was assumed to be a routine diagnostic test, and was therefore not considered as a cost component in the model
Utility and disutility (Section 3.4)	• Base-case health utilities are dependent on health state; additionally, the utility value for PF health state depends on the first-line treatment received. PF utilities for ceritinib were obtained from the CSR for ASCEND-4; the PF utility for crizotinib was obtained from PROFILE 1014, and the PD utility (used for both the ceritinib and crizotinib treatment arms) was obtained from published literature.

Felip *et al.,* 2015[53]; Chouaid *et al.,* 2013[54]

Table 11 Summary of variables applied in the economic model

Variable		Value	Measurement of uncertainty: SE or 95% CI	Reference to section in submission
Model settings	Discount rate (costs)	3.5%	NA	Refer to CE Model
	Discount rate (benefits)	3.5%	NA	
	Time horizon	20 years	NA	
PFS and OS with ceritinib	Exponential rate parameter: PFS	0.041	SE=0.004	Refer to CE Model
	Exponential rate parameter: OS	0.015	SE=0.002	
Hazard ratios for PFS and OS with crizotinib vs. ceritinib	Hazard ratio: PFS	1.56	95% CI: 1.15-2.13	Refer to CE Model
	Hazard ratio: OS	1.21	95% CI: 0.79-1.85	
Drug costs: first-line treatments (list price per package)	Ceritinib	£4,923.45	NA	Section B3.5.1
	Crizotinib	£4,689.00	NA	
Relative dose intensity: first-line treatments	Ceritinib	77.3%	SE=1.4%	Section B3.5.1
	Crizotinib	92.0%	SE=1.0%	
Drug administration costs	Monthly cost of oral drug administration	£14.26	NR	Section B3.5.1
Exponential rate of first-line treatment discontinuation	Ceritinib	0.045	NR	Refer to CE Model
	Crizotinib	0.064	NR	
Health state utilities	Utility for PF: ceritinib	0.810	SE=0.015	section B 3.4.2

Variable		Value	Measurement of uncertainty: SE or 95% CI	Reference to section in submission
	Utility for PF: crizotinib	0.810	NR	
	Utility for PD	0.641	SE=0.024	
Health state costs	Medical costs per cycle in PF	£184.42	NR	Section B3.5.2
	Medical costs per cycle in PD	£267.19	NR	Section B3.5.3
	One-time terminal care cost	£7,328.93	NR	section B3.5.6
Cost of second-line treatment, by first-line treatment	Ceritinib	£8,135.41	NR	Section B3.5.4
	Crizotinib	£8,645.67	NR	
Cost of AEs, by first-line treatment	Ceritinib	£340.27	NR	Section 3.5.5
	Crizotinib	£218.23	NR	

CI, confidence interval; NA, not applicable; NR, not reported; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; SE, standard error

A.12 Base-case ICER (deterministic) (Section B3.7)

Table 12 and Table 13 summarise the results for the base case (with and without application of the PAS price for ceritinib). At the list price ceritinib is a cost-effective treatment for the first-line treatment of ALK+ advanced NSCLC having an ICER of £27.936 per QALY; ceritinib is dominant when the agreed PAS price is applied to ceritinib.

Table 12 Base-case results

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	**106,954**	**4.51**	**3.22**	**14,985**	**0.66**	**0.54**	**27,936**
Crizotinib	91,970	3.85	2.68	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 13 Base-case results with PAS

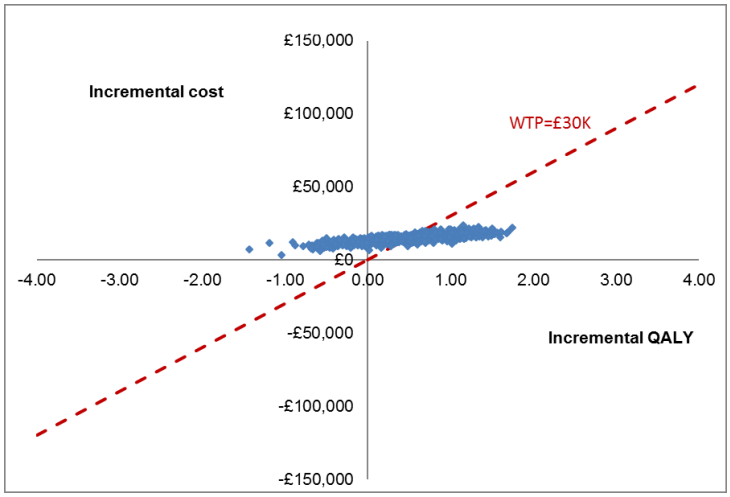
Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
Crizotinib	89,714	3.85	2.68	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A.13 Probabilistic sensitivity analysis (Section B3.8.1)

Across the 1,000 iterations of the PSA, the average incremental cost was £14,978, and the average incremental QALY gain was 0.51 for ceritinib vs. crizotinib. The resulting probabilistic ICER per QALY for ceritinib vs. crizotinib was £29,239, similar to the deterministic base-case ICER. Based on the scatter plot, ceritinib was associated with higher costs than crizotinib in all iterations, and higher QALYs than crizotinib in 87% of iterations (Figure 6). When ceritinib is provided at list price, ceritinib had a 53.2% probability of being cost-effective vs. crizotinib at a willingness-to-pay threshold of £30,000 per QALY gained.

Figure 6. Incremental cost-effectiveness plane for ceritinib vs. crizotinib



A.14 Key sensitivity and scenario analyses (Section B3.8.2)

Results of the DSAs are shown in Figure 7. Across the sensitivity analyses, ceritinib ranged from being a dominant strategy to having an incremental cost per QALY of £61,070 vs. crizotinib. The ICER was particularly sensitive to parameters related to OS (including the hazard ratio of OS for crizotinib vs. ceritinib and the choice of parametric function for modelling OS under ceritinib), as these parameters directly enter the calculation of expected QALYs for each treatment arm. Other important drivers of cost-effectiveness included parameters related to drug costs – including relative dose intensity and the list prices of ceritinib and crizotinib – and assumptions about treatment duration.

Figure 7. Tornado diagram based on DSA results for ceritinib vs. crizotinib

AE, adverse event; OS, overall survival; PFS, progression-free survival; ToT, time on treatment
ε Ceritinib is dominant over crizotinib in this sensitivity analysis

A.15 Innovation (Section B2.11)

Ceritinib is an innovative therapy that has helped transform the management of patients with ALK+ NSCLC through its use in the second-line setting, and it is expected to provide further substantial benefits with its extension to the first-line setting. The innovative nature of ceritinib was acknowledged in the Promising Innovative Medicine designation of the product by the Medicines and Healthcare Products Regulatory Agency, on 10 February 2015, for the treatment of adult patients with previously treated ALK+ NSCLC.[55] The unmet need also applies to the first-line setting where, currently, crizotinib is the only treatment option. Ceritinib has a greater potency and specificity than crizotinib, the current standard of care for newly diagnosed ALK+ advanced NSCLC. This has translated into improved clinical efficacy compared with crizotinib, resulting in a [redacted] reduction in the risk of disease progression or death and providing a substantially longer PFS (median, [redacted] vs 10.8 months). These therapeutic benefits are accompanied by a reduction in lung cancer-specific symptoms and an improvement in HRQoL compared with CT. Ceritinib also offers clinically meaningful benefits over crizotinib in terms of tolerability, including a much lower incidence of grade 3/4 neutropenia and any-grade constipation, oedema and vision disorders. Furthermore, ceritinib is administered once daily, as opposed to the twice-daily administration required for crizotinib. The improved efficacy and safety profile of ceritinib is expected to reduce productivity loss, carer burden, and the impact of disease on the patient's family.

A.16 Budget impact (Section D)

Table 14 summarises the results of the budget impact analysis described in document D.

Table 14 Budget impact

	Company estimate	Cross reference
Number of people in England who would have treatment	[redacted] (from year 2 onwards)	Section D3
Average treatment cost per person	[redacted]	Section D4 table 4
Estimated annual budget impact on the NHS in England	[redacted] (from year 3 onwards)	Section D7 table 7

A.17 Interpretation and conclusions of the evidence

The introduction of ceritinib as an alternative to crizotinib for first-line treatment of ALK+ advanced NSCLC addresses a current unmet need for the management of a group of patients with a poor prognosis in the absence of effective ALK inhibitor therapy. Ceritinib is a highly selective, potent, second-generation ALK inhibitor that has greater affinity and specificity for ALK than crizotinib. The efficacy of ceritinib has been demonstrated in a large, international, open-label phase III trial, ASCEND-4. Results for ASCEND-4 are expected to be generalizable to the anticipated patient population given that the baseline characteristics of enrolled patients were similar to those for patients with diagnosed with ALK+ advanced NSCLC in England and Wales. Furthermore, the trial investigated ceritinib given according to the licenced indication, and the dose adjustments and monitoring employed corresponded to those recommended for ceritinib.[2]

Ceritinib offers significant clinical benefits over crizotinib, including a more prolonged remission and an improved safety profile. Results of a MAIC have shown that, compared to crizotinib, ceritinib significantly reduces the risk of disease progression or death by [redacted]. Ceritinib is also associated with a lower incidence of grade 3/4 neutropenia and any-grade oedema and vision disorders.

These clinical benefits mean ceritinib is associated with an increase in QALYs and LYs compared with crizotinib, and a minimal increase in cost when provided at the list price. The resulting ICER is £27,936 per QALY over a 20-year time horizon for ceritinib at the list price. Sensitivity analyses indicated the ICER is robust to plausible changes in most parameters considered, while a budget impact analysis suggests that the introduction of ceritinib in this indication will result in a net budget impact of approximately [redacted] from year 3 onwards. Thus ceritinib represents a clinically-effective and cost-effective option for NHS England and NHS Wales.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ceritinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer [ID1117]

Document B

Company evidence submission

22nd September 2017

File name	Version	Contains confidential information	Date
ID1117 Ceritinib untreated ALK NSCLC Document B	Final	Yes	22 September 2017

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Abbreviations

1L	first-line
2L	second-line
AEs	adverse events
AIC	Akaike information criterion
ALK	anaplastic lymphoma kinase
ALK+	anaplastic lymphoma kinase-positive
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BIC	Bayesian information criterion
BSA	body surface area
BSC	best supportive care
CAD	Canadian dollar
CEA	cost-effectiveness assessments
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CR	complete response
CSR	clinical study report
CT	chemotherapy
CYP	cytochrome P
DCR	disease control rate
DOIR	duration of intracranial response
DOR	duration of response
DVLA	Driver and Vehicle Licensing Agency
DSA	deterministic sensitivity analysis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFR	epidermal growth factor receptor
EIAED	enzyme-inducing anti-epileptic drugs
eMIT	electronic Market Information Tool
EML4	echinoderm microtubule-associated protein-like 4
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQol Group 5-Dimension questionnaire
ESMO	European Society for Medical Oncology
ESS	effective sample size
FAS	full analysis set
FISH	fluorescence in situ hybridisation
GBP	Great British pound sterling
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GP	general practitioner
HR	hazard ratio
HRQoL	health-related quality of life
ICBR	intracranial clinical benefit rate
ICER	incremental cost-effectiveness ratio
IDCR	intracranial disease control rate

IHC	immunohistochemistry
IQR	interquartile range
ITT	intention-to-treat
JAK/STAT	janus kinase/signal transducer and activator of transcription
LCSS	Lung Cancer Symptom Scale
LS	least squares
LY	life-year
LYG	life-year gained
MAIC	matching-adjusted indirect comparison
MEK	mitogen-activated protein kinase/extracellular signal-regulated kinase
MIMS	Monthly Index of Medical Specialties
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
N/A	not applicable
NCRNPD	non-complete response/non-progressive disease
NE	not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reported
NS	not significant
NSAIDs	non-steroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
OIRR	overall intracranial response rate
ORR	objective response rate
ORR	overall response rate
OS	overall survival
PAP	patient assistance program
PAS	patient access scheme
PbR	payment by results
PD	progressive disease
PEM	pemetrexed
PF	progression-free
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PPIs	proton pump inhibitors
PPS	per-protocol set
PR	partial response
PROs	patient-reported outcomes
PS	performance status
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QLQ-C30	Quality-of-Life Core Questionnaire
QLQ-LC13	Quality-of-Life Lung Cancer Specific Questionnaire
qRT-PCR	quantitative real-time reverse transcription polymerase chain reaction
RAF	rapidly accelerated fibrosarcoma
RAS	rat sarcoma
RCT	randomised controlled trial
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SmPC	summary of product characteristics
SOD	sum of diameters

TK	tyrosine kinase
TKIs	tyrosine kinase inhibitors
ToT	time on treatment
TTR	time to response
ULN	upper limit of normal
USD	United States dollar
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization

B 1. Decision problem, description of the technology and clinical care pathway

B 1.1 Decision problem

Ceritinib is currently approved and recommended by NICE for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive (ALK+) advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.[1,2] This submission relates to the extension of the indication for ceritinib to include first-line treatment of adult patients with ALK+ advanced NSCLC. The submission covers the full marketing authorisation for this first-line indication. Table 1 summarises the decision problem considered in this submission.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated ALK+ advanced NSCLC	People with untreated ALK+ advanced NSCLC	
Intervention	Ceritinib	Ceritinib	
Comparator(s)	• Crizotinib • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) and with or without pemetrexed maintenance treatment	Crizotinib	Crizotinib is now the standard of care for first-line treatment of ALK+ advanced NSCLC. Clinical expert opinion suggests that > 90% of these patients would be treated with crizotinib in England and Wales.[3]
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	
Economic analysis		Cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year gained. The time horizon of the model is 20 years, which is sufficient for this patient population to reflect any differences in costs or outcomes	

		between the technologies being compared. Costs have been considered from an NHS and Personal Social Services perspective.	
Special considerations including issues related to equity or equality		ALK testing will not be included in the analysis.	ALK testing is currently performed routinely in this group of patients due to the availability of crizotinib as a first-line ALK inhibitor.

ALK+, anaplastic lymphoma kinase-positive; NSCLC, non-small cell lung cancer

B 1.2 Description of the technology being appraised

Table 2 summarises the mechanism of action, method of administration and status of the marketing authorisation for ceritinib as a first-line treatment for adult patients with ALK+ advanced NSCLC.

Table 2 Ceritinib for first-line treatment of ALK+ advanced NSCLC

UK approved name and brand name	Zykadia®; ceritinib[1]
Mechanism of action	Ceritinib is a highly selective, potent, second-generation TK inhibitor of ALK, a protein involved in regulation of the RAS and JAK/STAT signalling pathways. ALK is a TK receptor protein. Under normal conditions, ALK is only activated in response to ligand binding, which induces dimerisation and, in turn, autophosphorylation. Activated ALK phosphorylates downstream signalling proteins in the RAS and JAK/STAT signalling pathways, leading to cell growth and proliferation, promoting angiogenesis and decreasing apoptosis.[1,4] ALK+ tumours have rearrangements of the *ALK* gene, which result in constitutive activation of the ALK protein.[5,6] In the majority of ALK+ NSCLCs, a somatic gene rearrangement generates an EML4-ALK fusion protein that contains the N-terminal domain of EML4 fused to the C-terminal domain of ALK.[1,6-10] Constitutive activation of the ALK protein results in aberrant downstream signalling of the RAS and JAK/STAT pathways, leading to uncontrolled proliferation. Ceritinib specifically targets the ALK protein, competing with adenosine triphosphate for binding to the active site. Ceritinib thus directly inhibits autophosphorylation of ALK and its subsequent activation thus, in turn, inhibiting ALK-mediated phosphorylation and activation of the downstream regulatory proteins in the signalling pathways. In this way, in ALK+ NSCLC, ceritinib inhibits signalling pathways that would otherwise

	promote cell proliferation.[7,11,12] Ceritinib is a second-generation ALK inhibitor that has greater affinity and specificity for ALK than the first-generation ALK inhibitor, crizotinib. Ceritinib has been shown to overcome resistance to crizotinib in preclinical and clinical (phase 1) studies,[1,13,14] and has demonstrated superior efficacy to crizotinib as a first-line therapy for ALK+ NSCLC (as described in section B 2.6).
Marketing authorisation/CE mark status	Marketing authorisation for ceritinib as a first-line treatment option for adult patients with ALK+ advanced NSCLC was received on 26 June 2017. Ceritinib received marketing authorisation on 6 May 2015 as a second-line treatment for adult patients with ALK+ advanced NSCLC previously treated with crizotinib.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication (in relation to this submission) is the first-line treatment of adult patients with ALK+ advanced NSCLC.
Method of administration and dosage	Ceritinib is an oral therapy, taken once daily continuously. The capsules must be taken on an empty stomach and no food should be eaten for at least 2 hours before and 2 hours after the dose is taken.[1] The recommended dose of ceritinib is 750 mg (5 x 150 mg capsules) and therapy should be continued for as long as clinical benefit is observed.[1] Dose reductions may be required due to adverse reactions, and should be achieved using decrements of 150 mg daily. Approximately 68% of patients initiating treatment at the recommended dose of 750 mg required at least one dose adjustment due to adverse reactions, with a median time to first dose reduction of approximately 9 weeks.[15] Ceritinib is formulated as hard gelatine oral capsules, to be swallowed whole.
Additional tests or investigations	Identification of the specific ALK+ NSCLC patient population in whom first-line ceritinib is indicated requires genetic testing. This testing is currently recommended for all patients with advanced NSCLC to determine eligibility for therapy with an ALK inhibitor (see section B 1.3.4).[16] Thus, no additional tests over and above current clinical practice are required for selection of patients to receive first-line therapy with ceritinib. Recommended monitoring during treatment with ceritinib is largely the same as that recommended for first-line crizotinib in this patient population, and includes:[1] • Liver laboratory tests (including ALT, AST and total bilirubin) prior to the start of treatment, every 2 weeks for the first month and monthly thereafter • Monitoring for gastrointestinal toxicity and for pulmonary symptoms indicative of pneumonitis

	• Periodic monitoring of ECG and electrolytes, heart rate and blood pressure • Monitoring fasting plasma glucose prior to treatment and periodically thereafter • Monitoring of lipase and/or amylase prior to treatment and thereafter as clinically indicated Use of ceritinib in the first-line treatment of adult patients with ALK+ advanced NSCLC will not adversely impact or alter the current infrastructure and service provision requirements, and is not expected to increase resource use. This reflects the fact that: • Currently, the majority of patients with ALK+ advanced NSCLC receive crizotinib. The tests for identifying these eligible patients and the monitoring required during therapy are largely the same as for ceritinib (although full blood counts and monitoring for renal function are additionally recommended during therapy with crizotinib[17]) • Interventions for the management of gastrointestinal adverse events (e.g. anti-emetics and anti-diarrhoeals) are likely to be comparable for ceritinib and crizotinib
List price and average cost of a course of treatment	The list price is £4,923.45 for a 30-day supply, and this is the price agreed with the Department of Health for 3 packs of 50 x 150 mg capsules each.
Patient access scheme (if applicable)	A confidential simple discount PAS of [redacted] is currently in place.

ALK, anaplastic lymphoma kinase; ALK+, anaplastic lymphoma kinase-positive; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHMP, Committee for Medicinal Products for Human Use; ECG, electrocardiogram; EML4, echinoderm microtubule-associated protein-like 4; JAK/STAT, janus kinase/signal transducer and activator of transcription; NSCLC, non-small cell lung cancer; PAS, patient access scheme; RAS, rat sarcoma; TK, tyrosine kinase

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

B 1.3.1 Disease overview and pathogenesis

Lung cancer is the most common cancer in the world and the second most common cancer in the UK, after breast cancer in women and prostate cancer in men.[18] In both men and women, lung cancer is the most common cause of cancer-related mortality in the UK.[18,19] Most lung cancers (80-90%) are NSCLC; the National Lung Cancer Audit for 2015 recorded 38,269 cases of lung cancer (all types) in England and Wales, and reported that 88% of these cases were NSCLC.[19] NSCLC can be further subdivided into three histological subtypes: squamous cell carcinoma (25-30%), adenocarcinomas (~40%) and large cell undifferentiated carcinoma (10-15%).[20,21] The last two categories are grouped together as non-squamous NSCLC. Approximately 75% of patients are diagnosed with advanced disease (i.e. stage III/IV).[22]

Patients with ALK+ NSCLC are a unique lung cancer subpopulation

Patients with ALK+ NSCLC are a unique subpopulation, estimated to represent around 2-7% of all NSCLC,[23,24] and these tumours are almost exclusively non-squamous.[23] For England and Wales, this corresponds to approximately 466 patients (Table 3). ALK positivity and other genetic mutations (e.g. mutations in the endothelial growth factor receptor [EGFR] tyrosine kinase [TK]) tend to be mutually exclusive, except in a few rare cases.[12,25-28] Therefore, patients with ALK+ tumours do not benefit from treatment with EGFR TK inhibitors (TKIs) and vice versa,[24,26] and the absence of other oncogenic drivers in ALK+ lung cancers is consistent with the idea that ALK rearrangement defines a unique molecular subset of NSCLC.[29-31] Patients diagnosed with an EGFR mutation are therefore a separate molecular subgroup of NSCLC and they are not relevant to this submission.

Table 3 Estimate of the number of patients in England and Wales diagnosed with ALK+ advanced NSCLC

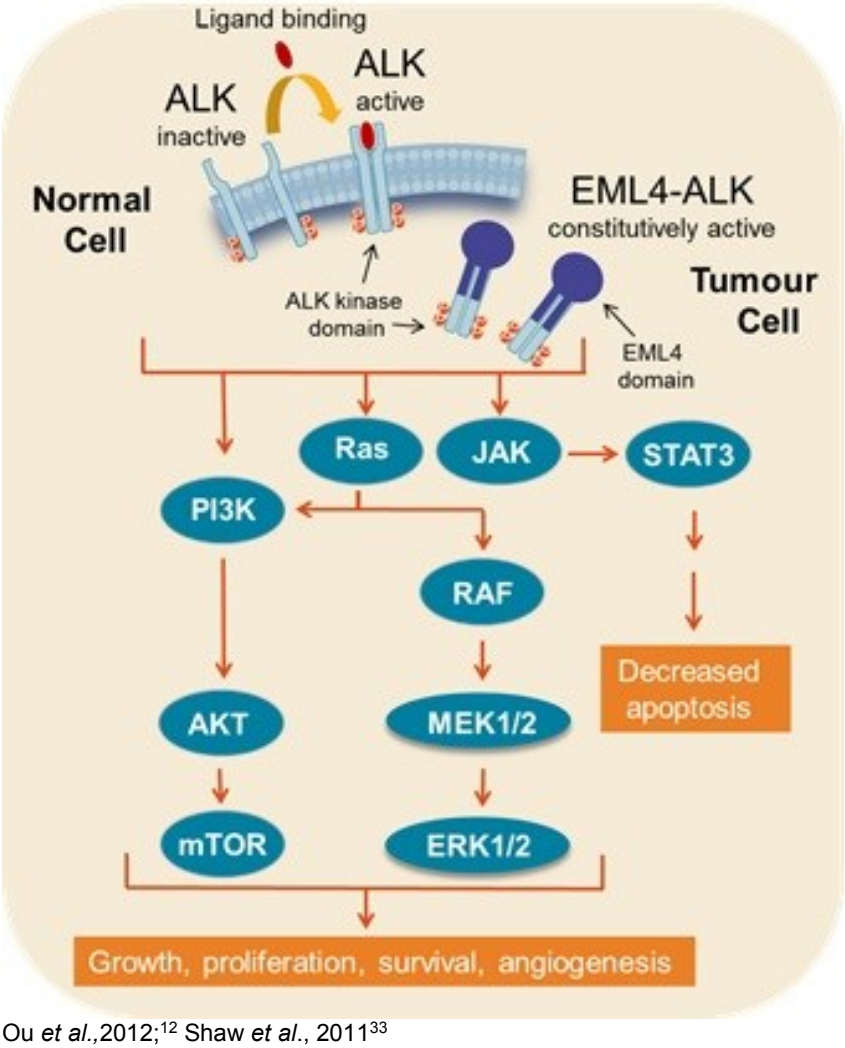
	Proportion, %	Number of patients
Annual number of lung cancer cases in England and Wales[19]	-	38,269
Patients presenting with NSCLC[19]	88	33,677
Patients diagnosed at stage III/IV[22]	74	24.921
Patients with non-squamous histology[20,21]	55	13706
Patients with ALK+ advanced NSCLC[32]	3.4	466

EML4-ALK is a key driver of tumourigenesis in NSCLC

Study of *ALK* mutations has shown that the *ALK* gene can be aberrantly activated by mutation, gene amplification or chromosomal rearrangement, leading to the expression of a potent oncogenic

driver.[14] ALK rearrangements result from the fusion of so-called end partners, such as echinoderm microtubule-associated protein-like 4 (EML4), to the intracellular TK domain of the ALK protein, leading to aberrant expression of the ALK fusion protein in the cytoplasm (rather than on the cell membrane).[6,11] In addition, the domains in the partner proteins promote dimerisation and oligomerisation of the fusion proteins, leading to constitutive activation of the ALK kinase, and of downstream signalling pathways.[6,11] This results in cell transformation and tumourigenesis (Figure 1).[5,12,33] *EML4* is the most common ALK fusion partner in lung cancer, and the fusion oncogene *EML4-ALK* defines a molecular subset of NSCLC with distinct clinical and pathological features.[11,26]

Figure 1 Activation of signalling pathways by constitutively activated ALK



Ou *et al.,*2012;[12] Shaw *et al*., 2011[33]
ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; JAK, janus kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; STAT, signal transducer and activator of transcription

Patients with ALK+ NSCLC are generally younger than other patients diagnosed with NSCLC, and most have adenocarcinomas

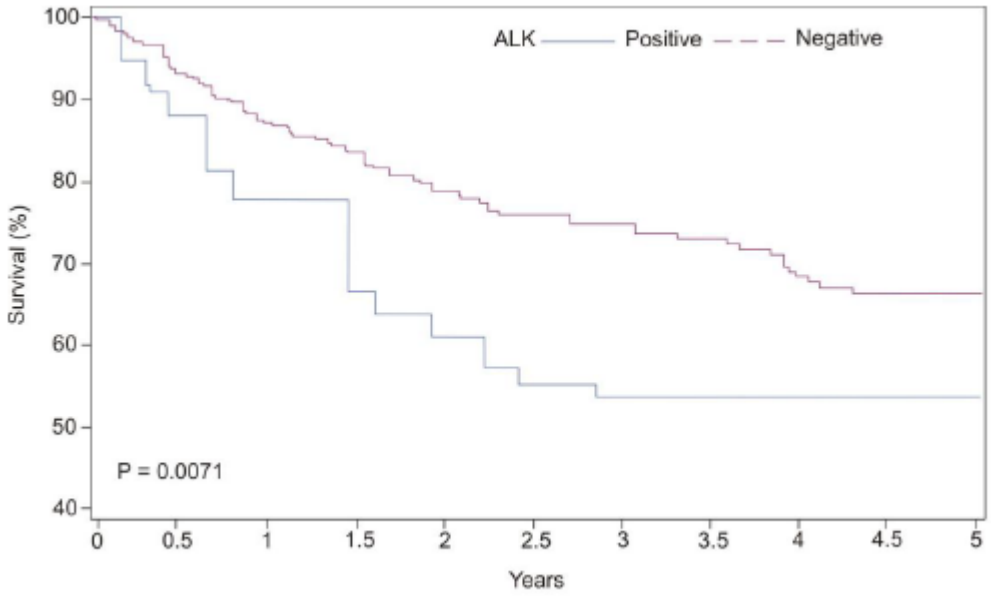
Most patients with ALK-rearranged NSCLC are younger than other subgroups of NSCLC patients, often being diagnosed in their 50s, rather than their mid-60s.[26,34] Furthermore, the majority of ALK+ patients have never smoked (or have a light smoking history), and the tumours generally have adenocarcinoma histology.[5,26,34,35] In addition to these distinct clinical and pathological features, data from Europe show that most patients with NSCLC (>70%) present with advanced disease (stage IIIB or IV),[20] and a meta-analysis of studies defining the characteristics of ALK+ NSCLC further confirms that ALK+ disease is predominantly observed in patients diagnosed at an advanced clinical stage.[28] Testing for ALK rearrangements is now recommended for all patients with advanced non-squamous NSCLC, given the availability of specific targeted therapies for ALK+ tumours.[16]

B 1.3.2 Prognosis and survival

ALK+ NSCLC has a poor prognosis, but this is being transformed by the introduction of ALK inhibitors

As stated above, most patients with ALK+ NSCLC are diagnosed at an advanced stage of disease, for which prognosis is poor. The 5-year survival for NSCLC drops precipitously as disease stage progresses. Cancer Research UK notes that 5-year survival in NSCLC is between 7% and 24% for patients with stage III disease, and between 2% and 13% for those patients with stage IV disease.[36] Prior to the introduction of ALK inhibitors, the outcome for patients with ALK+ was less favourable than for patients with ALK-negative disease.[23] For example, one study reported that the risk of disease progression at 5 years was at least two-fold higher in patients with ALK+ versus ALK-negative disease (Figure 2).[35]

Figure 2 Progression free survival in patients with and without ALK+ NSCLC (untreated with ALK inhibitors)



Yang et al., 2012[35]
ALK, anaplastic lymphoma kinase-positive

However, the advent of ALK inhibitors has considerably improved the outlook for patients with ALK+ disease. While the published overall survival (OS) data from the pivotal phase III trial for crizotinib (the only ALK+ inhibitor therapy currently reimbursed in the UK) are immature, a median OS of 21.7 months and mean of 29.0 months have been estimated for crizotinib, based on the results of the PROFILE 1014 trial.[37] This value is further supported by the results from a real-world study of crizotinib, which reported a median OS of 24 months.[37]

Although the introduction of crizotinib has improved the outlook for patients with ALK+ NSCLC, approximately a quarter of patients failed to respond to crizotinib in the phase III trial. Furthermore, intracranial disease control is poor, with many patients developing brain metastases during therapy with crizotinib.[38,39] One study reported that among the patients without brain metastases at baseline who developed progressive disease (n=253), 20% developed brain metastases during therapy with crizotinib.[40] Of particular concern is the observation that OS may be shorter in patients who develop brain metastases while receiving crizotinib, compared with those who had brain metastases before starting the drug.[41] Other studies have shown that progression-free survival (PFS) is significantly shorter in patients with brain metastases at initiation of therapy.[42-44]

B 1.3.3 Effects of ALK+ advanced NSCLC on patients and carers

ALK+ advanced NSCLC is associated with a high symptom burden

In addition to the significant mortality associated with ALK+ NSCLC, patients experience a high symptom burden, as they are often diagnosed when the disease is already advanced and they may have metastases.[20] The presenting symptoms of ALK+ advanced NSCLC are similar to those in any NSCLC patient, although the type of symptoms may vary according to the extent of tumour metastases.[45] Patients with advanced lung cancer typically experience chest-related symptoms including dyspnoea (shortness of breath), cough, haemoptysis (coughing blood), wheezing, hoarseness and pain.[45,46] Fatigue, lack of appetite and psychological distress are also common.[45-48] Indeed, one study has reported that depression and anxiety were each detected in approximately a third of patients with recently diagnosed advanced NSCLC, and both were associated with a decrease in aspects of health-related quality of life (HRQoL).[48] Furthermore, the presence of metastases is often associated with additional non-pulmonary symptoms. For example, patients with bone metastases experience bone pain and fractures, while those with brain metastases suffer neurological symptoms, as described below.

Brain metastases occur in up to 60% of patients with advanced NSCLC, and they are associated with many complications

The brain is one of the most frequent sites of metastases in patients with ALK+ disease, and there is evidence to suggest that brain metastases are more likely to recur or progress in patients with ALK+ NSCLC compared with patients with ALK-negative tumours.[35,40,42,49,50] Data from clinical studies in patients with ALK+ advanced NSCLC suggest that brain metastases may be present at initial diagnosis in 15–35% of patients,[29,51,52] and the incidence can increase to approximately 60% over the course of first-line therapy.[53]

Brain metastases add to the debilitating symptomatic burden of disease. Focal neurological symptoms can include: seizures, numbness, altered sensations, motor weakness, visual disturbances and speech difficulties. Patients may also have general symptoms secondary to raised intracranial pressure such as fatigue, shortness of breath, nausea, vomiting, dull non-throbbing headache and pain.[54] Furthermore, the incidence of symptoms such as fatigue, headache and depression has been reported to more than double following the development of brain metastases in patients with ALK+ NSCLC.[54] A further concern for these patients is the legal requirement to report a diagnosis of brain metastases to the Driver and Vehicle Licensing Agency (DVLA) for consideration of suspension or withdrawal of a licence.[55] Thus, the presence of brain metastases can have a significant impact on many aspects of a patient's everyday functioning, and the poor prognosis associated with these metastases in ALK+ NSCLC further exacerbates their diminished HRQoL.[56]

Advanced NSCLC exacts a heavy burden on caregivers

Caregivers often support lung cancer patients in managing multiple symptoms and in dealing with the patient's changing nutritional needs as the disease advances and function declines. The caregiver burden in NSCLC can result in deterioration in carer psychological well-being and overall HRQoL over time. For example, a study assessing psychological distress and HRQoL in caregivers of patients with NSCLC found that caregivers experienced high levels of burden related to patients' subjective demands and these increased significantly over time.[57] As symptoms became more severe, the costs of carer time also increased.[58]

Direct medical costs associated with the management of lung cancer include those related to hospitalisation, A&E attendance and outpatient visits, as well as treatment costs.[59] Within Europe, the healthcare burden attributed to lung cancer accounts for 15% of overall cancer cost according to an analysis performed in 2009.[60]

B 1.3.4 Clinical pathway and current guidelines

Mutation testing has allowed a paradigm shift in the management of advanced NSCLC

There has been a major paradigm shift in the treatment of advanced NSCLC, first established with the discovery of EGFR mutations sensitive to TKIs and, more recently, with the discovery of NSCLC ALK translocations sensitive to ALK inhibitors.[6] As a result, molecular subtyping is considered an important component of the NSCLC diagnostic process and is essential to guide personalised treatment of advanced NSCLC.[16] The current European Society for Medical Oncology (ESMO) guidelines on the diagnosis, treatment and follow-up of metastatic NSCLC recommend ALK testing in patients with NSCLC using fluorescence in situ hybridisation or immunohistochemistry.[16] In the UK, The Royal College of Pathologists has also suggested a pathway for NSCLC that encompasses testing for ALK positivity.[61]

The management of NSCLC in the UK follows National Institute for Health and Care Excellence (NICE) and ESMO guidance

The management of patients with advanced NSCLC in clinical practice in the UK follows the guidelines and recommendations of NICE and ESMO.[16,62]

For Stage III or IV NSCLC, NICE Clinical Guideline 121 recommends crizotinib for untreated ALK+ advanced NSCLC in adult patients, based on the agreed patient access scheme (PAS).[62] Options for previously treated ALK+ advanced NSCLC are: crizotinib, and ceritinib for adults who have previously received crizotinib.

Current ESMO guidelines on the management of NSCLC broadly concur with NICE guidance and recommend that patients with ALK+ advanced NSCLC should receive crizotinib first-line, with ceritinib

and alectinib being recommended for patients who progress or who are intolerant of crizotinib, including for patients with intracranial progression on crizotinib.[15]

Local radiotherapy can be used to treat brain metastases.[16] However, results recently reported from the QUARTZ trial, performed in centres in the UK and Australia, suggest that radiotherapy does not improve OS or HRQoL over best supportive care.[63] Expert UK clinical opinion clearly takes account of this trial and suggests that radiotherapy may now only be given to approximately 15% of patients with brain metastases.[3]

Current treatment options for ALK+ NSCLC are limited

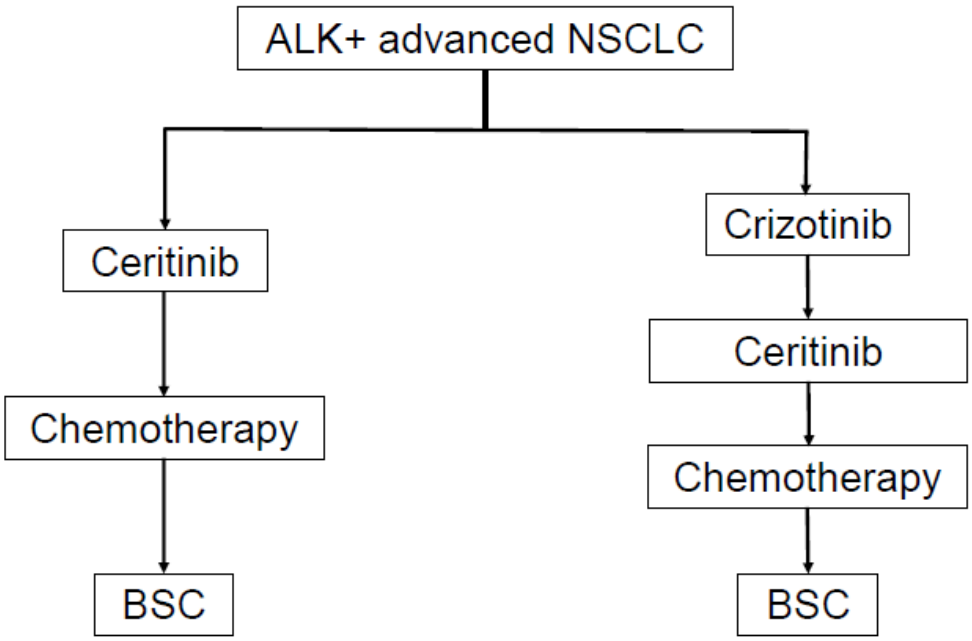
The current options for untreated patients with ALK+ advanced NSCLC remain limited. Available data from randomised controlled trials (RCTs) suggest that chemotherapy (CT) regimens have limited benefit as first-line treatment for advanced NSCLC, including ALK+ NSCLC, with a reported median PFS of around 4–8 months[64-66] (compared with 2.8 months for placebo[65]) and a reported OS for CT of between 10 and 26 months.[64-68] CT has therefore been superseded by crizotinib, which is the currently recommended treatment option for patients with newly diagnosed ALK+ NSCLC. According to medical expert opinion, over 90% of eligible patients in England and Wales currently receive crizotinib in the first-line setting. However, despite initial responses to crizotinib, the majority of patients relapse within 12 months, and PFS is shorter in patients with brain metastases, as reported in the pivotal trial comparing crizotinib and CT (PROFILE 1014).[39,42]

B 1.3.5 The place of ceritinib in the treatment pathway for ALK+ advanced NSCLC

Ceritinib targets key oncogenic drivers of ALK+ NSCLC with improved potency and central nervous system (CNS) penetration compared with crizotinib

Ceritinib is a next-generation ALK inhibitor therapy that extends the armamentarium available for treating ALK+ NSCLC by providing a new first-line therapeutic option.[13,66] Thus, it is envisaged that ceritinib would be an alternative first-line option to crizotinib (Figure 3). Following disease progression, patients receiving first-line ceritinib would then progress to CT, followed by best supportive care (BSC). Of note, crizotinib is not appropriate following ceritinib, as confirmed by clinical experts, as mutations that lead to resistance to second-generation ALK inhibitors confer an increased risk of resistance to crizotinib as a first-generation ALK inhibitor.[69] Currently, patients receiving crizotinib as first-line therapy receive ceritinib as second-line therapy, followed by chemotherapy and then BSC.

Figure 3 Place of ceritinib in the treatment of ALK+ NSCLC



ALK+, anaplastic lymphoma kinase-positive; BSC, best supportive care

Ceritinib as a second-generation ALK inhibitor offers a number of advantages over crizotinib. Ceritinib has a higher potency than crizotinib, having a 20-times greater target affinity for the ALK protein, with a half maximal inhibitory concentration of 0.15 nM compared with 3 nM for crizotinib.[13] Ceritinib also has greater specificity for binding and inhibition of the ALK protein compared with crizotinib.[13] These differences can be expected to translate into improved efficacy for ceritinib compared with crizotinib, as is observed from a PFS comparison reported for the pivotal phase III trials for both drugs (see section B 2.9). Furthermore, ceritinib effectively crosses the blood brain barrier.[1,66] This is an important innovation, since penetration of crizotinib into the cerebrospinal fluid is negligible, and the CNS remains one of the prominent sites for tumour progression during crizotinib treatment.[39,40,42] Indeed, the ESMO guidelines describe this pharmacological limitation of crizotinib as extremely relevant in treatment decisions, given the high propensity of ALK-rearranged NSCLC to metastasise to the brain.[16] In addition, ceritinib is an oral, once daily therapy, offering a simpler dosing regimen than twice-daily crizotinib therapy.

B 1.4 Equality considerations

The introduction of ceritinib is not anticipated to raise any equality issues. There is nothing in the profile of ceritinib, or regarding its first-line indication for ALK+ advanced NSCLC, to suggest the exclusion of anyone protected by the NICE equality legislation within this indication. There are no issues that would make it more difficult in practice for a specific group to access the technology, or

that could lead to recommendations that have an adverse impact on people with a particular disability or disabilities. Furthermore, no equality issues were raised when considering crizotinib in this indication.[70]

B 2. Clinical effectiveness

Summary of Clinical Evidence

The clinical effectiveness of ceritinib in patients with ALK+ NSCLC, untreated with any systemic anti-cancer therapy (except neoadjuvant or adjuvant therapy), has been established in a multicentre, randomised, open-label, phase III study (ASCEND-4) comparing ceritinib versus CT (cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance therapy). Data are reported for a median duration of follow-up of 19.7 months (data cut off, June 2016).

Primary outcome – PFS

- The study met its primary endpoint (PFS), demonstrating a significant improvement in median PFS for ceritinib over CT (hazard ratio [HR] 0.55; p<0.00001)
- Median PFS was 16.6 months in patients receiving ceritinib (vs. 8.1 months for CT) and estimated 24-month PFS was 47.6% for ceritinib (vs. 18.6% for CT)
- The improvement in PFS achieved with ceritinib over CT was observed across most patient subgroups considered, including demographics and clinical presentation
- Median PFS in patients receiving ceritinib was greater in patients without brain metastases at baseline compared with those with brain metastases (26.3 vs. 10.7 months)

Key secondary outcome – OS

- OS data were immature at the time of data cut-off, and thus the study is ongoing
- At the time of the data cut-off, 48 (25.4%) patients in the ceritinib group had died; 2-year OS was estimated at 70.6% (vs. 58.2% for CT)

Other secondary outcomes – tumour response, symptoms and HRQoL

- An overall response rate of 72.5% was achieved with ceritinib (vs. 26.7% for CT)
- The median time to first response was 6.1 weeks in the ceritinib group (vs. 13.4 months in the CT group), and the median duration of response in patients with a confirmed complete response or partial response was 23.9 months (vs. 11.1 months for CT)
- Ceritinib prolonged the time to definitive deterioration in lung cancer specific symptoms (pain, cough and dyspnoea) compared with CT, with the median time to definitive deterioration being 24 months according to the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life lung cancer module (QLQ-LC13); it was not reached according to the Lung Cancer Symptom Scale
- Ceritinib was associated with an improved HRQoL compared with CT, as evident from the least square mean utility score of 0.81 vs. 0.77 (p < 0.001)

Safety

- The safety profile for ceritinib was consistent with that previously observed in studies in patients with ALK+ NSCLC
- All patients receiving ceritinib experienced adverse events (AEs); grade 3/4 AEs related to ceritinib were seen in 65% of patients
- Most AEs were grade 1/2 in severity. The most commonly observed AEs (any grade, ≥35% of patients) suspected to be related to the study drug were elevation of liver enzymes, diarrhoea, nausea and vomiting
- Elevated liver enzymes were the most frequently reported treatment-related grade 3/4 AEs, reported in ≥15% of patients; all other grade 3/4 AEs related to treatment were reported in ≤5% of patients
- Most of the AEs were managed by dose adjustment or interruptions, which were required in 68% and 78% of the patients, respectively. Only 5% of patients discontinued ceritinib due to AEs suspected to be related to treatment

B 2.1 Identification and selection of relevant studies

The systematic literature review used to identify relevant studies reporting the effectiveness of ceritinib as a first-line treatment for ALK+ NSCLC is described in Appendix D 1.1 and D 1.2.

B 2.2 List of relevant clinical effectiveness evidence

One relevant phase III RCT, the ASCEND-4 trial, was identified (Table 4).

Table 4 Overview of the relevant RCT, ASCEND-4

Study	**ASCEND 4, NCT01828099, CLDK378A2301, Soria *et al*., 2017**				
Study design	Phase III open-label RCT				
Population	Untreated adult patients with stage IIIB/IV ALK+ NSCLC				
Intervention(s)	Ceritinib				
Comparator(s)	Platinum-based chemotherapy, i.e. cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance therapy				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	Efficacy data for ceritinib from ASCEND-4 are used in the model, as this study provides relevant data for ceritinib in the patient population of interest.				
Reported outcomes specified in the decision problem	Primary outcome: PFS Key secondary outcome: OS Other outcomes: response rate, safety and HRQoL				
All other reported outcomes	Other secondary outcomes: PFS (local assessment), ORR, DOR, DCR, TTR, OIRR, IDCR, DOIR, PRO: EORTC QLQ-C30, QLQ-LC13, LCSS, EQ-5D and safety				

Soria *et al.,* 2017[66]
ALK+, anaplastic lymphoma kinase-positive; DCR, disease control rate; DOIR, duration of intracranial response; DOR, duration of response; EORTC-QLQ, European Organisation for Research and Treatment of Cancer core Quality of Life questionnaire; HRQoL, health-related quality of life; IDCR, intracranial disease control rate; LCSS, lung cancer symptom scale; NSCLC, non-small cell lung cancer; OIRR, overall intracranial response rate; ORR, objective overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcomes; QLQ-LC13, lung cancer specific questionnaire; TTR, time to response

B 2.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of the methodology of the phase III RCT, ASCEND-4, is given in Table 5 and the following sections provide a detailed description of the study design and methodology. ASCEND-4 was a multicentre, randomised, open-label, phase III study conducted in 134 sites across 28 countries including seven sites in the UK.[15,66,71] This trial assessed the efficacy and safety of ceritinib versus platinum-based CT in patients with advanced non-squamous ALK+ NSCLC, untreated with any systemic anti-cancer therapy (except neoadjuvant or adjuvant therapy). Results have been reported for the primary endpoint, PFS, the key secondary endpoint, OS, and a number of other secondary

endpoints including response rates and patient reported outcomes (PROs). Safety data are also reported.

Table 5 Summary of methodology for ASCEND-4

Trial number (acronym)	**NCT01828099, CLDK378A2301 (ASCEND–4)**
Location	Multinational (134 sites in 28 countries: Australia, New Zealand, Austria, Brazil, China, Colombia, Denmark, France, Germany, Greece, India, Ireland, Italy, Japan, South Korea, Lebanon, Mexico, Netherlands, Norway, Portugal, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, and UK)
Trial design	Randomised, open-label phase III trial
Eligibility criteria for participants	Inclusion criteria: • Adult patients with a histologically or cytologically confirmed diagnosis of non-squamous NSCLC that is ALK+ as assessed by the Ventana immunohistochemistry test • Newly diagnosed stage IIIB or stage IV NSCLC, or relapsed locally advanced or metastatic NSCLC, not previously treated with any systemic anti-cancer therapy (e.g. cytotoxic drugs, monoclonal antibody therapy, crizotinib or other ALK inhibitors, or other targeted therapies, either experimental or not), with the exception of neoadjuvant or adjuvant therapy. Patients who had received previous neoadjuvant or adjuvant systemic therapy were eligible for enrolment only if relapse had occurred more than 12 months from the end of the systemic therapy • Measurable disease as per RECIST 1.1 criteria • WHO performance status 0–2 • Asymptomatic or neurologically stable brain metastases (for ≥2 weeks) • In patients who had received previous radiotherapy to the brain, radiotherapy must have been completed at least 2 weeks prior to commencing ceritinib • Life expectancy ≥12 weeks • The following criteria were to be met at the screening visit: ▪ WBC count ≥4.0×10^9/L ▪ Absolute neutrophil count ≥1.5×10^9/L ▪ Platelets ≥100×10^9/L ▪ Haemoglobin ≥9 g/dL ▪ Serum creatinine <1.5 mg/dL and/or calculated creatinine clearance (using Cockcroft–Gault formula) ≥50 mL/min ▪ Total bilirubin <1.5×ULN, except for patients with Gilbert's syndrome, who were included only if total bilirubin <3.0×ULN or direct bilirubin <1.5×ULN ▪ AST<2.5×ULN, except for patients with liver metastasis, who were included only if AST <5×ULN ▪ ALT<2.5×ULN, except for patients with liver metastasis, who were included only if ALT<5×ULN ▪ Alkaline phosphatase <5.0×ULN ▪ Serum amylase ≤2×ULN ▪ Serum lipase ≤ ULN ▪ Fasting plasma glucose ≤175 mg/dL (≤9.8 mmol/L) • The following laboratory parameters were to be within normal limits or corrected to within normal limits with supplements during screening: potassium, magnesium, phosphorus and total calcium (corrected for serum albumin)

Trial number (acronym)	NCT01828099, CLDK378A2301 (ASCEND–4)
	Exclusion criteria: • Patients with known hypersensitivity to ceritinib, platinum-containing drugs, pemetrexed, or any known excipients of these drugs • History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis • History of carcinomatous meningitis • A concurrent malignancy or history of a malignant disease diagnosed or requiring therapy within the previous 3 years[a] • Patients with symptomatic CNS metastases who were neurologically unstable or had required increasing doses of steroids within the 2 weeks prior to screening to manage CNS symptoms • Patients who had received thoracic radiotherapy to lung fields ≤4 weeks before starting the study treatment, or who had not recovered from radiotherapy-related toxicities • Patients who had undergone major surgery ≤4 weeks before starting study treatment (≤2 weeks for resection of brain metastases), or had not recovered from the side effects of these procedures • Clinically significant, uncontrolled heart disease and/or a recent cardiac event (within 6 months) • Impairment of GI function or GI disease that could significantly alter the absorption of ceritinib • Patients treated with medications that met one of the following criteria and that could not be discontinued at least 1 week prior to the start of treatment with ceritinib and for the duration of the study: ▪ Strong inhibitors or strong inducers of CYP3A4/5 ▪ Medications with a low therapeutic index that are primarily metabolised by CYP3A4/5 or CYP2C9 ▪ Medications with a known risk of prolonging the QT interval, or inducing Torsades de Pointes • Patients who had received unstable or increasing doses of corticosteroids. If patients were receiving corticosteroids for endocrine deficiencies or tumour-associated symptoms (non-CNS), the dose was to be stabilised (or decreased) for at least 5 days before the first dose of study treatment • Patients treated with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants • Patients treated with any enzyme-inducing anticonvulsant that could not be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients receiving non-enzyme-inducing anticonvulsants were eligible • Pregnant or nursing (lactating) women and women of child-bearing potential, unless using highly effective contraception during the study and for 3 months after stopping ceritinib treatment (or 6 months after stopping CT) • Sexually active men were required to use a condom during intercourse while taking the drug, and for 3 months after the last dose of ceritinib treatment • History of pancreatitis, or history of increased amylase or lipase relating to pancreatic disease • Any other severe (acute or chronic) medical or psychiatric conditions, or laboratory abnormalities that might increase the risk associated with study participation, or that may interfere with the interpretation of study results
Settings and locations where	Tertiary care

Trial number (acronym)	NCT01828099, CLDK378A2301 (ASCEND–4)
the data were collected	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	• Ceritinib group (n=189): ceritinib 750 mg administered orally once daily (and continuously) in a fasted state • Chemotherapy group (n=187): pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or (based on investigator's choice) carboplatin (AUC 5–6), administered every 21 days. Patients who completed 4 cycles of treatment (induction) without progressive disease subsequently received pemetrexed as single-agent maintenance every 21 days • Patients in the chemotherapy group in the treatment and post-treatment follow-up phases were allowed to cross over to ceritinib after centrally confirmed, RECIST-defined progressive disease
Permitted and disallowed concomitant medications	Permitted concomitant medications/treatments • Stable doses of corticosteroid therapy (such as dexamethasone and prednisone) and topical, inhaled or intra-ocular corticosteroid therapies (e.g. for rash, obstructive airways disease or eye conditions) • Gastric protective agents, including antacids, H_2-receptor antagonists, and proton pump inhibitors • Bisphosphonates, palliative radiotherapy, and surgery • Non-enzyme-inducing anti-epileptic medication Concomitant medications requiring caution • NSAIDs with short elimination half-lives (e.g. diclofenac or indomethacin) were to be avoided for a period of 2 days before, the day of, and 2 days following administration of pemetrexed • Caution was to be exercised in patients receiving carboplatin or cisplatin and aminoglycosides, especially with other nephrotoxic drugs Prohibited concomitant medications • Warfarin sodium and coumarin derivatives, EIAEDs, strong inhibitors and inducers of CYP3A4/5, and CYP2C9 and CYP3A4/5 substrates with a narrow therapeutic index • Drugs known to have a high risk of increasing the QTc interval and drugs known to increase the QTc interval that are also primarily metabolised by CYP3A4/5
Primary outcomes (including scoring methods and timings of assessments)	• Median PFS, defined as the time from the date of randomisation to the date of the first radiologically documented disease progression per central review, or death due to any cause, was the primary outcome • Tumour assessments for response/progression determination were to be performed by computed tomography scan or MRI of the chest and abdomen at baseline and then every 6 weeks (2 cycles) after day 1 cycle 1 to month 33, and then every 9 weeks (3 cycles) thereafter. A final scan was required at the end of treatment • RECIST 1.1 criteria were used to assess response, and responses were to be confirmed within 4 weeks of the initial observation of a response
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	Key secondary objective: OS, defined as the time from date of randomisation to date of death due to any cause Other secondary endpoints[b]: • PFS (local assessment) • ORR • DOR • DCR

Trial number (acronym)	NCT01828099, CLDK378A2301 (ASCEND–4)
	• TTR • OIRR • IDCR • DOIR • PROs: EORTC QLQ-C30, QLQ-LC13, LCSS, EQ-5D • Safety Tumour responses were assessed by computed tomography scan or MRI as described for the primary efficacy outcome. Computed tomography scans or MRI assessments of the brain were performed at each assessment point for patients with brain metastases. PROs were assessed at the same time points as the tumour assessments
Pre-planned subgroups	Subgroups defined based on baseline characteristics • Geographic area: South America, Europe, Asia Pacific • Age • Gender • Brain metastasis at screening: absence or presence • WHO status: 0 or ≥1 • Race: Asian, Caucasian • Previous adjuvant chemotherapy • Disease burden per central assessment: baseline SOD for target lesions <median SOD for target lesions; baseline SOD for target lesions ≥median SOD for target lesions • Smoking history

Soria *et al*., 2017[66], ASCEND-4 CSR[15]

[a]Exceptions included patients with completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.

[b]For definitions of the outcomes, see section B 2.3.5 and Table 7.

ALK+, anaplastic lymphoma kinase-positive; ALT, alanine transaminase; AST, aspartate transaminase; AUC, area under the concentration time curve in mg/mL.min; CNS, central nervous system; CSR, clinical study report; CT, chemotherapy; CYP, cytochrome P; DCR, disease control rate; DOR, duration of response; DOIR, duration of intracranial response; EIAED, enzyme inducing anti-epileptic drugs; EORTC-QLQX, European Organisation for Research and Treatment of Cancer's core QoL questionnaire; EQ-5D, EuroQol Group 5-Dimension questionnaire; GI, gastrointestinal; IDCR, intracranial disease control rate; LCSS, lung cancer symptom scale; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; NSCLC, non-small cell lung cancer; OIRR, overall intracranial response rate; ORR, objective overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PPIs, proton pump inhibitors; PRO, patient reported outcomes; QLQ-LC13, lung cancer specific questionnaire; RECIST, Response Evaluation Criteria In Solid Tumours; SOD, sum of diameters; TTR, time to response; ULN, upper limit of normal; WBC, white blood cell; WHO, World Health Organization

B 2.3.1 Patients

The study included patients with advanced or metastatic non-squamous ALK+ NSCLC, untreated with systemic therapy (with the exception of adjuvant or neoadjuvant therapy if relapse had occurred at least 12 months after the end of therapy). If present, brain metastases were required to be asymptomatic or neurologically stable. Patients with symptomatic CNS metastases who were neurologically unstable or had required increasing doses of steroids within the two weeks prior to

screening to manage CNS symptoms were excluded. The detailed inclusion and exclusion criteria are listed in Table 5.

B 2.3.2 Baseline patient demographics and clinical characteristics

Patient baseline disease and demographic characteristics are summarised in Table 6, and they were well balanced between the two treatment groups. Overall, the median age of patients was 54 years, and approximately three-quarters of patients (78.5%) were aged <65 years. In both groups there were slightly more women than men (overall, 57.4% were women), approximately half (53.7%) were Caucasian and 42.0% were Asian. Most patients had a World Health Organization (WHO) performance status of ≥1 (63% of both groups). At the time of study entry, the majority of patients in both groups (ceritinib, 95%; CT, 97%) had stage IV disease and approximately one-third (ceritinib, 31%; CT, 33%) had brain metastases. Overall, 36.4% of patients had received at least one prior anti-neoplastic therapy (radiotherapy/surgery/adjuvant or neoadjuvant chemotherapy), and the number of patients who had received prior therapy was well balanced between the two treatment groups. Of those with brain metastases, 24/61 (39.3%) of those in the ceritinib group had received prior radiotherapy, as had 24/60 (40.0%) of the CT group.

Table 6 Characteristics of patients in ASCEND-4 (FAS)

Baseline characteristics	**Ceritinib (n=189)**	**Chemotherapy (n=187)**
Age, median years (range)	55 (22–81)	54 (22–80)
Gender, n (%)		
Female	102 (54)	114 (61)
Male	87 (46)	73 (39)
Race, n (%)		
Asian	76 (40)	82 (44)
Caucasian	104 (55)	98 (52)
Other	9 (5)	7 (4)
WHO performance status, n (%)		
0	69 (37)	70 (37)
1	107 (57)	105 (56)
2	13 (7)	11 (6)
Missing	0 (0)	1 (1)
Smoking history, n (%)		
Current smoker	15 (8)	15 (8)
Ex-smoker	66 (35)	50 (27)
Never smoked	108 (57)	122 (65)
Histology or cytology, n (%)		
Adenocarcinoma	180 (95)	183 (98)
Stage at time of study entry, n (%)		
Locally advanced (stage IIIb)	9 (5)	5 (3)
Metastatic (stage IV)	180 (95)	182 (97)
Metastatic site of cancer, n (%)		
Bone	77 (41)	80 (43)

Baseline characteristics	Ceritinib (n=189)	Chemotherapy (n=187)
Brain	59 (31)	62 (33)
Liver	34 (18)	39 (21)
Previous antineoplastic therapy, n (%)		
Surgery		
No	145 (77)	144 (77)
Yes	44 (23)	43 (23)
Radiotherapy		
No	152 (80)	147 (79)
Yes	37 (20)	40 (21)
Previous radiotherapy to the brain		
No	165 (87)	161 (86)
Yes	24 (13)	26 (14)
Time from radiotherapy to the brain to randomisation ≤3 months, n/N[a] (%)	22/24 (92)	23/26 (89)
Medication: chemotherapy setting		
Adjuvant	10 (5)	7 (4)
Neoadjuvant	0	2 (1)
Receipt of one previous regimen of neoadjuvant or adjuvant chemotherapy	10 (5)	9 (5)

Soria et al., 2017[66], ASCEND-4 CSR[15]
FAS, full analysis set; WHO, World Health Organization
[a]Denominator is the number of patients with previous radiotherapy to the brain.

B 2.3.3 Trial design

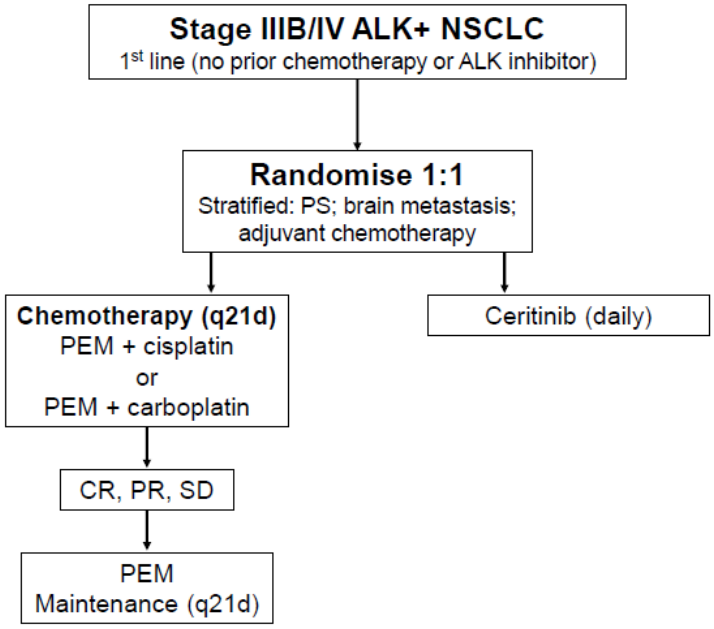
The trial design and treatment plan for ASCEND-4 are summarised in Figure 4. Patients were randomised 1:1 to ceritinib or CT (cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance therapy, if appropriate). Randomisation was performed via interactive response technology and was stratified according to WHO performance status (0 vs. 1–2), prior adjuvant therapy (yes vs. no) and brain metastases at screening (yes vs. no).

Ceritinib was administered orally once daily (in the fasted state, i.e. at least one hour before or two hours after food), at a dose of 750 mg (5 x 150 mg capsules) continuously for the 21-day treatment cycle. Chemotherapy was administered intravenously, comprising cisplatin (75 mg/m²) or carboplatin (area under the concentration time curve [AUC] 5–6 mg/mL.min) plus pemetrexed (500 mg/m²) given every 21 days for four cycles, and patients who completed the four cycles of CT without disease progression subsequently received pemetrexed maintenance (500 mg/m²) every 21 days. In both treatment groups, patients continued to receive therapy until disease progression (according to Response Evaluation Criteria In Solid Tumours [RECIST] 1.1 criteria, central assessment) or unacceptable toxicity. Patients could continue therapy beyond disease progression if the investigator judged that they were experiencing clinical benefit, but these patients were not followed for efficacy or PROs beyond progression.

Patients could undergo dose reductions or treatment interruptions for management of AEs. A maximum of three dose reductions were allowed for patients treated with ceritinib (150 mg per reduction, to a minimum dose of 300 mg/day). Patients randomly assigned to CT were allowed to cross over to ceritinib after centrally confirmed, RECIST-defined progressive disease. Table 5 provides details for allowed and prohibited concomitant therapies.

This being an open label study, the investigators and patients were not masked to treatment assignment, but the study sponsor personnel remained blinded until data lock for the primary analysis.

Figure 4 Trial design and treatment plan for ASCEND-4



Soria et al., 2017[66]
ALK+, anaplastic lymphoma kinase-positive; CR, complete response; NSCLC, non-small cell lung cancer; PEM, pemetrexed; PR, partial response; PS, performance status; SD, stable disease

B 2.3.4 Efficacy and PRO assessments

Efficacy outcomes were based on determination of tumour response according to RECIST 1.1 criteria and were performed both locally and centrally, based on computed tomography scans or MRI of the chest and abdomen. Assessments were completed at baseline, every six weeks from cycle 1 day 1 to month 33, every nine weeks thereafter, and then at the end of treatment. Responses (complete response [CR] and partial response [PR]) were to be confirmed within four weeks of the initial assessment. Intracranial responses were assessed in patients with brain metastases by computed tomography scan or MRI performed at each tumour assessment time point. The intracranial response

was determined based on images assessed by an independent central neuroradiologist, who was masked to treatment. RECIST 1.1 criteria were modified to allow a more rigorous evaluation of intracranial response to the treatment. Thus, a maximum of five target lesions located in the brain could be selected at baseline and evaluated at each subsequent time point.

PROs were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30), the corresponding lung cancer module (QLQ-LC13), the Lung Cancer Symptom Scale (LCSS), and the EuroQol Group 5-Dimension (EQ-5D) self-report questionnaire.

- The EORTC-QLQ-C30 contains 30 questions that incorporate nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale.[72] Several single-item symptom measures are also included: dyspnoea (i.e. shortness of breath), insomnia, appetite, constipation, diarrhoea and financial impact. All scales range from 0 to 100, with a higher score indicating better level of functioning or a worse symptom experience.
- The EORTC QLQ-LC13 complements the QLQ-C30, and measures disease symptoms and treatment-related AEs.[73] The lung cancer module incorporates one multi-item scale to assess dyspnoea and nine other single items: pain (three items – chest, arm/shoulder and other parts), coughing, sore mouth, dysphagia (difficulty swallowing), peripheral neuropathy, alopecia (hair loss) and haemoptysis (coughing blood). All scales and item scores are linearly transformed to a 0 to 100 scale, with higher scores indicating increased symptom levels.
- The LCSS patient scale uses a 24-hour recall period and contains nine items: six measuring major symptoms of lung cancer (appetite loss, fatigue, cough, dyspnoea, haemoptysis, pain), and three summary items related to total symptom distress, normal activity status, and overall HRQoL.[74] The LCSS uses a 100 mm visual analogue scale (VAS) to measure the intensity of patient responses, with 0 corresponding to the lowest rating (best status) and 100 representing the highest rating (worst status).
- The EQ-5D is a standardised measure of health status that provides a simple, generic measure of health for clinical and economic appraisal.[75]

As for tumour responses, assessments were completed at baseline, every six weeks from cycle 1 day 1 to month 33, every nine weeks thereafter, and then at the end of treatment.

B 2.3.5 Efficacy and PRO outcomes

The primary endpoint was PFS, assessed centrally according to RECIST 1.1, and the key secondary endpoint was OS. A complete list of the efficacy endpoints (and their definitions) is provided in Table 7.

Table 7 Definitions of efficacy outcomes

Endpoint	Definition
Primary	
Progression-free survival (PFS)	Time from the date of randomisation to the date of the first radiologically documented disease progression per central assessment, or death due to any cause
Key secondary	
Overall survival (OS)	Time from date of randomisation to date of death due to any cause
Other secondary	
Overall response rate (ORR)	Proportion of patients with a best overall response (BOR) defined as complete response or partial response (i.e. CR+PR)
Duration of response (DOR)	Time from first documented response (PR or CR) to the date of first documented progressive disease (PD), or death due to any cause
Disease control rate (DCR)	Proportion of patients with BOR of CR, PR, stable disease (SD), or non-CR/non-PD as per RECIST 1.1
Time to response (TTR)	Time from the date of randomisation to the date of the first documented response (CR or PR, which was confirmed subsequently) for patients with confirmed CR or PR
Overall intracranial response rate (OIRR)	ORR was based on assessment of target and non-target lesions (and new lesions, if applicable) in the brain. Rates are calculated as the proportion of patients with a best overall confirmed response of CR or PR in the brain as per modified RECIST 1.1 criteria. Responses were assessed by a blinded central neuroradiologist
Intracranial disease control rate (IDCR)	IDCR was based on assessment of target and non-target lesions (and new lesions, if applicable) in the brain. Rates are calculated as the proportion of patients with a best overall confirmed response of CR or PR or a response of SD (or non-CR/non-PD) in the brain as per modified RECIST 1.1 criteria. Responses were assessed by a blinded central neuroradiologist
Intracranial clinical benefit rate (ICBR)	Proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or non-CR/non-PD that lasts for a minimum time duration (i.e. 12, 18 and 24 weeks)
Duration of intracranial response (DOIR)	DOIR was based on assessment of target and non-target lesions (and new lesion, if applicable) in the brain. DOIR is calculated from the time of first documented intracranial response (PR or CR) to the date of first documented intracranial PD or death due to any cause, as per modified RECIST 1.1 criteria. Responses were assessed by a blinded central neuroradiologist

ASCEND-4 CSR[15]

The primary analysis of interest for the PRO outcomes was the time to definitive deterioration of symptom scores for chest pain, cough, or dyspnoea (composite end point), assessed using the LCSS and the QLQ-LC13 questionnaires.[76] This was determined using Kaplan-Meier methodology and was defined as the time from randomisation to the time at which a patient's score had a ≥10-point increase from baseline in any of the QLQ-LC13 scores, or death due to any cause. Similarly, a threshold of ≥15 mm increase from baseline was used for the LCSS. A Cox regression model, stratified by randomisation stratification factors, was used to estimate the hazard ratio (HR), along with a 2-sided 95% confidence interval (CI).

In addition, descriptive statistics were used to summarise the scored scales for each cycle of the EORTC QLQ-C30, QLQ-LC13, LCSS, and EQ-5D questionnaires, both at baseline and during treatment. A repeated measures model for longitudinal data was used to compare the two treatment arms in terms of domain scores for each measure.

B 2.3.6 Safety assessment and monitoring

Safety assessments included recording of all AEs and serious AEs (SAEs). In addition, vital signs, blood chemistry, and haematology were assessed and an electrocardiogram (ECG) was performed at the screening visit, day 1 and day 15 of cycle 1, day 1 of all subsequent cycles, and at the end of treatment.

B 2.3.7 Pre-planned subgroup analyses

Subgroup analysis of PFS as per central assessment was to be performed if the primary analysis of this endpoint was statistically significant, to determine whether the benefits of ceritinib over CT were consistent across different patient subgroups. The pre-planned subgroups to be analysed were geographic region, age group, gender, race, baseline metastases, prior adjuvant CT, WHO performance status, disease burden per central assessment, and smoking history (see Table 5).

B 2.4 Statistical analysis and patient disposition

Table 8 summarises the statistical analyses included in ASCEND-4.

B 2.4.1 Populations

The following populations were considered:

- The full analysis set (FAS) consisted of all randomised patients and was used for the primary efficacy analysis
- The safety analysis was based on the safety set that included all patients who received at least one dose of study drug (ceritinib, pemetrexed, carboplatin or cisplatin).

B 2.4.2 Sample size calculation

Assuming a median PFS of eight months in the CT group, it was expected that ceritinib would result in a 38% risk reduction in the hazard rate.[66] On the basis of an expected true HR of 0.62, under the alternative hypothesis, about 205 PFS events were required to have 90% power at a one-sided 2.5% level of significance to reject the null hypothesis (HR=1). This was using a log-rank test and a two-look group sequential design. Thus, approximately 348 patients were required to be randomly assigned to the two treatment groups in a 1:1 ratio.

B 2.4.3 Planned analyses

One futility interim analysis was planned for the primary endpoint of PFS as per the central assessment when approximately 72/205 (35%) PFS events were documented. A final PFS analysis was planned for when 205 PFS events had occurred, and results are reported in section B 2.6.

A maximum of four analyses was planned for OS: 1) an interim analysis at the time of the interim analyses for PFS (provided PFS was significant); 2) an interim analysis at the projected time of the final analysis for PFS (provided PFS was significant); 3) an interim analysis for OS after observing 215 deaths, and 4) a final analysis for OS after observing 253 deaths. The second of these OS analyses has been performed, and results are reported in section B 2.6.3.

B 2.4.4 Statistical tests

A Cox regression model stratified by randomisation stratification factors was used to estimate the HR of the PFS and 95% CIs were estimated based on the Wald test. PFS was tested using the stratified log-rank test. Kaplan–Meier methodology was used for time-to-event endpoints. The statistical basis for a claim of efficacy was the statistical significance (at the 2.5% one-sided level of significance) for PFS in favour of ceritinib.

Table 8 Summary of statistical analyses in ASCEND-4

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT01828099, CLDK378A2301 **ASCEND-4**	To compare the anti-tumour activity of ceritinib versus CT, as measured by PFS determined by a central assessment	• PFS was tested using the stratified log-rank test (stratified according to randomisation stratification factors) • A hierarchical testing strategy, where OS was to be statistically evaluated and interpreted only if PFS was significantly different between treatment groups, was to be used to control the overall type-I error rate • A stratified log-rank test was used for comparison of OS • The primary analysis was planned after approximately 72/205 (35%) PFS events were documented by central assessment • A final PFS analysis is planned for when 205 PFS events have occurred • A maximum of four analyses were planned for OS: 1) an interim analysis at the time of the interim analyses for PFS (provided PFS is significant); 2) an interim analysis at the projected time of the final analysis for PFS (provided PFS is significant); 3) an interim analysis for OS when 215 deaths are observed, and 4) a final analysis for OS when 253 deaths are observed	• Assuming a median PFS of eight months in the CT group, it was expected that ceritinib would result in a 38% risk reduction in the hazard rate • About 205 PFS events were required to have 90% power at a one-sided 2.5% level of significance to reject the null hypothesis (HR=1) using a log-rank test and a two-look group sequential design • The final analysis (PFS) was expected at approximately 253 deaths • The statistical basis for a claim of efficacy was the statistical significance (at 2.5% one-sided level of significance) for PFS in favour of ceritinib	• Patients could cross over to the extension treatment phase if they had centrally confirmed progressive disease and met all required criteria for cross-over • All patients who discontinued treatment during the treatment phase for reasons other than death, lost to follow-up, pregnancy or disease progression as per central assessment were to continue tumour and PRO assessments as per schedule • Patients who discontinued study treatment were not considered withdrawn from the study unless the final visit assessments were performed, or when it was clear that the patient would not return for these assessments

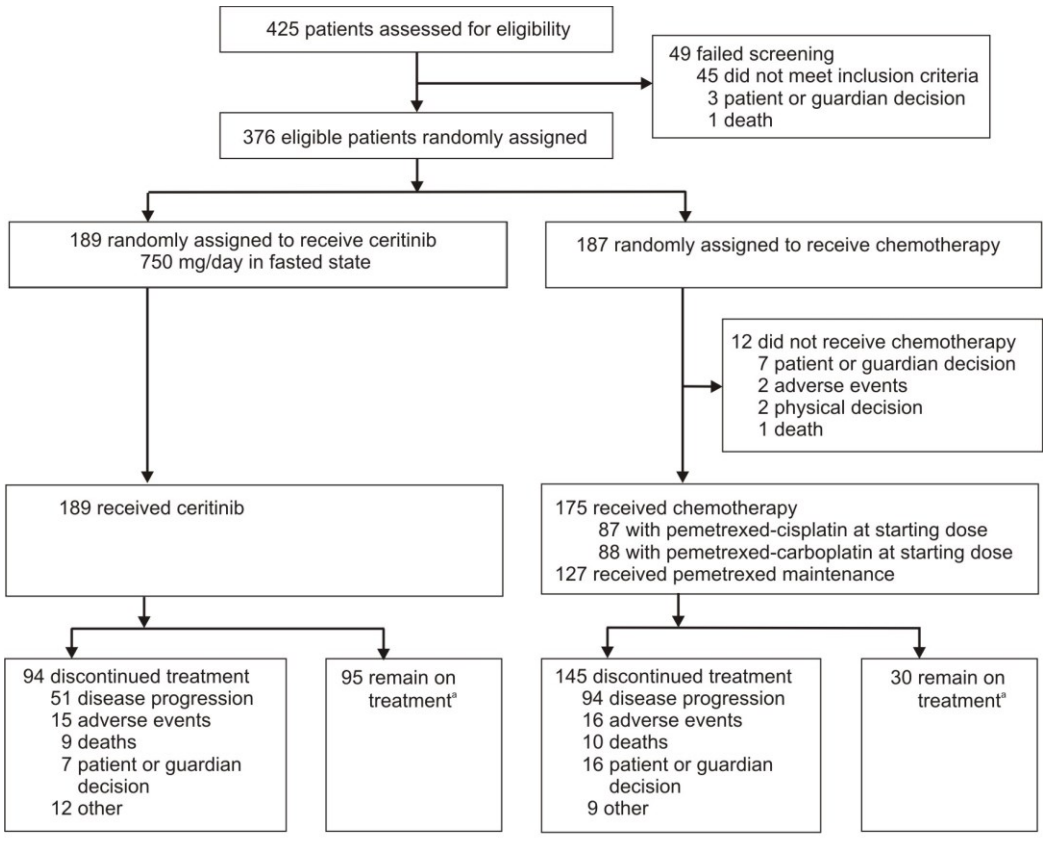
Soria et al., 2017[66], ASCEND-4 CSR[15]
CT, chemotherapy; PFS, progression-free survival; PRO, patient reported outcomes

B 2.4.5 Patient disposition

Figure 5 summarises the patient disposition for ASCEND-4. In total, 376 patients completed screening, of whom 189 patients were randomised to ceritinib and 187 patients were randomised to CT. Among the 187 patients in the CT group, 87 patients started therapy with cisplatin/pemetrexed and 88 patients started therapy with carboplatin/pemetrexed; 127 patients received pemetrexed maintenance therapy.

At database lock, 95 (50%) patients in the ceritinib group and 30 (16%) patients in the CT group were still receiving treatment. Rates of discontinuation were considerably higher in the CT group (78%) compared to the ceritinib group (50%), largely reflecting the higher rate of discontinuation due to disease progression in the CT group. Thus, although the primary reason for discontinuation was disease progression in both groups, the proportion of patients discontinuing for disease progression was approximately two-fold higher in the CT group (50% vs. 27%). Similarly, discontinuation due to AEs considered related to treatment occurred in a higher proportion of patients in the CT group (5% for ceritinib and 11% for CT).

Figure 5 Patient disposition in ASCEND-4



Soria *et al.,* 2017[66]

[a]At data cut-off, 24 June 2016

B 2.5 Quality assessment of the relevant clinical effectiveness evidence

Assessment of the risk of bias for ASCEND-4 (see Table 9) indicates that the study has a low risk of bias except for the open-label design, necessitated by the different routes of administration for ceritinib and the comparator treatment. However the primary endpoint, PFS, was assessed by central assessors who were masked to treatment, thus avoiding bias in the primary endpoint.

Table 9 Quality assessment for ASCEND-4

Trial number (acronym)	**NCT01828099 (ASCEND-4)**
Was randomisation carried out appropriately?	Yes, 376 patients were randomised 1:1 to ceritinib or CT using interactive response technology.
Was the concealment of treatment allocation adequate?	Not applicable, as this was an open label study. However, measurement of response was based on blinded central assessment of computerised tomography scans.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline characteristics were well balanced.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, care providers and participants were not blinded, as ceritinib is an oral therapy and CT is given via the intravenous route. Central assessors (primary endpoint) were masked to treatment.
Were there any unexpected imbalances in drop-outs between groups?	No. As expected, more discontinuations were observed in the CT group than in the ceritinib group, reflecting the greater incidence of disease progression.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All the primary and secondary objectives (as defined in the CSR), are reported in the primary paper, except characterisation of the pharmacokinetics of ceritinib.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the primary analysis of PFS used an ITT approach. PFS was censored at the date of the last adequate tumour assessment before an event or reason for censoring occurred. PFS censoring reasons included: ongoing without event, lost to follow-up, withdrew consent, adequate assessment no longer available, new cancer therapy received prior to an event, and an event occurring after ≥2 missing tumour assessments.

Soria *et al.,* 2017[66], ASCEND-4 CSR[15]
CSR, clinical study report; CT, chemotherapy; ITT, intention-to-treat; IV, intravenous; PFS, progression-free survival

B 2.6 Clinical effectiveness results for ASCEND-4

B 2.6.1 Overview

Results for ASCEND-4 are based on an analysis performed after 202 PFS events (central assessment), corresponding to a median duration of follow-up of 19.7 months (data cut off, June 2016), and are summarised in Table 10.[15,66,71] The study met its primary endpoint, demonstrating a median PFS of 16.6 months for ceritinib compared to 8.1 months for CT. An ORR of 73% was attained with ceritinib, responses were achieved within a median of six weeks, and these responses were sustained for a median of 24 months. Furthermore, these efficacy outcomes translated into a 2-year event-free survival of 48% and 2-year OS of 71%, and were accompanied by a delay in the time to significant worsening in lung cancer-specific symptoms compared with CT. HRQoL was also better in the ceritinib group, as evident from an EQ-5D utility value of 0.81 vs. 0.77 for CT.

Table 10 Summary of efficacy data for the phase III trial ASCEND-4

	Central assessment			Local assessment		
Endpoints	**Ceritinib (n=189)**	**Chemotherapy (n=187)**	**p-value or HR**	**Ceritinib (n=189)**	**Chemotherapy (n=187)**	**p-value or HR**
Median PFS, months (95% CI)	16.6 (12.6–27.2)	8.1 (5.8–11.1)	HR 0.55 p <0.001	16.8 (13.5–25.2)	7.2 (5.8–9.7)	HR 0.49 p <0.001[a]
Median OS, months (95% CI)	NE (29.3–NE)	26.2 (22.8–NE)	HR 0.73 p = 0.056	-	-	-
2-year OS, % (95% CI)	70.6 (62.2–77.5)	58.2 (47.6–67.5)	NA	-	-	-
ORR,[b] % (95% CI)	72.5 (65.5–78.7)	26.7 (20.5–33.7)	-	73.5 (66.7–79.7)	32.1 (25.5–39.3)	-
Median TTR, weeks[c](range)	6.1 (5.1–61.7)	13.4 (5.1–90.1)	-	6.3 (5.1–71.9)	12.6 (4.7–84.0)	-
Median DOR,[c] months(95% CI)	23.9 (16.6–NE)	11.1 (7.8–16.4)	-	23.3 (17.6–NE)	8.0 (5.8–13.4)	-
EFS, % (95% CI)			-			-
At 21 months	59.0 (49.3–67.4)	NE[d]		53.9 (42.9–63.6)	13.8 (1.6–39.1)	
At 24 months	48.2 (32.3–62.4)	NE[d]		41.5 (26.6–55.8)	NE[d]	

Soria *et al.*, 2017[66], Soria et al Supplementary appendix[71], ASCEND-4 CSR[15]
[a]Nominal p-value
[b]ORR = CR+PR
[c]Patients with a best overall response of CR or PR
[d]Not estimable as no responders were at risk at the time point
CI, confidence interval; CR, complete response; CSR, clinical study report; DOR, duration of response; EFS, event-free survival; HR, hazard ratio; NA, not applicable; NE, not estimable; ORR, overall response rate; OS,

overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response

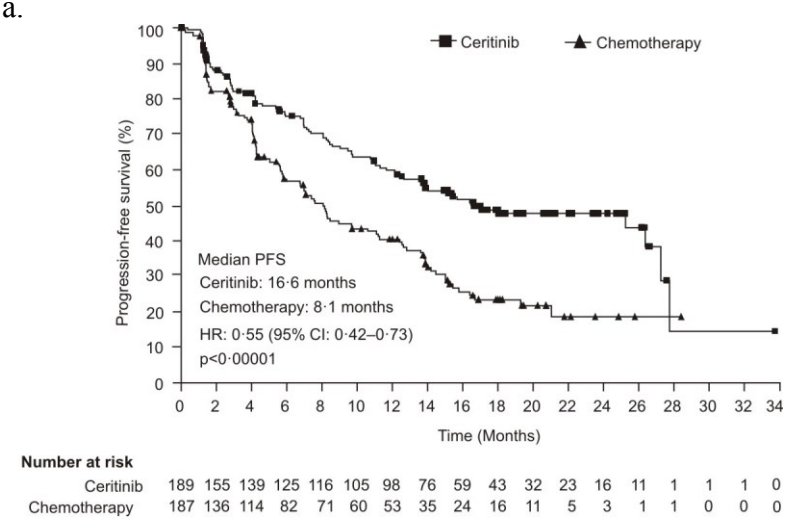
B 2.6.2 Primary efficacy outcome – PFS

Ceritinib provided a median PFS of 16.6 months in the overall population

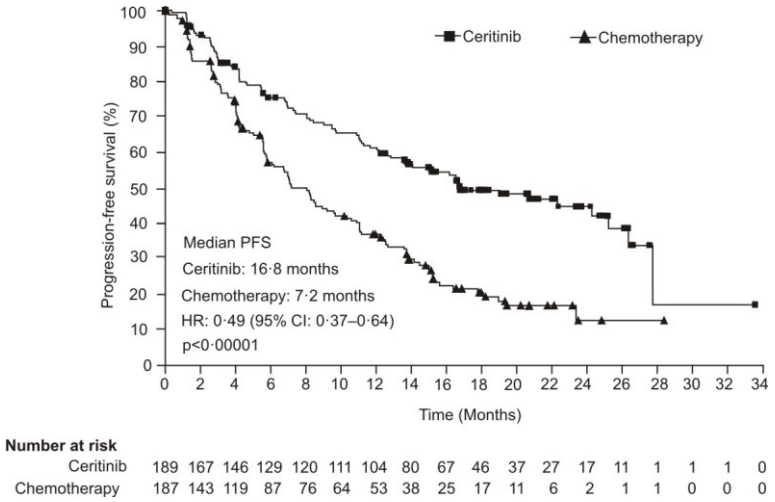
The ASCEND-4 study met its primary objective, demonstrating a statistically significant and clinically meaningful improvement in PFS for ceritinib over CT (Figure 6 and Table 11). The median PFS was 16.6 months for ceritinib compared with 8.1 months for CT (central assessment) (HR, 0.55; p<0.00001). The PFS advantage was apparent from approximately three months onwards in the Kaplan–Meier plots, and the event-free probability estimates remained higher throughout the study period for ceritinib compared with CT. At 24 months, the Kaplan–Meier-estimated PFS was 47.6% for ceritinib compared with 18.6% for CT.

Figure 6 Kaplan–Meier plots of PFS in ASCEND-4: a) central assessment, b) local assessment

a.



b.



Soria *et al.,* 2017[66]
CI, confidence interval; HR, hazard ratio

Table 11 Summary of PFS (central assessment) in ASCEND-4

	Ceritinib (n=189)	**Chemotherapy (n=187)**
Median PFS, months (95% CI)	16.6 (12.6–27.2)	8.1 (5.8–11.1)
HR (95% CI), p-value	0·55 (0.42–0.73); p<0.00001	
n/N (%)	89/189 (47.1)	113/187 (60.4)
Censored (%)	52.9	39.6
Percent event-free probability estimate		
At 12 months, % (95% CI)	59.9 (52.1–66.8)	40.4 (32.5–48.2)
At 24 months, % (95% CI)	47.6 (39.3–51.4)	18.6 (10.9–27.9)

Soria *et al.,* 2017;[66] ASCEND-4 CSR[15]
CI, confidence interval; CSR, clinical study report; HR, hazard ratio; n, number of events; N, total number of patients in the subgroup; PFS, progression-free survival

The primary reason for censoring patients in the PFS analyses was that the patient was still receiving therapy and was event-free (progression or death) at the time of the data cut-off (40.2% in the ceritinib arm and 16.6% in the chemotherapy arm).

Results for local assessment corroborated those reported for central assessment, with median PFS being 16.8 months for ceritinib (Table 10 and Figure 6). The concordance rates between central and local review were high, being 88% for ceritinib, and 87% for CT.

Ceritinib prolonged PFS compared with CT in patients both with and without brain metastases (Table 12).[15,66] Median PFS achieved with ceritinib was 26.3 months in patients without brain metastases and 10.7 months in patients with brain metastases according to central assessment, and similar results were reported for local assessment. In patients without brain metastases, a statistically significant improvement in PFS was observed for ceritinib vs. CT according to both central and local assessment. In contrast, in patients with brain metastases (where the improvement in PFS was less marked), the difference between treatments was not statistically significant according to either assessment.

Table 12 Median PFS in patients with or without brain metastases at baseline in ASCEND-4

	Patients with brain metastasis		Patients without brain metastasis	
	Ceritinib	**Chemotherapy**	**Ceritinib**	**Chemotherapy**
Central assessment				
PFS events, n/N (%)	35/ 58 (60.3)	36/ 57 (63.2)	54/131 (41.2)	77/130 (59.2)
Median PFS months (95% CI)	10.7 (8.1–16.4)	7.0 (4.2–11.1)	26.3 (15.4–27.7)	8.2 (5.8–12.8)
HR (95% CI)	0.80 (0.50–1.28) p=NS		0.45 (0.32–0.64) p<0.05	
Local assessment				
PFS events, n/N (%)	35/58 (60.3)	39/57 (68.4)	57/131 (43.5)	87/130 (66.9)
Median PFS months (95% CI)	13.5 (9.0–16.7)	7.0 (4.2–11.1)	25.2 (15.2–NE)	8.2 (5.7–10.9)
HR (95% CI)	0.66 (0.41–1.05) P=NS		0.42 (0.30–0.59) p<0.05	

Soria *et al.*, 2017[66], Soria et al Supplementary appendix;[71] ASCEND-4 CSR[15]
CI, confidence interval; HR, hazard ratio; n, number of events; N, total number of patients in the subgroup; NE, not estimable; NS, not significant; PFS, progression-free survival

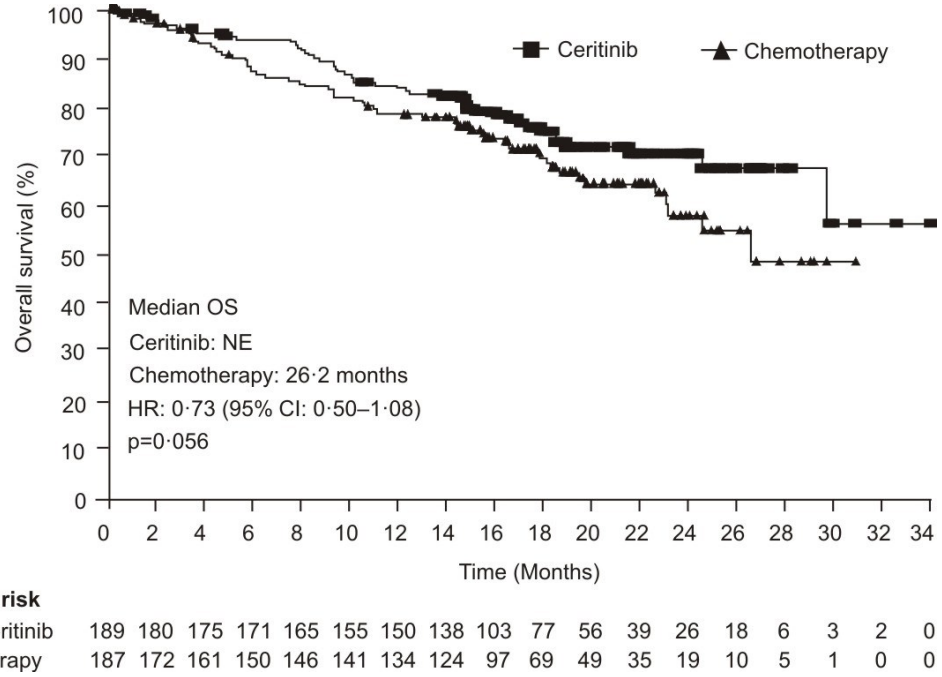
B 2.6.3 Key secondary efficacy outcome – OS

The interim analysis reported a 2-year OS of 71% for ceritinib

At the time of the analysis, the OS data were immature; only 107 events (42% of the required OS events) had occurred. The study did not cross the efficacy stopping boundary for OS (–3.2546 [Z-scale], corresponding to p=0.0006 on the p-value scale), and is therefore ongoing.

At the data cut-off, 48 (25.4%) patients in the ceritinib group had died, resulting in an estimated 24-month OS rate of 70.6% (Table 13). This compares with a 24-month OS of 58.2% for CT. Median OS was 'not reached' in the ceritinib group and was estimated as 26.2 months in the CT group (HR, 0.73; p=0.056). Thus, ceritinib reduced the risk of death by 27% compared with CT. The OS Kaplan–Meier plots for the two treatment groups diverged from four months onwards, indicating a positive trend in favour of ceritinib (Figure 7).

Figure 7 Kaplan–Meier plot of OS in ASCEND-4



Soria *et al*., 2017[66]
CI, Confidence interval; HR, Hazard ratio

Table 13 OS– events and percent survival at data cut-off in ASCEND-4

	Ceritinib	Chemotherapy
n/N (%)	48/189 (25.4)	59/187 (31.6)
Median OS	NE (29.3–NE)	26.2 (22.8–NE)
HR (95% CI), p-value	0.73 (0.50–1.08) p=0.056	
Percent event-free probability estimate		
At 12 months, % (95% CI)	83.6 (77.4–88.2)	78.7 (71.9–84.1)
At 24 months, % (95% CI)	70.6 (62.2–77.5)	58.2 (47.6–67.5)

Soria *et al.*, 2017[66], ASCEND-4 CSR[15]
CI, confidence interval; CSR, clinical study report; HR, hazard ratio; n, number of events; N, total number of patients in the subgroup; NE, not estimable; OS, overall survival

Crossover and sensitivity analysis

At the time of the OS analysis, 105 (72%) of 145 patients initially randomised to CT had received an ALK inhibitor after CT discontinuation; this included 80 patients who crossed over to receive ceritinib. Of the other 25 patients, 23 received crizotinib. Conversely, in the ceritinib group, 34 (18%) of 189 patients had received subsequent anti-cancer therapy, of whom 24 received platinum-based doublet

CT, and six received an ALK inhibitor (ceritinib, n=1; crizotinib, n=3; lorlatinib, n=2). A sensitivity analysis using rank-preserving structural failure time (RPSFT) methodology was performed to correct for the confounding introduced by patients crossing over from CT to ceritinib. The resulting HR estimate was similar to that from the primary OS analysis, suggesting that cross-over from CT to ceritinib on disease progression did not affect the difference in OS between the treatment groups for this data-cut (HR 0.73; 95% CI, 0.49–1.10). The duration of follow-up is currently insufficient to conclude whether there is a difference in OS according to the RPSFT analysis.

B 2.6.4 Whole-body tumour response rates

Almost three-quarters of patients achieved a tumour response to ceritinib and responses were sustained for a median of two years

Table 14 summarises the tumour responses achieved in ASCEND-4. Overall, 72.5% of patients receiving ceritinib achieved a tumour response, with most being classified as a PR (72.0%). The median time to response was 6.1 weeks. Among patients with a confirmed CR or PR, the median duration of response (DOR) was 23.9 months. These results compare favourably with those for the CT group, where the ORR was 26.7%, time to response was 13.4 weeks and median DOR was only 11.1 weeks. Similar results were reported for local assessment, with concordance rates between central and local assessment for best overall response being 79.9% for ceritinib and 73.3% for CT.

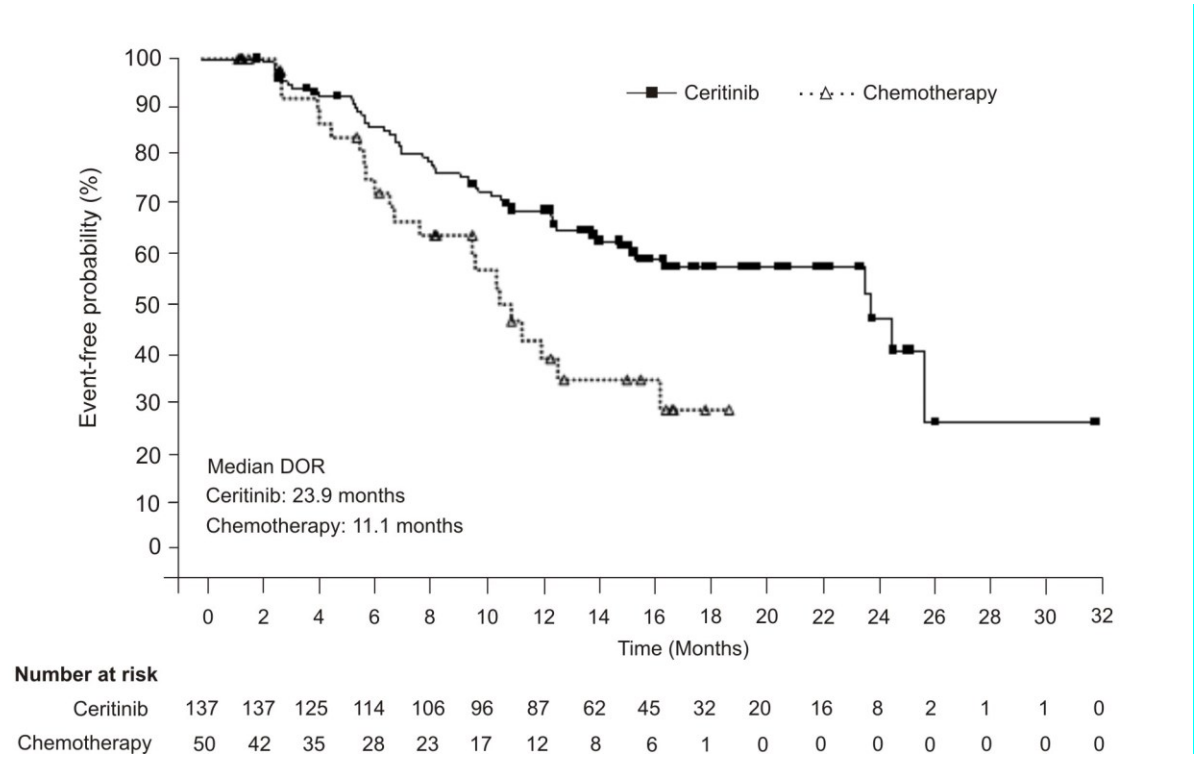
Table 14 Summary of whole-body tumour response rates in ASCEND-4

Response	Central assessment		Local assessment	
	Ceritinib (n=189)	Chemotherapy (n=187)	Ceritinib (n=189)	Chemotherapy (n=187)
ORR, n (%) (95% CI)	137 (72.5) (65.5–78.7)	50 (26.7) (20.5–33.7)	139 (73.5) (66.7–79.7)	60 (32.1) (25.5–39.3)
CR, n (%)	1 (0.5)	0	5 (2.6)	0
PR, n (%)	136 (72.0)	50 (26.7)	134 (70.9)	60 (32.1)
SD, n (%)	23 (12.2)[a]	88 (47.1)[b]	30 (15.9)	82 (43.9)
PD, n (%)	19 (10.1)	26 (13.9)	11 (5.8)	21 (11.2)
Unknown, n (%)	10 (5.3)	23 (12.3)	9 (4.8)	24 (12.8)
Median time to first response (in responders), weeks (range)	6.14 (5.1–61.7)	13.36 (5.1–90.1)	6.29 (5.1–71.9)	12.64 (4.7–84.0)
Median DOR (in responders), months (95% CI)	23.9 (16.6–NE)	11.1 (7.8–16.4)	23.3 (17.6–NE)	8.0 (5.8–13.4)
Estimated 21-month event-free rate, % (95% CI)	59.0 (49.3–67.4)	NE	53.9 (42.9, 63.6)	13.8 (1.6–39.1)

Soria et al Supplementary appendix[71]
[a]Three NCRNPD cases are based on patients with non-measurable disease.
[b]Nine NCRNPD cases are based on patients with non-measurable disease,
CI, confidence interval; CR, complete response; DOR, duration of response; NCRNPD, non-CR/non-PD; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

In the Kaplan–Meier plots for duration of response, the curves separated from approximately three months onwards and the event-free probability remained higher in the ceritinib arm, indicating a longer duration of response with ceritinib. The estimated event-free rate at 24 months was 48.2% for patients in the ceritinib arm (Figure 8 and Table 15).

Figure 8 Kaplan–Meier plot of duration of response per central assessment by treatment arm in ASCEND-4 (FAS – patients with confirmed CR or PR)



ASCEND-4 CSR.[15]
CSR, clinical study report; NE, not estimable

Table 15 Summary of data for duration of response in ASCEND-4

	Ceritinib	Chemotherapy
n/N (%)	54/137 (39.4)	22/50 (44.0)
Median DOR, months (95% CI)	23.9 (16.6–NE)	11.1 (7.8–16.4)
Percent event-free probability estimate		
At 12 months, % (95% CI)	69.8 (61.1–76.8)	44.2 (26.8–60.4)
At 24 months, % (95% CI)	48.2 (32.3–62.4)	NE

Soria et al Supplementary appendix,[71] ASCEND-4 CSR[15]
CI, confidence interval; CSR, clinical study report; DOR, duration of response; n, number of events; N, total number of patients in the analysis; NE, not estimable

B 2.6.5 Intracranial responses

In total, 121 patients (61 patients in the ceritinib group and 60 patients in the CT group) had brain metastases (measurable or non-measurable) at baseline. Of these 121 patients, only 22 patients in each group had ≥1 post-baseline assessment for measurable brain metastases. Table 16 summarises their responses to treatment.

Firstly, the overall intracranial response rate in patients with measurable brain metastases at baseline was 72.7% in the ceritinib group and 27.3% in the CT group. Secondly, the median duration of intracranial response (DOIR) was 16.6 months in the ceritinib group, and not estimable in the CT group (as four of six patients had not progressed at the time of the analysis). These results provide evidence for the intracranial activity of ceritinib, but are necessarily limited by the small size of the patient population in each treatment group.

Table 16 Summary of intracranial tumour responses in patients with measurable brain metastases at baseline in ASCEND-4

	Ceritinib (n=22)	**Chemotherapy (n=22)**
OIRR, n (%, 95% CI)	16 (72.7, 49.8–89.3)	6 (27.3, 10.7–50.2)
CR, n (%)	2 (9.1)	2 (9.1)
PR, n (%)	14 (63.6)	4 (18.2)
SD, n (%)	3 (13.6)	14 (63.6)
PD, n (%)	1 (4.5)	1 (4.5)
Unknown, n (%)	2 (9.1)	1 (4.5)
ICBR at ≥12 weeks, n (%, 95% CI)	19 (86.4, 65.1–97.1)	15 (68.2, 45.1–86.1)
ICBR at ≥24 weeks, n (%, 95% CI)	19 (86.4, 65.1–97.1)	11 (50.0, 28.2–71.8)

Soria *et al.,* 2017[66]
CI, confidence interval; CR, complete response; ICBR, intracranial clinical benefit rate; OIRR, overall intracranial response rate; PD, progressive disease; PR, partial response; SD, stable disease

B 2.6.6 Impact on symptoms and HRQoL

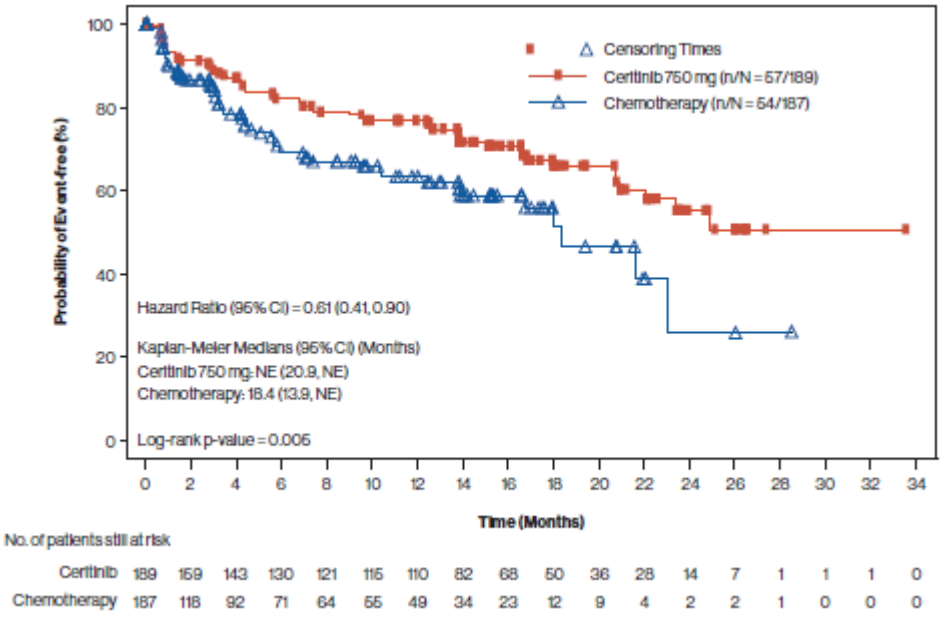
Symptom severity and HRQoL were assessed while patients were receiving treatment using the QLQ-C30, QLQ-LC13, LCSS and EQ-5D instruments. Compliance was good, with ≥80% of patients completing the questionnaires at most time points. The results of these assessments thus provide a comprehensive measure of the impact of treatment on lung-cancer specific symptoms, general functioning, and HRQoL.

Ceritinib significantly delayed time to definitive deterioration in symptoms (pain, cough and dyspnoea) compared with chemotherapy

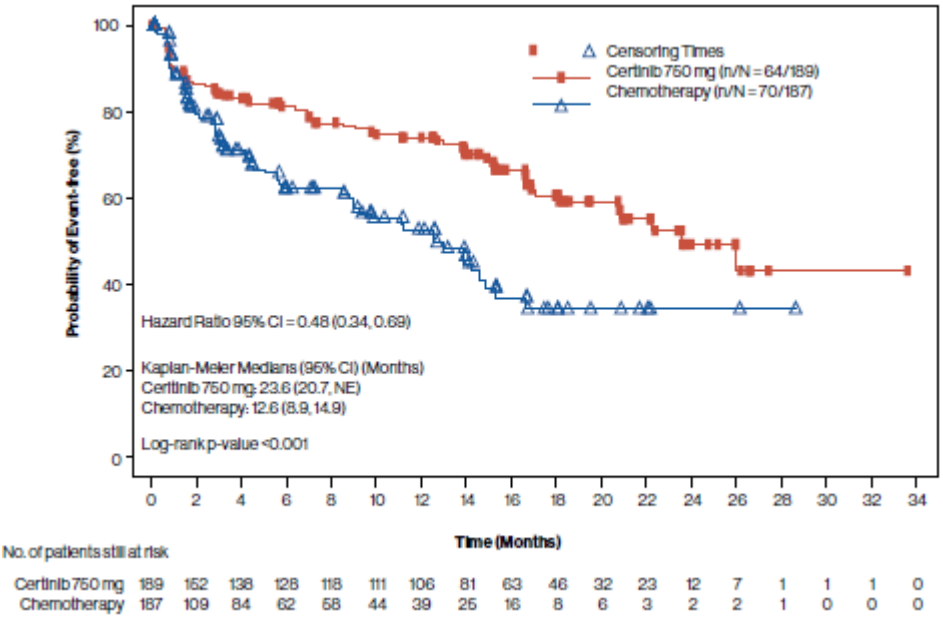
The primary PRO outcome of interest was the time to definitive symptom deterioration for the composite endpoint of lung cancer specific symptoms (pain, cough and dyspnoea). This was assessed using both the LCSS and QLQ-LC13 questionnaires, and results for both tools demonstrated a statistically significant difference in favour of ceritinib. According to the LCSS, median time to definitive deterioration (an increase of ≥15 mm) was not reached in the ceritinib group, compared with 18.4 months in the CT group (p<0.005, Figure 9). Similarly, according to the QLQ-LC13 assessment, median time to definitive deterioration (an increase of ≥10 points) was 23.6 months for the ceritinib group, compared with 12.6 months in the CT group (p<0.001).[76]

Figure 9 Time to definitive deterioration in symptoms (pain, cough and dyspnoea) in ASCEND-4 as assessed using the a) LCSS and b) QLQ-LC13 questionnaires

a)



b)

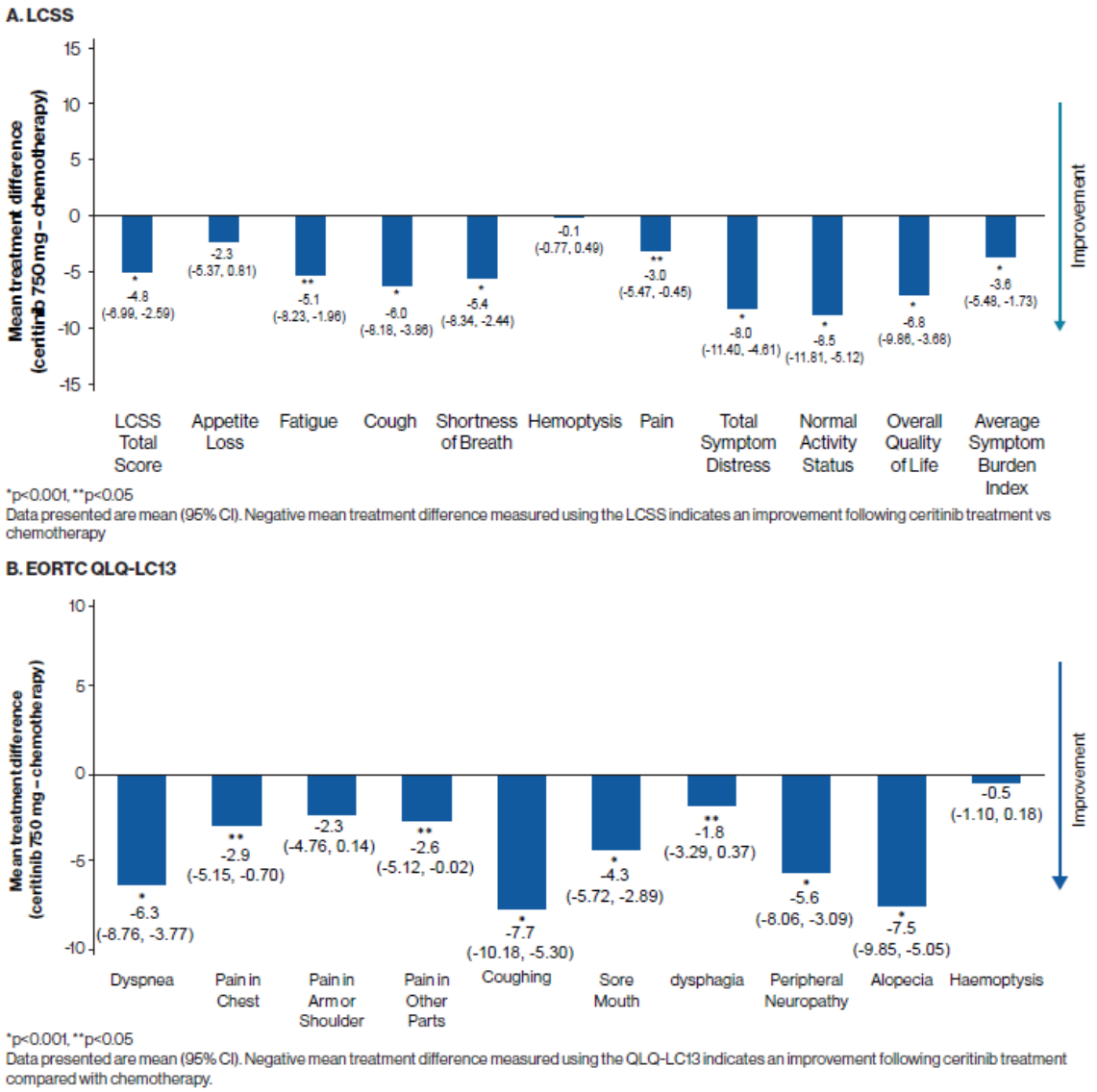


Tan *et al*., 2016[76]

Ceritinib provided greater improvements over time in lung cancer symptoms compared with chemotherapy

Data collected using the LCSS and QLQ-LC13 were also used to compare improvements in symptom severity during the time on therapy in the two treatment groups. According to these assessments, ceritinib demonstrated significantly greater improvements over time in most scores compared with CT (Figure 10). Thus, ceritinib was associated with improvements in all LCSS symptom scores compared with CT, with the difference being statistically significant for four out of six of the individual scores. Furthermore, average symptom burden index, total symptom distress and normal activity status improved significantly, as well as total score and overall HRQoL. All QLQ-LC-13 symptom scores were also indicative of a greater improvement with ceritinib compared with CT, and the difference was statistically significant for eight of the 10 symptoms.

Figure 10 Improvement in lung cancer symptoms over time with ceritinib versus CT in ASCEND-4: a) LCSS and b) EORTC QLQ-LC13



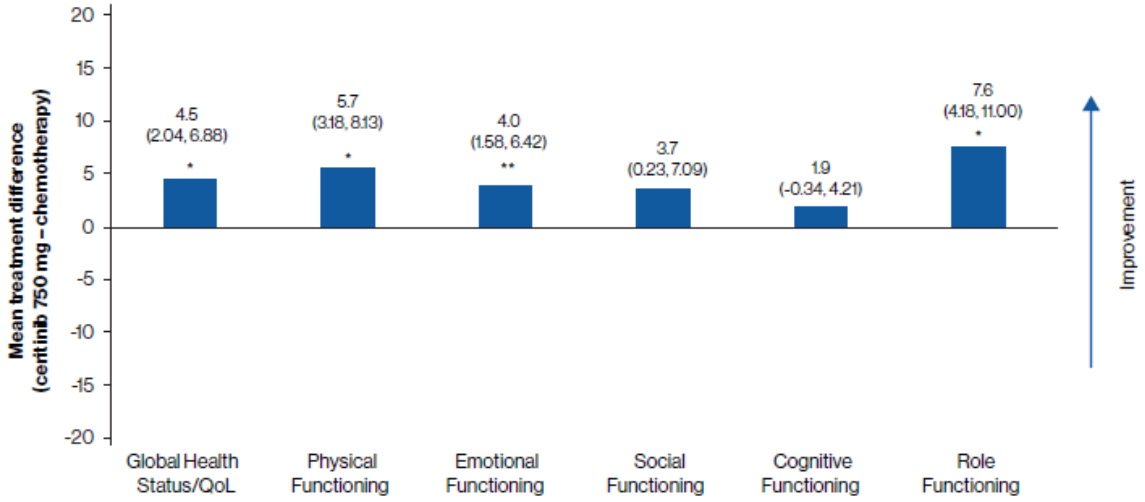
EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Lung Cancer-specific Quality of Life module; LCSS, lung cancer symptom scale
Tan et al 2016[76]

Ceritinib was associated with greater improvements in HRQoL and cancer-related symptoms over time compared with chemotherapy

Comparison of scores for functional domains as well as symptoms scores in the EROTC QLQ-C30 demonstrated greater improvements over time in the ceritinib group compared with the CT group for most domains (Figure 11). The difference between treatment groups was statistically significant for Global Health Status/QoL, four of the five functional domains and six of the nine symptom scales.

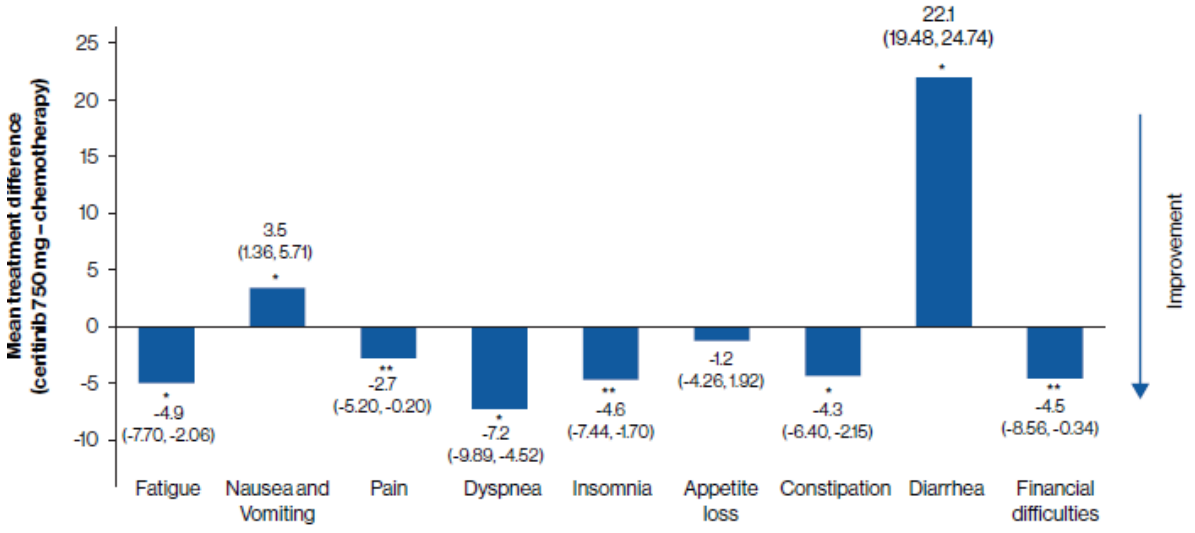
However, two of the symptom scores – nausea and vomiting, and diarrhoea – were significantly higher (indicating more severe symptoms) in the ceritinib group.

Figure 11 a) Improvements in functional domains and b) changes in symptoms scores according to the EORTC QLQ-C30 over time during treatment with ceritinib or chemotherapy in ASCEND-4



*p<0.001, **p<0.05
Data presented are mean (95% CI). Positive mean treatment difference measured using the EORTC QLQ-C30 indicates an improvement following ceritinib treatment vs chemotherapy for multi-item functional scores

b)



*p<0.001, **p<0.05
Data presented are mean (95% CI). Negative mean treatment difference measured using the EORTC QLQ-C30 indicates an improvement following ceritinib treatment vs. chemotherapy for symptom scores of fatigue, pain, dyspnoea, insomnia, appetite loss, constipation and financial difficulties.
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire

Tan *et al.,* 2016[76]

Based on EQ-5D scores, patients experienced a better HRQoL during therapy with ceritinib compared with chemotherapy

HRQoL was also assessed using the EuroQol (EQ-5D) index and the VAS (EQ-VAS). Scores for both measures were indicative of better HRQoL during treatment for the ceritinib group than for the CT group (Table 17) (see section B 3.4 for further details)

Table 17 EQ-5D scores during treatment with ceritinib or chemotherapy in ASCEND-4

Time window (overall)	Ceritinib (N=189)	Chemotherapy (N=187)	Treatment difference (Ceritinib vs. chemotherapy)	p-value
EQ-5D Index				
N	180	159	-	<0.001
LS Mean	0.8132	0.7708	0.04	
95% CI	(0.78408-0.84231)	(0.73905-0.80264)	(0.02, 0.07)	
EQ-VAS				
N	180	156	-	0.053
LS Mean	77.0	74.7	2.3	
95% CI	(74.18-79.73)	(71.64-77.71)	(-0.03, 4.59)	

ASCEND-4 CSR;[15] Tan *et al.,* 2016[76]
CI, confidence interval; CSR, clinical study report; LS, least squares; n, number of patients with observed score at the corresponding time point

In conclusion, the results of the PRO assessments clearly demonstrate that patients in general experience less severe symptoms (including both those related to lung cancer and to the side effects of treatment), together with better functioning and HRQoL, during therapy with ceritinib compared with CT. The only exception was gastrointestinal (GI) symptoms, which were more severe with ceritinib compared with CT, and these are discussed further in section B 2.10.

Furthermore, median time to a definitive deterioration in lung cancer symptoms was 24 months according to scores obtained with the QLQ-LC13, indicating that ceritinib provides patients with a prolonged period with minimal worsening of disease-specific symptoms. This is supported by the EQ-5D score (0.81) and EQ-VAS score (77.0) reported for patients receiving ceritinib, which are indicative of a good HRQoL. These data suggest that the clinical benefits reported for ceritinib therapy (section B 2.6.1) translate into meaningful improvements in symptoms and HRQoL, and that the effects of AEs are mitigated by the impact of treatment on disease-related symptoms.

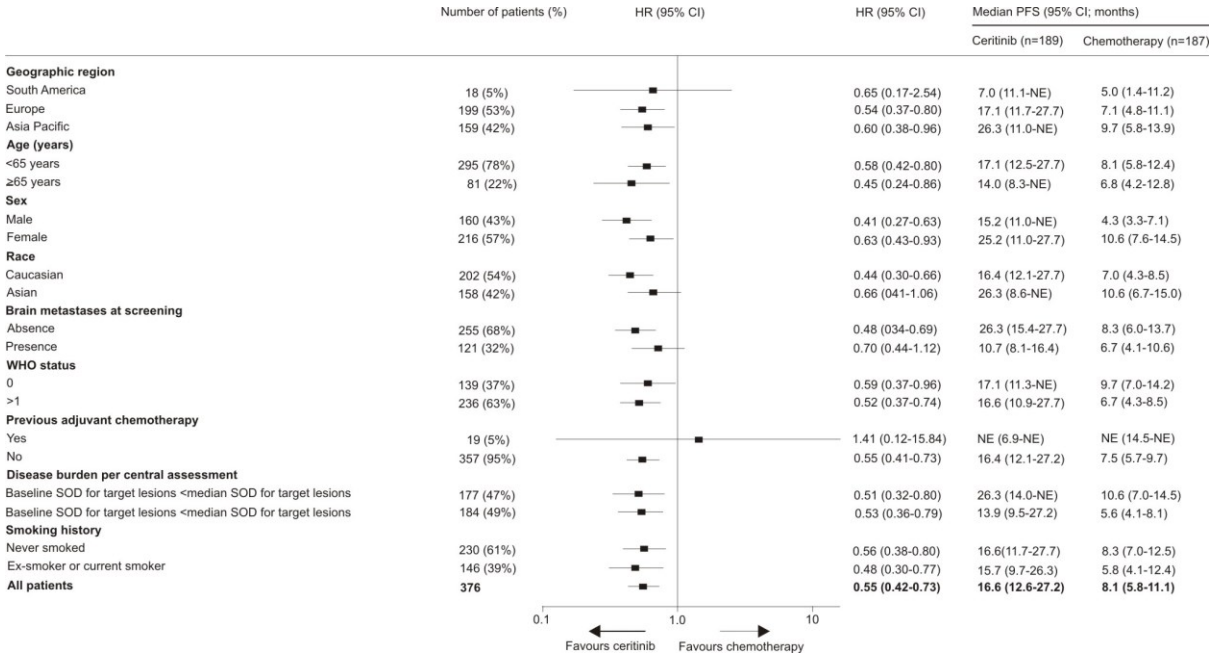
B 2.7 Subgroup analysis

B 2.7.1 Subgroups and rationale

Given that the primary endpoint was met, a Cox regression model stratified by randomisation stratification factors was performed to evaluate the effect of baseline demographic and disease characteristics on the estimated HR for PFS per central assessment. The fitted model adjusted the treatment difference for key prognostic factors including: stage of disease, geographic region, age, race and gender.

The results of the sub-group analysis are shown in Figure 12, and these indicate that the effects of ceritinib were consistent across all subgroups considered, except for the subgroups where the sample size was very small.

Figure 12 PFS in different subgroups in ASCEND-4



Soria *et al.*, 2017[66]

B 2.8 Meta-analysis

Only one relevant RCT was identified, as described in section B 2.2. Thus, a meta-analysis could not be performed.

B 2.9 Indirect and mixed treatment comparisons

Summary

- A systematic review identified that there are no direct head-to-head trials of ceritinib versus crizotinib in ALK+ advanced NSCLC
- Comparing the design and patient populations involved in the pivotal phase III trials for ceritinib (ASCEND-4) and crizotinib (PROFILE 1014) indicated that a matching-adjusted indirect comparison (MAIC) would be feasible, and the most appropriate approach for comparing key efficacy outcomes for ceritinib and crizotinib in the relevant patient population
- In the MAIC, weights were applied to patients enrolled in ASCEND-4 to exactly balance all baseline characteristics between the two trial populations. The extent of weighting required to achieve this was mild, with the effective sample size (ESS) in ASCEND-4 being reduced by 10% after weighting, and there was no evidence of extreme weights
- After weighting, ceritinib was found to reduce the risk of disease progression or death compared with crizotinib by [redacted] ([redacted]). Median PFS was [redacted] months for ceritinib versus 10.8 months for crizotinib, and 1-year PFS increased from 47.8% for crizotinib to [redacted] for ceritinib ([redacted])
- Comparison of OS data from both studies showed that, after weighting, ceritinib provided a greater reduction in the risk of death compared with crizotinib of [redacted], but the difference was not statistically significant ([redacted])
- These results suggest that ceritinib offers significant clinical benefits over crizotinib for the management of adults with ALK+ advanced NSCLC untreated with prior systemic therapy

B 2.9.1 Introduction and objectives

The ALK inhibitor, crizotinib, is indicated for the first-line treatment of adults with ALK+ advanced NSCLC and is considered the only relevant comparator to ceritinib for this submission as chemotherapy has now been succeeded by crizotinib as the standard of care for ALK+ advanced NSCLC (see section B 1.3.4). The efficacy and safety of crizotinib in this indication has been demonstrated in the phase III trial, PROFILE 1014 (which compared crizotinib and cisplatin-based CT),[39] but no direct head-to-head studies have compared ceritinib and crizotinib in the relevant patient population.

In the absence of relevant head-to-head randomised trials, an indirect comparison approach is required to provide evidence for the relative efficacy of ceritinib and crizotinib. However, an anchor-based indirect comparison is not feasible, due to lack of an appropriate common comparator. Although the two relevant trials – ASCEND-4 and PROFILE 1014 – both included CT as the comparator group, the CT treatments used in the two studies were not comparable (see section B 2.9.2) and thus cannot serve as a proper anchor. A matching-adjusted indirect comparison (MAIC) approach in a non-anchor based setting was therefore used to compare efficacy outcomes between these two treatments. The MAIC approach indirectly compares two treatments while adjusting for cross-trial differences in patient characteristics. It is also well-suited to compare time-to-event outcomes, whereas other existing indirect comparison methodologies rely on multivariable regression, and hence could possibly introduce bias.[77]

The objective was to indirectly compare efficacy outcomes for ceritinib and crizotinib as first-line treatments for patients with untreated advanced or metastatic ALK+ NSCLC based on data for ceritinib from ASCEND-4 and for crizotinib from PROFILE 1014.

B 2.9.2 Identification of relevant trials and assessment of feasibility of performing an indirect comparison

A systematic literature review was conducted to identify relevant studies providing evidence for the efficacy and safety of ceritinib and crizotinib in patients with advanced or metastatic non-squamous ALK+ NSCLC, untreated with systemic therapy (see Appendix D 1.1). Two relevant studies were identified (Table 18):

- ASCEND-4, the pivotal phase III trial concerning ceritinib (as described in sections B 2.3 to B 2.7). Individual patient data for patients from the ceritinib and chemotherapy arms were obtained for this study from the ASCEND-4 CSR[15]
- PROFILE 1014 (NCT01154140), a phase III randomised trial for patients with advanced or metastatic ALK+ NSCLC who received crizotinib (250 mg orally twice daily) or chemotherapy as the first-line treatment. Aggregate data for baseline characteristics and efficacy outcomes in patients treated with crizotinib or chemotherapy in this study were obtained from the primary publication.[39]

Table 18 Summary of the trials used in the MAIC

References of trial	Ceritinib	Platinum-based CT[a]	Crizotinib
ASCEND-4[66]	Yes	Yes, followed by pemetrexed maintenance therapy	–
PROFILE 1014[39]	–	Yes, but without pemetrexed maintenance therapy	Yes

[a] Cisplatin or carboplatin plus pemetrexed

A further trial was identified from the systematic literature review – a phase III trial (NCT01639001)[78] comparing crizotinib and pemetrexed-cisplatin/carboplatin as the first-line treatment for ALK+ NSCLC. However, it was decided that this was not relevant for the MAIC, as it only enrolled Asian patients and hence was not representative of the UK population.[79,80]

While ASCEND-4 and PROFILE 1014 enrolled similar patient populations and included CT as a comparator, the treatment protocols for the CT arms differed. Four cycles of CT were administered in ASCEND-4, whereas up to six cycles were permitted in PROFILE 1014. In addition, while maintenance pemetrexed was included in the chemotherapy treatment protocol for ASCEND-4 (for eligible patients who did not progress during the initial cycles), patients randomised to chemotherapy in PROFILE 1014 did not have on-protocol access to maintenance pemetrexed or other

chemotherapies. Maintenance pemetrexed has been shown to improve survival among advanced NSCLC patients who have not progressed during pemetrexed-cisplatin induction therapy.[81] Thus the chemotherapy group in the ASCEND-4 trial would be expected to have a better outcome than the corresponding group in PROFILE 1014. This means that comparing the treatment difference between chemotherapy and the ALK inhibitor in the two studies would underestimate the benefit of ceritinib. (Details of the design of ASCEND-4 are described in section B 2.3 and B 2.4. The design of PROFILE 1014 is described in Appendix D 2.1).

A further difference between the two trials was the inclusion criteria relating to patients with brain metastases. Among patients with brain metastases at baseline, all patients in the PROFILE 1014 trial had received radiotherapy, had stable disease for at least two weeks before entering the trial and were no longer receiving corticosteroid therapy. In contrast, in ASCEND-4 only 39% of patients with brain metastases received radiotherapy prior to study entry. This difference in inclusion criteria is likely to favour crizotinib, as the benefits of radiotherapy may have contributed to the intracranial responses observed in PROFILE 1014.

Based on the difference between CT regimens in the two trials, it was considered not possible to perform an 'anchor-based' analysis of first-line ceritinib and crizotinib. An alternative option would be a doubly indirect comparison in which a 'bridge' between ceritinib and crizotinib is constructed using a third randomised trial that includes a head-to-head comparison of the chemotherapy regimens used in ASCEND-4 and PROFILE 1014. However, such doubly indirect comparisons have important limitations even when suitable bridging trials are available,[82] and no suitable trial was identified for the present analysis based on a further systematic literature review (not described here). Thus, based on the similarity in patient populations (see section B 2.9.4) and differences between the CT regimens used in ASCEND-4 and PROFILE 1014, it was decided that a MAIC would be the best approach to compare the efficacy for ceritinib and crizotinib. Clinical experts and specialists in Health Technology Assessment (School of Health and Related Research, Sheffield) agreed with this decision, and this approach was accepted as being the most appropriate during discussions with NICE.[3]

B 2.9.3 Efficacy outcomes

The efficacy outcomes compared were PFS and OS. The definition of each outcome measure is detailed below:

- PFS: the time from randomisation to progression or death due to any cause, assessed by central review. Disease progression was assessed by the blinded independent review committee in ASCEND-4 and by independent radiologic review in PROFILE 1014
- OS: the time from randomisation to death due to any cause

Response rates were not formally compared between ASCEND-4 and PROFILE 1014 due to differences in assessment. In ASCEND-4, a conservative definition was used, with responses having to be confirmed no less than four weeks after the response criteria were first met (see section B 2.3.4). Conversely, confirmation of response was not required in PROFILE 1014, which could potentially have resulted in patients being considered to have a response in PROFILE 1014 that would not have been classified as a response in ASCEND-4.

Both ASCEND-4 and PROFILE 1014 also reported PFS for patients with and without brain metastases. However, given the differences between the two trials in the use of radiotherapy prior to study entry it was considered inappropriate to perform the analysis for these subgroups.

See Appendix D2.2 for details of the statistical methods employed.

B 2.9.4 Results

Matching of the baseline characteristics required only mild weighting

The comparison of baseline characteristics between the pooled populations in the ceritinib and crizotinib trials is shown in Table 19. Prior to matching, the ceritinib trial population had a significantly higher proportion of current smokers compared to the crizotinib trial population (8.0% vs. 4.4%, p = 0.046). After applying weights to patients enrolled in ASCEND-4, however, all baseline characteristics were exactly balanced between the two trial populations, and the effective sample size for ASCEND-4 was 340 (as compared to the actual sample size of 376). The extent of weighting required to achieve this balance was mild and there was no evidence of extreme weights (Figure 13), consistent with good overlap between the populations.

Table 19 Comparison of baseline characteristics before and after matching (primary analysis)[a]

	Before Matching			After Matching		
	ASCEND-4 (ceritinib and CT) (N =376)	**PROFILE 1014 (crizotinib and CT) (N=343)**	**p-value**	**ASCEND-4 (ceritinib and CT) (N =376) (ESS = 340)**	**PROFILE 1014 (crizotinib and CT) (N=343)**	**p-value**
Age < 65 years, %	78.5	84.0	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	57.4	61.8	[redacted]	[redacted]	[redacted]	[redacted]
Race – White[c], %	53.7	51.3	[redacted]	[redacted]	[redacted]	[redacted]
Race – Asian[c], %	42.0	45.8	[redacted]	[redacted]	[redacted]	[redacted]
Current smoker, %	8.0	4.4	[redacted]	[redacted]	[redacted]	[redacted]
Former smoker, %	30.9	32.1	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma[d]	96.5	93.9	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance score 0 or 1[e,f], %	93.6	94.8	[redacted]	[redacted]	[redacted]	[redacted]

Metastatic disease[g], %	96.3	98.0	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases[h], %	32.2	26.8	[redacted]	[redacted]	[redacted]	[redacted]

CT, chemotherapy
[*]p-values < 0.05 were considered significant
[a] The matching-adjusted indirect comparison (MAIC) was implemented to balance baseline patient and disease characteristics. All variables are categorical variables and were matched on proportions only.
[b] Chi-square tests were used to compare baseline characteristics between the two trials before matching. Weighted chi-square tests were used to compare baseline characteristics between the two trials after matching.
[c] Other race included black, Native American, and other (ASCEND-4 vs. PROFILE 1014: 4.3% vs. 2.9%).
[d] In ASCEND-4, other histologic types included adenosquamous cell carcinoma, large cell carcinoma, undifferentiated carcinoma, and other types and were reported in 3.5% of patients. In PROFILE 1014, non-adenocarcinoma was reported in 6.1% of patients.
[e] The ECOG performance status score assessed at baseline in ASCEND-4 was assumed to be comparable to that assessed at screening in PROFILE 1014. The score was not reported for one chemotherapy patient in ASCEND-4 and one crizotinib patient in PROFILE 1014; both were imputed as having an ECOG performance status score of 0 or 1.
[f] 6.4% of patients in ASCEND-4 and 5.2% of patients in PROFILE 1014 had an ECOG performance status score of 2 at baseline.
[g] 3.7% of patients in ASCEND-4 and 2.0% of patients in PROFILE 1014 had locally advanced disease.
[h] The presence of brain metastases assessed at randomisation in ASCEND-4 was assumed to be comparable to that reported at baseline in PROFILE 1014.

Figure 13 Histogram of weights for patients in ASCEND-4

According to the MAIC, ceritinib was associated with a significantly longer PFS compared with crizotinib

Median follow-up for ASCEND-4 and PROFILE 1014 was similar, being 19.7 months for ASCEND-4 and 17.4 months for PROFILE 1014. The comparison of efficacy outcomes between ceritinib and crizotinib before and after matching is shown in Table 20. Compared to crizotinib, ceritinib was

associated with a significantly longer PFS before matching (median: 16.6 vs. 10.8 months; [redacted]). After adjustment, the HR became [redacted] and median PFS increased to [redacted] months for ceritinib (versus 10.8 months for crizotinib, [redacted]). The adjustment did not alter the 95% CI for ceritinib substantially ([redacted] before matching; [redacted] after matching). This was consistent with the shift of an apparent plateau on the Kaplan-Meier curve, which was below the median PFS before adjustment and above after adjustment (Figure 14). Before matching, the 95% CIs for median PFS of crizotinib and ceritinib had a slight overlap, whereas after adjustment, the 95% CIs were no longer overlapping, consistent with a statistically significant difference in median PFS. In terms of OS, there was no significant difference between ceritinib and crizotinib before ([redacted]) or after matching ([redacted]), as would be expected given the immaturity of the data (see section B 2.6.3).

The proportional hazards assumption held for PFS both before ([redacted]) and after matching ([redacted]), and similarly held for OS before ([redacted]) and after matching ([redacted]). Log-cumulative hazard plots are presented in Figure 15 and support the same conclusion (that the proportional hazards assumption is reasonable in this case), as for both PFS and OS, the curves for ceritinib and crizotinib are approximately parallel during the period of time in which most events occurred.

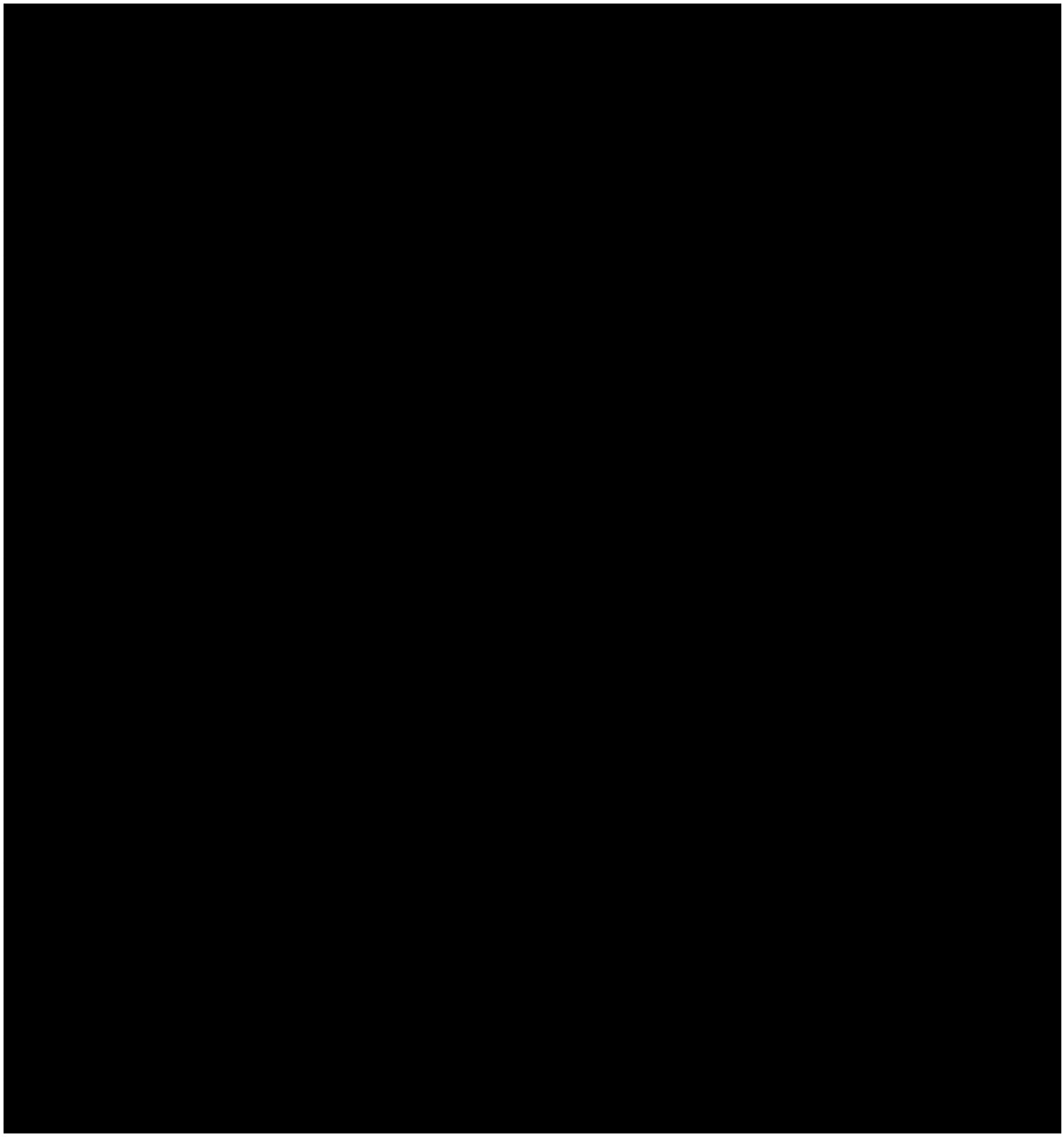
Table 20 Comparison of efficacy outcomes of ceritinib and crizotinib before and after matching

	Before matching				After matching			
	Ceritinib (ASCEND-4) N=189 [A]	**Crizotinib (PROFILE 1014) N=172 [B]**	**Response difference (95% CI) [A]- [B]**	**p-value[a]**	**Ceritinib (ASCEND-4) N=189 (ESS=171) [C]**	**Crizotinib (PROFILE 1014) N=172 [D]**	**Response difference (95% CI) [C]- [D]**	**p-value[b]**
Progression-free survival								
Median, month (95% CI)[c]	16.6 (12.6-27.2)	10.8 (8.5-13.8)			[redacted]	10.8 (8.5-13.8)		
Log-rank test, p-value				[redacted]				[redacted]
HR (CER vs. CRZ), 95% CI	[redacted]			[redacted]		[redacted]		[redacted]
1-year PFS rate, 95% CI[d]	59.9	47.8	12.0 [redacted]	[redacted]	[redacted]	47.8	[redacted]	[redacted]
Overall survival								
Median (month)	NR	NR			NR	NR		
Log-rank test, p-value				[redacted]				[redacted]
HR (CER vs. CRZ), 95% CI	[redacted]			[redacted]		[redacted]		[redacted]
1-year OS rate, 95% CI[d]	83.6	83.3	0.3 [redacted]	[redacted]	[redacted]	83.3	[redacted]	[redacted]

ASCEND-4 CSR;[15] Felip *et al.,* 2015[83]
Median follow-up was 19.7 months for ASCEND-4 and 17.4 months for PROFILE 1014.
* p<0.05 was considered significant; CER, ceritinib; CI, confidence interval; CRZ, crizotinib; ESS, effective sample size after weighting; KM, Kaplan-Meier; NR, not reached
[a] Before matching, PFS/OS rates at 1-year were compared using the Chi-squared test; PFS and OS were compared using the log-rank test and the Cox proportional hazards model. If the proportional hazards assumption was violated, the HR estimated from the Cox model may not be valid.
[b] After matching, the weighted Chi-squared test, the weighted log-rank test, and the weighted Cox model were used for the comparison. The weights were estimated from matching the patient baseline characteristics between ASCEND-4 and PROFILE 1014.
[c] Before matching, the 95% CIs for median PFS in both trials were calculated on the log-log scale using the KM estimator. After matching, the weighted 95% CI for ASCEND-4 was calculated on the log scale using the Nelson-Aalen estimator. The 95% CI for PROFILE 1014 was the same before and after matching.
[d] After matching, the PFS and OS rates at 1-year were estimated using the weighted KM method.

Figure 14 KM curves for PFS and OS before and after matching - ceritinib vs. crizotinib

Figure 15 Log-cumulative hazard plot for PFS and OS before and after matching - ceritinib vs. crizotinib



B 2.9.5 Discussion

In the absence of head-to-head randomised clinical trials of ceritinib and crizotinib, MAIC methodology was used to conduct an indirect comparison for patients with untreated, advanced or metastatic ALK+ NSCLC. MAIC are becoming widely used in Health Technology Assessments where data are not available for anchor-based indirect comparisons, including a number of recent NICE submissions,[84] and a MAIC was deemed to be the most appropriate methodology to use for this comparison. Using this approach, cross-trial differences in patient characteristics (including demographics and multiple disease features that are potentially associated with efficacy outcomes), were balanced between the ceritinib and crizotinib trials.

After adjusting for heterogeneity in patient characteristics between the two clinical trials, ceritinib was associated with significantly prolonged PFS, and numerically longer OS compared to crizotinib. The adjusted median PFS for ceritinib was [redacted] months compared with 10.8 months for crizotinib ([redacted], and ceritinib reduced the risk of disease progression or death by [redacted] ([redacted]. The adjusted OS rate for ceritinib was numerically higher than that for crizotinib ([redacted], and ceritinib was associated with an [redacted] reduction in the risk of death ([redacted]). Taken together, these results suggest that ceritinib provides a statistically significant and clinically meaningful reduction in the risk of disease progression or death compared with crizotinib, and that it may also improve OS. However, OS data from both studies are immature and should be interpreted cautiously.

As this indirect comparison evaluates non-randomised treatment groups, the potential for unobserved confounding is of primary concern. Like any other comparison of non-randomised treatment groups, the MAIC should be evaluated based on the similarity of the populations being compared and the objectivity and adequacy of the variables included for adjustment. The current MAIC adjusted for all of the baseline characteristics that were available from both the ceritinib and crizotinib trials. Therefore, the list of adjustment factors was objectively selected. The multiple baseline characteristics available for adjustment, including age, gender, race, ECOG performance score, tumour histology, extent of the disease, presence of brain metastases, and smoking status, are also consistent with previously reported prognostic factors for NSCLC outcomes.[14,30,85,86] This suggests that the adjustments are likely to have accounted for any clinically meaningful differences in baseline characteristics between the two populations. Furthermore, the extent of weighting required to achieve this balance was mild, with the ESS in ASCEND-4 being reduced by only 10% after weighting.

The overall study designs were largely consistent across the ceritinib and crizotinib trials in terms of inclusion/exclusion criteria and protocols for assessing key efficacy outcomes (e.g., PFS, OS), although differences in the definition for CR made it inappropriate to compare CR rates across the two studies. This consistency in study designs further limits the potential for unobserved confounding.

However, MAICs, like any comparison of non-randomised treatment groups, are subject to potential unobserved confounding and model misspecification bias. Only a well-conducted head-to-head randomised trial can avoid these limitations. In addition, despite the adjustment for multiple characteristics, the lack of a common comparator arm in the ceritinib and crizotinib trials is an important limitation. A valid common comparator arm would have provided an opportunity to detect and potentially further adjust for residual confounding differences between the ceritinib and crizotinib populations.

In summary, the MAIC presented here represents the best currently available comparative evidence for ceritinib and crizotinib in NSCLC. The analyses utilised studies with highly similar trial designs and adjusted for an objective and adequate list of important baseline characteristics. In addition, the MAIC provided valid 95% CIs to quantify uncertainty in comparative estimates for relevant decision makers.

B 2.10 Adverse reactions

Results from the phase III ASCEND-4 trial provide a robust assessment of the safety profile for ceritinib in patients with advanced non-squamous ALK+ NSCLC and are consistent with the safety profile reported for earlier studies in this patient population, e.g. ASCEND-1,[87] ASCEND-2,[88] ASCEND-3,[89] and ASCEND-5[90] (see Appendix F). While the data from ASCEND-4 provide an assessment of the safety profile for both ceritinib and CT, only the data for ceritinib are relevant to this submission, and hence are reported here. The rationale for this is that CT is no longer the standard of care for patients with newly diagnosed ALK+ NSCLC, as it has been superseded by crizotinib. Full safety data for ASCEND-4 are provided in Appendix F.

B 2.10.1 Drug exposure

Extent of exposure

The median duration of treatment exposure in the ceritinib group was approximately 66 weeks, and 73% of patients received ceritinib treatment for a period of ≥33 weeks. This exposure was considered long enough to assess the safety profile of the treatment.

In addition to receiving ceritinib until disease progression, 84% of patients received at least one dose of ceritinib beyond disease progression (as permitted by the study protocol), and 49% continued ceritinib (at the investigator's discretion for ongoing clinical benefit) for at least two cycles after progression. This resulted in a median additional exposure of 9.6 weeks.

Dosage

Ceritinib was generally well tolerated. Approximately a third (34%) of patients achieved a relative dose intensity (RDI) of 90–110%, and the median RDI for ceritinib was 78.4%. The corresponding average daily dose was 626 mg compared with an intended dose of 750 mg.

AEs related to ceritinib were largely managed by dose reductions or interruptions, with 68% of the patients requiring at least one dose reduction and 78% of patients requiring at least one dose interruption (Table 21). Dose reductions and treatment interruptions occurred throughout the treatment period, but their frequency was highest during weeks three to six, and these were primarily due to GI toxicity and liver function abnormalities, respectively.

Table 21 Summary of ceritinib exposure and dose adjustments in ASCEND–4

	Ceritinib (n=189)
Median duration of treatment exposure, weeks (IQR)	66.4 (30.0-83.7)
Median relative dose intensity, % (IQR)	78.4 (63.2-97.5)
Average dose, mg (mean±SD)	626.0±124.8
Proportion of patients requiring ≥1 dose reduction, n (%)	128 (67.7)
Median time to first dose reduction, weeks	9.1
Proportion of patients requiring ≥1 dose interruption, n (%)	148 (78.3)
Median time to first dose interruption, weeks	6.1

Soria *et al.*, 2017[66], ASCEND-4 CSR[15]
CSR, clinical study report; n, number of patients who had at least one dose of the corresponding drug; IQR, interquartile range; SD, standard deviation

Safety profile

An overall summary of the AEs recorded in the ASCEND-4 trial is presented in Table 22. While most (97%) patients reported AEs related to ceritinib treatment, and 65% of patients experienced grade 3/4 treatment-related AEs, only 5% of patients discontinued therapy due to AEs considered related to treatment. Thus, AEs due to ceritinib were generally manageable and reversible with dose adjustments, dose interruptions, and with supportive medication. Importantly, no new safety information emerged that would substantially alter the safety profile of ceritinib demonstrated in earlier studies in ALK+ NSCLC.

Table 22 Overall summary of AEs in the ceritinib treatment group of ASCEND-4 (n=189)

	All grades	**Grade 3 or 4**
AEs, n (%)	189 (100)	148 (78)
AEs suspected to be related to treatment, n (%)	184 (97)	123 (65)
SAEs, n (%)	70 (37.0)	59 (31.2)
SAEs suspected to be related to treatment, n (%)	30 (15.9)	23 (12.2)
Withdrawal due to AEs, n (%)	21 (11.1)	12 (6.3)
Withdrawal due to AEs considered related to treatment, n (%)	10 (5%)	
Total deaths during treatment[a], n (%)	11 (6)	
Deaths related to study drug	None	

Soria *et al.*, 2017[66], ASCEND-4 CSR[15]
[a]Total on-treatment deaths, i.e. first dose date to last dose date plus 30 days
AE, adverse event; CSR, clinical study report; SAE, serious adverse event

Incidence of AEs

Table 23 and Table 24 summarise the most frequently reported AEs for the ceritinib group. Most were grade 1 or 2 in severity and were manageable with dose adjustments. The most common AEs (any grade, ≥35% of patients) were GI (i.e. diarrhoea, nausea and vomiting), followed by elevation in the serum levels of liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT)]. Elevated liver enzymes were also the most frequently reported grade 3/4 AEs (reported in ≥15% of patients); most other grade 3/4 AEs related to treatment were reported in less than 5% of patients.

Table 23 Summary of AEs, regardless of relationship to study drug, in the ceritinib treatment group of ASCEND-4 reported in ≥15% of patients (n=189)

Adverse event, n (%)	All grades	Grade 3 or 4
Any AE	189 (100)	148 (78)
Diarrhoea	160 (85)	10 (5)
Nausea	130 (69)	5 (3)
Vomiting	125 (66)	10 (5)
Alanine aminotransferase increased	114 (60)	58 (31)
Aspartate aminotransferase increased	100(53)	32 (17)
Gamma-glutamyltransferase increased	70 (37)	54 (29)
Decreased appetite	64 (34)	2 (1)
Alkaline phosphatase increased	55 (29)	14 (7)
Fatigue	55 (29)	8 (4)
Abdominal pain	47 (25)	4 (2)
Cough	46 (24)	0
Weight decreased	45 (24)	7 (4)
Creatinine increased	42 (22)	4 (2)
Upper abdominal pain	39 (21)	3 (2)
Non-cardiac chest pain	38 (20)	2 (1)
Back pain	36 (19)	3 (2)
Constipation	36 (19)	0
Pyrexia	34 (18)	0
Asthenia	33 (17.5)	5 (3)
Headache	31 (16)	0
Dyspnoea	29 (15)	4 (2)
Anaemia	28 (15)	4 (2)

Soria *et al.,* 2017[66]

Table 24 Summary of AEs related to treatment in the ceritinib group of ASCEND-4, reported in ≥10% of patients (n=189)

Adverse event, n (%)	All grades	Grade 3/4
Total, n (%)	184 (97.4)	123 (65.1)
Diarrhoea	152 (80.4)	8 (4.2)
Nausea	121 (64.0)	5 (2.6)
Alanine aminotransferase increased	112 (59.3)	56 (29.6)
Vomiting	108 (57.1)	9 (4.8)
Aspartate aminotransferase increased	96 (50.8)	30 (15.9)
Gamma-glutamyltransferase increased	66 (34.9)	50 (26.5)
Decreased appetite	48 (25.4)	1 (0.5)
Alkaline phosphatase increased	47 (24.9)	12 (6.3)
Fatigue	42 (22.2)	5 (2.6)
Abdominal pain	39 (20.6)	4 (2.1)
Creatinine increased	37 (19.6)	3 (1.6)
Upper abdominal pain	33 (17.5)	2 (1.1)
Weight decreased	29 (15.3)	4 (2.1)
Asthenia	21 (11.1)	5 (2.6)
Rash	21 (11.1)	1 (0.5)
Electrocardiogram QT prolonged	19 (10.1)	3 (1.6)

ASCEND-4 CSR[15]
AE, adverse event; CSR, clinical study report

Treatment-related AEs

Elevated serum levels of the liver enzymes, ALT, AST and GGT, were the most frequently reported grade 3/4 events during therapy with ceritinib, occurring in 30%, 16% and 26% of patients, respectively. However, there were no cases of Hy's law. One patient discontinued treatment due to increased ALT and one due to increased GGT, but most patients were managed with dose adjustment or treatment interruption. These data are consistent with those reported in other studies in ALK+ NSCLC (see Appendix F). Thus regular monitoring of liver enzyme levels is recommended during therapy with ceritinib.[1]

QTc prolongation has been observed in clinical studies in patients treated with ceritinib and may lead to an increased risk for ventricular tachyarrhythmias (e.g. Torsade de pointes) or sudden death.[1] Thus, patients receiving medications associated with a risk of QTc prolongation were excluded from the study. During the study, QTc prolongation was observed in 19 (10%) patients and was grade 3 in four patients. All grade 3 events were considered to be related to ceritinib treatment, and were managed with dose adjustment or interruption. No patients discontinued treatment for QTc prolongation, and there were no grade 4 events or cases of Torsade de pointes. A further six patients reported other bradycardia events, only two of which were considered related to ceritinib, and neither

were grade 3/4. Periodic monitoring of electrocardiograms and electrolytes is recommended in patients with known risk factors for QTc prolongation, and heart rate and blood pressure should be monitored regularly in all patients.[1]

GI toxicities have been commonly reported during therapy with ceritinib and they are generally managed with dose interruption and/or dose reduction, as well as supportive therapies (including anti-diarrhoeals, anti-emetics and fluid replacement).[1] In ASCEND-4, GI AEs related to treatment were reported in 93% of patients, and about one-tenth of these were grade 3/4. This is consistent with the incidence of GI toxicities reported in other ceritinib studies in this patient population (see Appendix F). Approximately a quarter of patients required dose adjustment/interruption, and three patients discontinued treatment due to GI toxicity. An ongoing study, ASCEND-8, is investigating whether the administration of ceritinib with a low-fat meal (instead of in a fasting state) and at lower doses (450 mg and 600 mg) reduces the incidence of GI toxicities (see section B 2.11 for further details).

Cases of hyperglycaemia (all grades) have been reported in less than 10% of patients treated with ceritinib in clinical studies, with grade 3/4 AEs occurring in approximately 5% of patients.[1] In ASCEND-4, hyperglycaemia was reported in 21 (11%) patients, half of which were considered related to ceritinib (n=10, 5.3%). Grade 3/4 hyperglycaemia related to treatment was reported in six patients; all of whom were managed by dose adjustment/interruption.

Severe, life-threatening, or fatal interstitial lung disease or pneumonitis has been observed in patients treated with ceritinib in clinical studies, with most cases improving or resolving with interruption of treatment.[1] In ASCEND-4, interstitial lung disease/pneumonitis was reported in four patients; only one case was grade 3, and there were no grade 4 cases. One grade 2 case was suspected to be related to treatment. Two patients required dose adjustment/interruption and two discontinued therapy. One patient died, but the pneumonitis was not considered related to treatment.

The incidence of haematological AEs during therapy with ceritinib was low, consistent with reports for other studies of ceritinib (see Appendix F). Only one patient (0.5%) reported grade 3/4 neutropenia related to ceritinib and one patient (0.5%) reported grade 3/4 anaemia related to ceritinib.

Serious AEs

Serious AEs reported in ≥2% of patients, regardless of relationship to ceritinib, are summarised in Table 25, and are generally consistent with the known safety profile of ceritinib. Nausea, vomiting and elevated AST were the only SAEs considered related to treatment, and they were reported in ≥2% of patients (nausea, 3.2%; vomiting, 3.2%; AST, 2.1%).

Table 25 Serious AEs reported in ≥2% of patients, regardless of relationship to study drug, in ASCEND-4 (n=189)

Adverse events, n (%)	All grades	Grade 3/4
Total	70 (37.0)	59 (31.2)
Pneumonia	8 (4.2)	6 (3.2)
Pleural effusion	7 (3.7)	4 (2.1)
Vomiting	7 (3.7)	5 (2.6)
Nausea	6 (3.2)	1 (0.5)
Dyspnoea	5 (2.6)	4 (2.1)
Hyperglycaemia	5 (2.6)	5 (2.6)
Aspartate aminotransferase increased	4 (2.1)	1 (0.5)
Pericardial effusion	4 (2.1)	2 (1.1)
Alanine aminotransferase increased	3 (1.6)	1 (0.5)
Back pain	3 (1.6)	3 (1.6)
Creatinine increased	3 (1.6)	1 (0.5)
Diarrhoea	3 (1.6)	2 (1.1)
Lung infection	3 (1.6)	2 (1.1)
Metastases to CNS	3 (1.6)	3 (1.6)
Pulmonary embolism	3 (1.6)	3 (1.6)

ASCEND-4 CSR[15]
CNS, central nervous system; CSR, clinical study report

On-treatment deaths

A total of 11 (6%) on-treatment deaths were reported in the ceritinib group; none of these were suspected to be related to the study drug. Seven patients died due to disease progression. The remaining four patients in the ceritinib group died due to myocardial infarction (n=1), respiratory tract infection (n=1), pneumonitis (n=1) and unknown causes (n=1), and one patient in the CT group died due to lung infection.

Safety data for ceritinib in patients with ALK+ NSCLC have also been reported for three non-RCTs (ASCEND-1, -2 and -3) and for the RCT, ASCEND-5, which compared ceritinib versus CT in previously treated patients. These safety data are summarised in Appendix F.

B 2.11 Ongoing studies

Table 26 summarises ongoing studies of ceritinib in patients with ALK+ NSCLC that will report data over the next 12 months. Further results from the ongoing ASCEND-8 study may be particularly relevant to this submission.

ASCEND-8 is an open-label, multicentre, randomised, parallel design, phase 1 study that will determine the systemic exposure, efficacy and safety of ceritinib administered at a daily dose of 450 mg or 600 mg with a low-fat meal versus 750 mg daily administered in a fasting state.[91] The study involved both treatment-naïve and previously treated patients with metastatic ALK+ NSCLC. The primary objective of this study is to assess the steady-state pharmacokinetics of 450 mg or 600 mg ceritinib taken with a low-fat meal compared with that of 750 mg ceritinib taken in the fasted state, and the key secondary objective is to compare anti-tumour activity for the three regimens. The safety profile (including the incidence of GI toxicities) of the three regimens will also be compared. Data from this study will help determine whether a lower dose of ceritinib and administration with a low-fat meal reduces the incidence of GI toxicities without adversely affecting efficacy.

Table 26 Ongoing ceritinib studies in patients with ALK+ NSCLC

Trial (NCT number)	Status	Therapy	Phase of study	Objective	Expected date of reporting	
					Primary completion	Study completion
NCT01685138 ASCEND-3[92]	Ongoing	Ceritinib	2	Assess efficacy and safety of ceritinib in patients with ALK+ NSCLC Patients must have received no prior crizotinib, and must be chemotherapy-naïve or have been pre-treated with cytotoxic chemotherapy (up to three prior lines)	June 2017	June 2018
NCT01828112 ASCEND-5[93]	Ongoing	Ceritinib	3	Assess efficacy and safety of ceritinib in patients with ALK+ NSCLC Patients must have received prior crizotinib and chemotherapy (up to two prior lines)		June 2018
NCT02336451 ASCEND-7[94]	Recruiting	Ceritinib 750 mg	2	Assess efficacy and safety of ceritinib in patients with ALK+ NSCLC with active lesions in the brain and/or a diagnosis of leptomeningeal carcinomatosis	May 2018	May 2018

NCT02299505 ASCEND-8[95]	Recruiting	Ceritinib, 450 or 600 mg with low-fat meal vs. 750 mg in fasted state	1	Assess systemic exposure, efficacy, and safety of ceritinib, at a dose of 450 or 600 mg with a low-fat meal vs. 750 mg in the fasted state in patients with ALK+ NSCLC	June 2018	October 2018
NCT02450903 [96]	Recruiting	Ceritinib	2	Assess efficacy and safety of ceritinib in patients with ALK+ NSCLC previously treated with alectinib	August 2017	December 2017
NCT02393625 [97]	Recruiting	Ceritinib plus nivolumab	1	Assess efficacy and safety of ceritinib plus nivolumab in patients with ALK+ NSCLC	October 2017	October 2017

ALK+, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer

B 2.12 Innovation

Ceritinib is an innovative therapy that has helped transform the management of patients with ALK+ NSCLC through its use in the second-line setting, and it is expected to provide further substantial benefits with its extension to the first-line setting. While some of the demonstrated benefits of ceritinib over the current standard of care, crizotinib, will be captured in the quality-adjusted life year (QALY) gain, as described in section B 3 of this submission, additional benefits relating to the impact on productivity and caregiver burden, as well as the psychological effects of having a longer remission, are likely to be significant and are not captured in the model.

Ceritinib is an innovative therapy, as recognised at a regulatory level

The innovative nature of ceritinib was acknowledged in the Promising Innovative Medicine designation of the product by the Medicines and Healthcare Products Regulatory Agency, on 10 February 2015, for the treatment of adult patients with previously treated ALK+ NSCLC.[98] This is part of the Early Access to Medicines scheme, which aims to grant earlier access to innovative treatments for patients with life-threatening and seriously debilitating conditions with an unmet need. The unmet need also applies to the first-line setting where, currently, crizotinib is the only treatment option. With crizotinib, approximately 5% of patients show primary resistance, and patients develop progressive disease after a median of less than 12 months.[39]

The greater potency and specificity for ceritinib over crizotinib allows once-daily dosing and translates into a clinically meaningful prolongation in PFS

As discussed in section B 1.3.5, ceritinib has a greater potency and specificity than crizotinib, the current standard of care for newly diagnosed ALK+ NSCLC. This has translated into improved clinical

efficacy compared with crizotinib, resulting in a [redacted] reduction in the risk of disease progression or death and providing a substantially longer PFS (median, [redacted] vs 10.8 months), as discussed in section B 2.9. In addition, ceritinib demonstrates better penetration of the blood–brain barrier – an important limitation of crizotinib – which may contribute to the observed superior PFS. These therapeutic benefits are accompanied by a reduction in lung cancer-specific symptoms and an improvement in HRQoL compared with CT (see section B 2.6.6). Furthermore, ceritinib is administered once daily, as opposed to the twice-daily administration required for crizotinib.

Ceritinib offers clinically meaningful benefits in safety profile over crizotinib

Ceritinib also offers clinically meaningful benefits over crizotinib in terms of tolerability. As discussed in further detail in section B 2.13.2, ceritinib is associated was a much lower incidence of grade 3/4 neutropenia and any-grade constipation, oedema and vision disorders. In addition, the following AEs have been reported for crizotinib, but not ceritinib, at an incidence of ≥15%: vision disorders, oedema, respiratory tract infections, dysgeusia, dizziness, pain in extremity, decreased appetite and neuropathy. Reflecting this, full blood counts should be monitored during therapy with crizotinib and regular monitoring of renal function is also recommended, based on observations of decreased creatinine clearance in clinical studies. Furthermore, ophthalmological evaluation is recommended for patients experiencing new onset visual loss during therapy with crizotinib. The improved safety profile observed with ceritinib compared to crizotinib can be expected to translate into improvements in HRQoL during therapy and reduced overall costs of treatment.

The clinical benefits associated with ceritinib can be expected to reduce productivity loss in patients and their carers

The benefits of ceritinib over crizotinib resulting from the more prolonged PFS and reduced incidence of AEs are accounted for in the model through the accompanying improvements in HRQoL, as reflected in the utility values employed. However, in addition to these benefits, the improved efficacy of ceritinib is expected to reduce productivity loss, carer burden, and the impact of disease on the patient's family. Indeed, a study of cancer patients in Europe has reported that lung cancer is associated with higher productivity losses than other cancers,[60] and a US study has reported that patients with brain metastases, often present at presentation in patients with ALK+ NSCLC, have substantial productivity loss costs and more days off work compared with patients without brain metastases.[99] Given that a significant proportion of patients diagnosed with ALK+ NSCLC are in their mid-50s (the median age for diagnosis in ASCEND-4 was 55 years), many of these patients are likely to be of working age, and some may well have family responsibilities. By reducing symptoms and improving functioning and HRQoL, ceritinib is likely to enable patients to continue working for longer and thus reduce the impact of their disease on their productivity. It may also allow them to continue caring for their family, and reduce their dependence on other family members, who may also be of working age. A further benefit of ceritinib is likely to be the psychological impact of prolonging the

duration of remission and reducing the number of disease progressions a patient experiences. The impact of ceritinib on these aspects of the burden of ALK+ NSCLC are not captured in the model, but they are likely to be significant.

B 2.13 Interpretation of clinical effectiveness and safety evidence

B 2.13.1 Efficacy

Statistically and clinically meaningful improvements in PFS and response duration have been demonstrated for ceritinib vs CT in the pivotal phase III RCT, together with a numerical improvement in OS

The efficacy of ceritinib has been demonstrated in a large, international, open-label phase III trial, ASCEND-4, involving 376 patients with ALK+ NSCLC, untreated with any systemic anti-cancer therapy (except neoadjuvant or adjuvant therapy). The study demonstrated statistically significant and clinically meaningful prolongation of PFS over CT in the overall study population (median PFS, 16.6 vs 8.1 months), and median PFS was longer in patients without brain metastases compared with those with brain metastases at study entry (26.3 vs 10.7 months). Responses were achieved in 73% of patients and the median time to first response was 6.1 weeks. Importantly, responses were durable, having a median duration of 23 months. Comparable results were reported for central assessment (primary endpoint) and local assessment, and subgroup analyses for PFS demonstrated that the benefits of ceritinib over CT were consistent across all pre-specified subgroups (except where patient numbers were very low). Overall survival data are as yet immature; at the time of the data cut-off, 48 (25.4%) patients in the ceritinib group had died, resulting in an estimated 2-year OS of 70.6% (vs. 58.2% for CT). These results thus provide conclusive evidence for the clinical benefits of ceritinib.

Results for the pivotal phase III trial for ceritinib are expected to be generalisable to the anticipated patient population in England and Wales.

Results for ASCEND-4 are expected to be generalizable to the anticipated patient population in England and Wales. This reflects the fact that the baseline characteristics of patients enrolled in the trial are similar to those for patients with diagnosed with ALK+ advanced NSCLC, as agreed by clinical experts.[3] Furthermore, the trial investigated ceritinib given according to the licenced indication, and the dose adjustments and monitoring employed also corresponded to those recommended for ceritinib.[1]

Ceritinib provides a clinically meaningful prolongation of PFS compared with crizotinib, according to results of a MAIC based on the pivotal trials for both drugs

Results from the MAIC indicate that the clinical benefits provided by ceritinib are superior to those provided by crizotinib, the current standard of care for this patient population and the only relevant comparator for ceritinib in this setting. The MAIC was based on data from ASCEND-4 and the equivalent phase III study for crizotinib (PROFILE 1014) that similarly: 1) involved patients with ALK+ NSCLC untreated with any systemic anti-cancer therapy; 2) treated patients until disease progression but also allowed patients to continue on crizotinib therapy if they were continuing to benefit from therapy; and 3) included PFS as the primary endpoint and OS as a secondary endpoint. Furthermore, the duration of follow-up of the two studies was similar (19.7 months for ASCEND-4 and 17.4 months for crizotinib in PROFILE 1014). After adjusting for heterogeneity in patient characteristics between the two clinical trials, ceritinib was associated with a [redacted] reduction in the risk of disease progression or death, and a significantly prolonged PFS (median, [redacted] vs 10.8 months, [redacted]). This difference in PFS is likely to be highly clinically meaningful for patients, and suggests that ceritinib offers important clinical benefits over crizotinib for the management of untreated patients with ALK+ NSCLC.

Ceritinib was associated with improvements in lung cancer symptoms compared with CT, resulting in improvements in HRQoL

ASCEND-4 also included PRO assessments that assessed the impact of treatment on disease-specific symptoms and side effects of treatment, as well as functioning and HRQoL. Assessments were performed regularly during treatment and were completed by over 80% of patients at most time points. Ceritinib prolonged the time to definitive deterioration in lung cancer specific symptoms (pain, cough and dyspnoea) compared with CT, according to results for both the QLQ-LC13 and LCSS, with the median time to definitive deterioration being 24 months (QLQ-LC13) and not being reached (LCSS). This suggests that the clinical benefits of ceritinib are translated into meaningful benefits for patients. Furthermore, all individual cancer symptom scores showed improvements with ceritinib compared with CT. Ceritinib was also associated with improvements in HRQoL and cancer-related symptoms over time compared with CT, based on scores for the EORTC QLQ-C30. The mean EQ-5D score was indicative of a more favourable HRQoL for ceritinib vs chemotherapy (least squares mean, 0.81 vs 0.77). These results thus indicate that the clinical benefits provided by ceritinib are translated into meaningful benefits for patients and that any adverse effects on HRQoL resulting from AEs were mitigated by the reduction in symptoms achieved with treatment.

In summary, available evidence indicates that ceritinib provides clinically meaningful benefits over crizotinib for the management of patients with advanced non-squamous ALK+ NSCLC untreated with any systemic anti-cancer therapy.

B 2.13.2 Safety

A substantial body of evidence supports the safety profile of ceritinib

Overall, safety data for ceritinib in patients with ALK+ advanced NSCLC are available from five completed studies (ASCEND-1,[87] ASCEND-2,[88] ASCEND-3,[89] ASCEND-4,[66] and ASCEND-5[90]) and two ongoing studies, ASCEND-6[100] and ASCEND-8.[91] Thus, evidence for the safety profile of ceritinib in NSCLC comes from over 1000 patients involved in the clinical trial programme. In addition, currently 46 patients in England and Wales are receiving ceritinib in a second or third-line setting. Taken together, these results indicate that ceritinib is generally well tolerated, with a side effect profile that is largely manageable with dose reductions and treatment interruptions.

Results from the pivotal trial, ASCEND-4, demonstrate that ceritinib is generally well tolerated, with a side effect profile that is largely manageable with dose reductions and treatment interruptions

Specifically, in ASCEND-4, all patients receiving ceritinib experienced AEs, and grade 3/4 AEs related to ceritinib were seen in 65% of patients. Most AEs were grade 1/2 in severity, with the most commonly observed AEs (any grade, ≥35% of patients) suspected to be related to the study drug being elevation of liver enzymes, diarrhoea, nausea and vomiting. Elevated liver enzymes were the most frequently reported treatment-related grade 3/4 AEs, reported in ≥15% of patients; all other grade 3/4 AEs related to treatment were reported in ≤5% of patients. Nausea, vomiting and elevated AST were the only SAEs considered related to treatment and they were reported in ≥2% of patients (nausea, 3.2%; vomiting, 3.2%; AST, 2.1%). A total of 11 (6%) on-treatment deaths were reported in the ceritinib group; none of these were suspected to be related to the study drug. Most of the AEs were managed by dose adjustment or interruptions, which were required in 68% and 78% of the patients, respectively. An ongoing study, ASCEND-8, is investigating whether a lower dose and administration with a low-fat meal may improve the safety profile. Only 5% of patients discontinued ceritinib due to AEs suspected to be related to treatment.

Ceritinib offers clinically meaningful improvements in safety profile over crizotinib, including a lower incidence of grade 3/4 neutropenia and any-grade oedema and vision disorders

As described above (section B 2.13.1) the patient populations for ASCEND-4 and PROFILE 1014 are similar; thus direct comparison of the safety data are clinically meaningful. A comparison of the data from the two studies indicates that while the safety profiles of ceritinib and crizotinib are largely similar, other aspects of the safety profile of ceritinib demonstrated clinically meaningful improvements over that associated with crizotinib (in PROFILE 1014).[39] Thus, in both studies grade 1/2 GI toxicities were the most frequently reported AEs, and grade 3/4 liver enzyme elevations were observed in approximately a third of patients. However, grade 3/4 neutropenia was observed in only 1% of patients receiving ceritinib compared with 11% receiving crizotinib, and any-grade vision disorders (70%), constipation (43%) and oedema (49%) were reported in ≥40% of patients receiving crizotinib

but only 19% (constipation) or <15% (vision disorders and oedema) of patients receiving ceritinib. Rates of discontinuation due to treatment-related AEs were 5% for both ceritinib and crizotinib.

In summary, the available evidence indicates that ceritinib is generally well tolerated, and may offer advantages over crizotinib for the management of patients with advanced non-squamous ALK+ NSCLC untreated with any systemic anti-cancer therapy.

B 2.13.3 Strengths of the evidence base

Evidence for the efficacy and safety of ceritinib for the treatment of ALK+ advanced NSCLC is based on the results of a large, multicentre, phase III trial in the relevant patient population and is supported by safety data from four other studies in patients previously treated with crizotinib and/or CT (ASCEND-1,[87] ASCEND-2,[88] ASCEND-3,[89] and ASCEND-5[90]). Comparative data regarding the efficacy of ceritinib compared with crizotinib, the only relevant comparator, are available from a robust MAIC based on data from the pivotal phase III trials for both therapies in this indication. The evidence base for the efficacy and safety of ceritinib in the relevant patient population is therefore robust, as discussed below.

Design

The pivotal trial for ceritinib involved patients corresponding to the anticipated population relevant to this submission

Patients included in ASCEND-4 corresponded to the licensed indication relevant to this submission and were similar to those who would be expected to receive therapy with ceritinib in England and Wales, according to expert clinical opinion.[3] Identification of patients for inclusion in ASCEND-4 was based on ALK+ testing and diagnostic procedures that are currently part of routine practice in England and Wales for the management of patients with advanced NSCLC.

Ceritinib dosing and patient monitoring in the pivotal trial corresponded to the licenced dose and management recommendations

In ASCEND-4, ceritinib was dosed according to the licence. This included the use of dose reductions or treatment interruptions for the management of AEs. Furthermore, monitoring of patients during the trial also corresponds to that recommended during treatment with ceritinib. This included regular liver laboratory tests, monitoring for GI toxicity and pulmonary symptoms indicative of pneumonitis, and periodic monitoring of ECG, electrolytes, heart rate, blood pressure, fasting plasma glucose and lipase and/or amylase. Thus, both the efficacy and safety outcomes reported for ASCEND-4 are likely to correspond to the expected experience in routine clinical practice.

Efficacy outcomes

The pivotal trial utilised a robust assessment of the primary efficacy outcome, PFS, based on local and central assessment and confirmation of responses within four weeks of the initial assessment

The efficacy endpoints reported in ASCEND-4 are considered relevant to the management of advanced NSCLC and reflect the impact of disease on the patient. They also correspond to the endpoints previously reported for studies in patients with ALK+ advanced NSCLC or advanced NSCLC in general. PFS, the primary endpoint, provides a robust measure of the effect of therapy on the duration of remission, an outcome that is highly relevant to clinical practice and to patients. Furthermore, PFS, unlike OS, is not confounded by the effects of subsequent treatments on disease progression. The assessment of response (on which PFS and response rates are dependent) was based on RECIST 1.1 criteria and required the response to be confirmed within four weeks of the initial assessment. Thus, the study employed a validated and robust assessment of tumour response. In addition, for the primary endpoint, response was to be assessed by a blinded central reviewer, and local assessment was included as a secondary endpoint. Similar results were reported for central and local assessment, thus providing confirmation of the accuracy of the assessment of response and hence PFS.

The impact of ceritinib on symptoms and HRQoL were assessed using validated disease-specific and generic instruments

ASCEND-4 also included assessment of the effect of treatment on symptoms, functioning and HRQoL. This was achieved with four PRO instruments. Two of the PROs were disease-specific and assessed symptoms associated with lung cancer – the EORTC QLQ-LC13 and the LCSS. The other two instruments employed were the widely-used generic cancer instrument, EORTC QLQ-C30, and the EQ-5D, which is the instrument recommended by NICE for determination of utility values for economic modelling. Assessments were performed regularly during treatment and were completed by over 80% of patients at most time points. The mean utility value obtained in ASCEND-4 during treatment with ceritinib is used in the economic model.

Median duration of follow-up in ASCEND-4 was 20 months. This is sufficient to assess the response to therapy, including the duration of response and PFS, in this patient population. However, follow-up was not sufficient to assess the impact on OS, as discussed in section B 2.13.4.

Safety

Results from ASCEND-4 provide a comprehensive assessment of the safety profile of ceritinib in the relevant patient population and are supported by additional safety data from three non-RCTs, and a further RCT, involving a total of over 1000 patients.

B 2.13.4 Weaknesses of the evidence base

There are two main weaknesses of the evidence base in relation to the economic model.

Firstly, the comparator for the pivotal phase III trial was CT, which has been superseded by crizotinib as the standard of care in the first-line setting. This has been addressed by performing a MAIC based on the pivotal phase III trial for ceritinib (ASCEND-4) and the corresponding study for crizotinib (PROFILE 1014), as described in detail in section B 2.9. MAIC methodology is considered an appropriate approach to provide comparative data when direct head-to-head evidence is not available. As described in section B 2.9, this approach is particularly applicable for the comparison between ceritinib and crizotinib, as the relevant phase III studies were similar in terms of patient population, design, efficacy outcomes and duration of follow-up. In addition, the similarities in patient population and design of the two studies imply that the results for ASCEND-4 are likely to correspond to the outcomes expected in clinical practice in the UK. Furthermore, MAIC methodology enabled adjustment for the minimal differences in baseline patient characteristics; this was reflected in the fact that the ESS in ASCEND-4 was only reduced by 10%. The results from the MAIC are thus considered to provide a reliable measure of the benefit of ceritinib over crizotinib with respect to PFS, and the MAIC is the best possible mitigating strategy for the fact that the CT comparator has been superseded by an alternative first-line treatment.

Secondly, OS data are as yet immature and hence data from ASCEND-4 cannot definitively predict the effect of ceritinib on OS. This reflects the fact that the data reported to date and in this submission are for the second pre-planned analysis of OS that was to be performed at the time of the analysis of the primary endpoint (PFS), if this was statistically significant. The study is however ongoing, and two further analyses of OS are planned.

B 2.13.5 Relevance of the evidence to the decision problem

Results from ASCEND-4, PROFILE 1014, and from the MAIC comparing ceritinib and crizotinib are considered relevant to clinical practice in England and Wales, and hence are highly relevant to the decision problem. Thus, results from these trials and the MAIC are used to populate the economic model.

Firstly, ASCEND-4 assessed ceritinib at the licensed recommended dose and regimen in the relevant patient population. Therefore, the PFS and OS data from ASCEND-4 are used in the model for

ceritinib. The corresponding inputs for crizotinib are taken for the MAIC, based on the fact that PROFILE 1014 similarly assessed the effects of crizotinib given according to the licensed indication and in the relevant patient population. Secondly, values for the incidence of grade 3/4 AEs during therapy with ceritinib and crizotinib for use in the model are similarly taken from ASCEND-4 and PROFILE 1014, respectively. Thirdly, both pivotal phase III trials included assessments of HRQoL using EQ-5D, and hence the progression-free (PF) utility values used in the model are taken directly from the two studies. Finally, treatment duration and post-progression treatments used in the model were also taken directly from ASCEND-4 and PROFILE 1014.

B 2.13.6 End-of-life criteria

Ceritinib does not meet the end of life criteria, as the mean and median OS for newly diagnosed patients with ALK+ NSCLC on crizotinib are >24 months.[101]

B 3. Cost effectiveness

B 3.1 Published cost-effectiveness studies

A systematic literature review identified seven publications reporting information on six cost-effectiveness assessments (CEA) (see Appendix G for further details). The identified models examined the cost-effectiveness of the following ALK targeted therapies: crizotinib (four studies), ceritinib (two studies), and alectinib (one study). Only one model was performed for the UK; the other were for the US (three studies) and one each for Canada and China. Five models reported their modelling method, which included: Markov model (two studies), partition survival methods (two studies), and semi-Markov model (one study). Four studies reported health states considered in the models, five reported cost inputs, and four reported utility inputs. Sensitivity analysis was only reported in half of the models (see Appendix G for further details).

Three studies related to cost-effectiveness of first line treatments and two related to second-line treatments. Three studies examined the cost-effectiveness of ALK targeted therapies versus chemotherapy, and one study examined the cost-effectiveness of replacing ceritinib with alectinib. In addition, three studies examined the cost-effectiveness of various molecular testing methods for ALK mutations. The results of these studies are summarised in Table 27.

The CEA that was performed for the UK (Morgan et al 2017[102]) assessed the cost-effectiveness of using crizotinib compared with CT for the first-line treatment of ALK+ advanced NSCLC. This was the only study considered to be relevant to the current submission, hence it was used to inform inputs for the *de novo* model, as described in the following sections.

Table 27: Results of the identified cost-effectiveness studies

Study	Patient Population		Currency (year)	LYG	QALYs	Costs	ICER	
	Disease subtype	Line of therapy					Cost/LYG[a]	Cost/QALY gained[a]
Atherly et al 2012[103]	ALK+ advanced NSCLC	NR	USD (NR)	NR	0.83 (patients who are positive for a predictive biomarker)	$1400 (FISH)[b] $875 (RT-PCR)[b] $600 (IHC assay)[b]	NR	$106,707 (FISH vs. no screening) $95,274 (RT-PCR vs. no screening) $57,165 (IHC assay vs. no screening)
Djalalov et al 2014[104]	EML4-ALK+ NSCLC	2L	CAD (NR)	NR	0.539 (pemetrexed) 0.429 (docetaxel)	$19,388 (pemetrexed) $33,226 (docetaxel)	NR	$333,595 (crizotinib[c] vs. pemetrexed) $125,812 (crizotinib[c] vs. docetaxel)
Upadhyay et al 2015[105]	ELM4-ALK+ NSCLC	1L	USD (NR)	NR	0.09 (incremental; ceritinib vs. chemotherapy)	NR	NR	$21,263 (ceritinib vs. chemotherapy)
Lu et al 2016[106]	ALK+ advanced NSCLC	1L	USD (2015)	0.437 (control) Crizotinib with PAP 0.470 (Ventana IHC testing) 0.469 (IHC testing + FISH confirmation) 0.468 (qRT-PCR testing) Crizotinib without PAP 0.470 (Ventana IHC testing)	0.737 (control) Crizotinib with PAP 0.766 (Ventana IHC testing) 0.765 (IHC testing + FISH confirmation) 0.764 (qRT-PCR testing)	$32,368 (control) Crizotinib with PAP $32,861 (Ventana IHC testing) $32,847 (IHC testing + FISH confirmation) $33,039 (qRT-PCR testing) Crizotinib without PAP $38,916 (Ventana IHC testing)	NR	Crizotinib with PAP $16,820 (Ventana IHC testing vs. no screening) $16,850 (IHC testing + FISH confirmation vs. no screening)

				0.469 (IHC testing + FISH confirmation) 0.468 (qRT-PCR testing)	Crizotinib without PAP 0.766 (Ventana IHC testing) 0.765 (IHC testing + FISH confirmation) 0.764 (qRT-PCR testing)	$38,717 (IHC testing + FISH confirmation) $39,368 (qRT-PCR testing)		$24,424 (qRT-PCR testing vs. no screening) Crizotinib without PAP $223,242 (Ventana IHC testing vs. no screening) $223,271 (IHC testing + FISH confirmation vs. no screening) $254,668 (qRT-PCR testing vs. no screening)
Carlson et al 2017, Carlson et al 2016[107,108]	ALK+ advanced NSCLC	2L	USD (2016)	2.39 (alectinib) 1.67 (ceritinib)	1.42 (alectinib) 0.98 (ceritinib) 0.44 (incremental QALY)	$255,657 (alectinib) $233,274 (ceritinib)	$19,313 (alectinib vs. ceritinib)	$31,180 (alectinib vs. ceritinib)
Morgan et al 2017[102]	ALK+ advanced NSCLC	1L	GBP (NR)	2.42 (crizotinib) 1.49 (pemetrexed + cisplatin/carboplatin)	Data redacted from NICE submission (TA406)	£79,884 (crizotinib) £21,480 (pemetrexed + cisplatin/carboplatin)	NR	£47,291 (crizotinib vs. chemotherapy)

1L, first-line; 2L, second-line; ALK, anaplastic lymphoma kinase; CAD, Canadian dollar; EML4, echinoderm microtubule-associated protein-like 4; FISH, fluorescence in situ hybridisation; GBP, Great British pound; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; LYG, life-year gained; NR, not reported; NSCLC, non-small cell lung cancer; QALY, quality-adjusted life year; qRT-PCR, quantitative real-time reverse transcription polymerase chain reaction; PAP, patient assistance program; USD, United States dollar

[a] ICERs are presented as treatment versus the comparator in parentheses

[b] Costs were assumed based on expert opinion

[c] Treatment with crizotinib in combination with EML4-ALK genetic testing

B 3.2 Economic analysis

B 3.2.1 Introduction to de novo model

A *de novo* model was designed to assess the cost-effectiveness of ceritinib compared to crizotinib for management of untreated patients with ALK+ advanced NSCLC, from the UK National Health Service (NHS) and Personal Social Service (PSS) perspective. During model development, the NICE technology appraisal for crizotinib as a first-line treatment for untreated ALK+ advanced NSCLC was reviewed to help inform the economic model structure and choice of parameter inputs.[109]

B 3.2.2 Model overview

Patient population

The patient population for the economic evaluation was patients with ALK+ advanced NSCLC, who had not received prior treatment with systemic anti-cancer therapy. This patient population is in line with the population defined in the NICE scope and the decision problem presented in this submission, as well as the indication for ceritinib to which this submission relates. This corresponds to the patient population included in the ASCEND-4 trial for ceritinib and PROFILE 1014 for crizotinib. In the NICE assessment of crizotinib as first-line therapy for patients with untreated ALK+ advanced NSCLC, the appraisal committee agreed that the trial population in PROFILE 1014 corresponds closely to the anticipated population in England and Wales which means that the results from this trial can be considered generalizable to the UK setting. [101]

Comparator selection

Crizotinib was selected as the comparator to ceritinib for management of untreated patients with ALK+ advanced NSCLC. Crizotinib is currently the only ALK inhibitor approved by NICE for untreated *ALK*+ NSCLC patients in the UK (TA406),[101] and was identified by clinical experts as the only relevant comparator in this population.[3]

Perspective

The cost-effectiveness analysis was conducted from the perspective of UK NHS and PSS. Therefore, only direct health care costs were considered in the model.

Time horizon

In the base case, a time horizon of 20 years was considered in order to comprehensively capture the expected costs and health outcomes of patients over their remaining lifetime from the initiation of first-line treatment. Since most patients with advanced NSCLC were expected to die within 20 years of initiating treatment, this timeframe was viewed as consistent with a lifetime model horizon. [According to the base-case parametric extrapolation for OS, described in section B 3.3.2, 2% (ceritinib) and 1%

(crizotinib) of patients would still be alive at 20 years after the initiation of first-line ceritinib, see Table 28]. Sensitivity analyses considered time horizons of 10 and 15 years.

Table 28 Predicted survival by treatment arm over 5-, 10-, 15-, and 20-year model timeframes

Model timeframe	Predicted survival by first-line treatment arm	
	Ceritinib (%)	Crizotinib (%)
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
15 years	[redacted]	[redacted]
20 years	2	1

Predictions of survival are from the base-case extrapolation of OS in the ceritinib and crizotinib treatment arms, as described in section B 3.3.2.

Model outputs

During the modelled time horizon, costs and effectiveness were estimated for each treatment arm included in the model. Costs included for ceritinib or crizotinib were: acquisition costs, associated drug administration, the management of treatment-related AEs, progression free (PF) medical input, progressed disease (PD) medical care, post-progression treatment and terminal care. Effectiveness measures included life years (LYs) and quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) of ceritinib versus crizotinib was evaluated in terms of the incremental cost per QALY gained and the incremental cost per LY gained.

Discount rate

In the base case, both costs and effectiveness were discounted at 3.5% annually. The deterministic sensitivity analysis considered annual discount rates of 0% and 6%.

B 3.2.3 Model structure

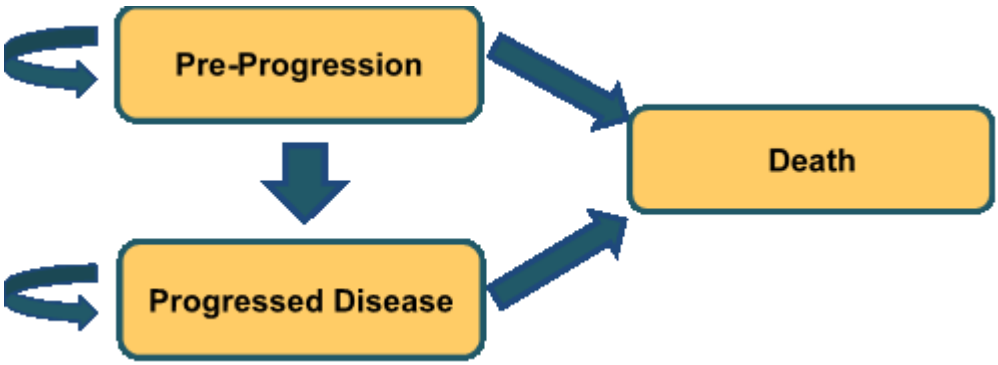
The cost-effectiveness model was developed in Microsoft Excel®. The analysis used a partitioned survival type model, which is a typical approach in modelling advanced or metastatic cancers and has been used in many previous NICE submissions (for example, the manufacturer's submission for crizotinib, TA406).[101] It captures the progressive nature of the disease, and reflects the main outputs measured in clinical trials (i.e. PFS and OS).

Three mutually exclusive health states were defined: (i) PF, (ii) progressed disease (PD) and (iii) death (Figure 16). The PF health state includes both patients achieving objective responses to treatment or stable disease. In the model, patients are assumed to transition between these three health states, with death being the absorbing state. The proportion of patients in the PD state at each

cycle was calculated as the difference between the proportion of patients surviving and the proportion of patients remaining in the PF state.

The cycle length was one month.

Figure 16 Partitioned survival model structure



The model aims to capture the progressive nature of ALK+ NSCLC disease for the relevant patient population, and is aligned with the main aim of all treatment interventions for patients with ALK+ advanced NSCLC; that is, to achieve and maintain a state of “progression free” survival and to extend overall survival. The chosen structure of the model is in line with the clinical treatment paradigm, as described in section B 1.3.4, whereby patients receive therapy with the aim of maintaining progression-free disease, before stopping or switching treatment (as appropriate) in the event of disease progression. Specifically, in the economic model, patients were assumed to receive subsequent active treatment and/or BSC following progression on first-line therapy; this was included in the PD health state.

Table 29 summarises the key features of the economic analyses and compares this analysis for ceritinib with the 2016 economic analysis of crizotinib as the first-line treatment for ALK+ advanced NSCLC.[101] Both assessments considered a lifetime horizon and involved a three-health state model with equivalent health states, i.e. PF, PD and death. In both cases, clinical data were taken from the pivotal trial for the respective product, although in the case of ceritinib, a MAIC was utilised to obtain data for the comparator, crizotinib, whereas in the crizotinib assessment, data for the comparator, CT, were obtained from the pivotal trial. Utility values for the PF health state were obtained from trial data in both assessments, whereas published literature was used for the utility value for the PD health state. Sources for costs were generally equivalent for the two assessments.

Table 29 Features of the economic analysis and comparison with the economic analysis for crizotinib as first-line treatment for ALK+ advanced NSCLC

	Crizotinib TA406[101]		Current appraisal	
	Chosen values	**Justification**	**Chosen values**	**Justification**
Time horizon	15 years	Sufficiently long that the majority of patients in the model have died by the end of the modelled time horizon	20 years	Sufficiently long that the majority of patients in the model have died by the end of the modelled time horizon
Health states	Progression-free, progressed, death	Reflects the aim of treatment: to maintain patients in progression-free state	Progression free, progressed disease, death	Reflects the aim of treatment: to maintain patients in progression-free state
Comparator	Pemetrexed plus platinum chemotherapy	Standard of care at the time of the submission	Crizotinib	Current standard of care
Treatment discontinuation	Treatment continued beyond progression based on data from the pivotal trial	Reflects the data source used for efficacy estimates	Treatment continued beyond progression based on data from the pivotal trial	Reflects the data source used for efficacy estimates
Transition through the model	Based on the pivotal trial, PROFILE 1014, and extrapolation using parametric survival models	Reflects the expected clinical outcomes	Based on the pivotal trial, ASCEND-4 for ceritinib, the MAIC for crizotinib, and extrapolation using parametric survival models	Reflects the expected clinical outcomes
Source of utilities	PROFILE 1014 data for PF utilities, and published literature for PD 2nd and 3rd line	PROFILE 1014 collected EQ-5D data for crizotinib and CT during treatment. Patients could continue on treatment beyond disease progression. However, data post-progression were not collected consistently in all	ASCEND-4 data for PF, published data from PROFILE 1014 for crizotinib, and published literature for PD	ASCEND-4 collected EQ-5D utilities for ceritinib during treatment and PROFILE 1014 collected equivalent data for crizotinib. Patients could continue on treatment beyond disease progression. However, data

		patients		post-progression were not collected consistently in all patients in either study
Source of costs	Drug acquisition costs were from the Monthly Index of Medical Specialities (MIMS) for branded products, and the electronic market information tool (eMit) for generic products. Administration costs and health state costs were from NHS reference costs 2014-15. Palliative care costs were from, Georghiou & Bardsley, 2014[110]		Drug acquisition costs were from the Monthly Index of Medical Specialities (MIMS) for branded products, and the electronic market information tool (eMit) for generic products. Drug administration costs were from PSSRU 2016 for the hourly rate of a hospital pharmacist. Administration costs and health state costs were from NHS reference costs 2015-16. Palliative care costs were from Georghiou & Bardsley, 2014[110]	

B 3.3 Clinical parameters and variables

B 3.3.1 Overview

Efficacy inputs included PFS and OS. PFS and OS inputs for ceritinib were based on ASCEND-4,[15] the head-to-head, phase III trial directly comparing first-line ceritinib versus CT (cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance therapy), as described in sections B 2.3 to B 2.6. PFS and OS inputs for crizotinib were based on PROFILE-1014,[39] a phase III trial comparing the efficacy of first-line crizotinib versus CT (cisplatin or carboplatin plus pemetrexed, but without pemetrexed maintenance therapy). Estimates of the relative efficacy of ceritinib versus crizotinib were obtained from an indirect comparison study that adjusted for observed differences between the two trial populations, as described in section B 2.9. In this MAIC, all the baseline characteristics of the reweighted ASCEND-4 trial population were exactly matched to the characteristics of the PROFILE 1014 trial population, as the latter was considered to reflect the characteristics of the UK patient population (see also section B 2.9.2).[101]

B 3.3.2 Modeling progression-free survival and overall survival

For each treatment arm, the cost-effectiveness model estimated the amount of time spent in the PF, PD and death states based on area under the PFS and OS curves during the 20-year model timeframe. PFS and OS curves for ceritinib were estimated by fitting parametric functions to patient-level time-to-event data from the ASCEND-4 trial. The HR method was used to estimate PFS and OS curves for the crizotinib arm using the relative efficacy estimated from the MAIC. The adjustment for observed heterogeneity in patient characteristics under this approach was expected to yield a balanced comparison between ceritinib and crizotinib.

As described in section B 2.9, the assumption of proportional hazards was assessed through both formal tests and visual inspection of the log-cumulative hazard plots for PFS and OS. The proportional hazards assumption held for both PFS and OS based on statistical testing (all $p>0.05$; Figure 14). For PFS, the log-cumulative hazard plots were approximately parallel, except at extreme time points when few events occurred; for OS, the plots showed few deviations from parallel lines (Figure 15). The proportional hazards assumption was considered appropriate based on these findings. Moreover, large shifts in the PFS and OS HRs over time were not expected, given the similarities between the treatment arms in terms of therapeutic class, route of administration, and treatment duration rules (i.e. neither treatment was subject to a maximum allowed duration).

During model development, three medical experts were individually consulted to evaluate efficacy inputs and other key model parameters from a clinical perspective. Details on the qualifications of each clinician are provided in Appendix K. Based on feedback from these model validation meetings, it was decided that it was not relevant to adjust efficacy inputs to reflect the characteristics of the UK

patient population,[3] as the ASCEND-4 and PROFILE 1014 trial populations were sufficiently representative of real-world patients. In TA406, the Committee agreed that PROFILE 1014 patient population reflected the UK ALK+ NSCLC patient population.[101]

Progression-free survival and overall survival for ceritinib

PFS and OS curves for ceritinib were derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, and log-normal distributions) to patient-level data from the ASCEND-4 trial to extrapolate efficacy outcomes beyond the trial period.[15] Because the HR method was used to estimate PFS and OS curves for crizotinib, only the proportional hazards models (including Weibull, exponential and Gompertz distributions) were considered when selecting parametric PFS and OS functions for ceritinib. However, non-proportional hazards models of PFS and OS for ceritinib (including log-logistic and log-normal parametric functions) were also fitted to patient-level ASCEND-4 data for testing purposes. Goodness-of-fit criteria [including the Akaike information criterion (AIC) and Bayesian information criterion (BIC)] were reported for each parametric function (Table 30). Selection of the base-case parametric models of ceritinib for PFS and OS was informed by:

- Comparisons of AIC/BIC fit statistics to assess the fit of different parametric models to the observed data, with lower values indicating better fit; and
- Expert opinion on the clinical plausibility of long-term outcome predictions under different models, based on meetings with three medical experts

Based on these criteria, the exponential function was selected as the most appropriate base-case parametric model for PFS. The Gompertz PFS function demonstrated the best fit with the observed trial data among the proportional hazards distributions, but yielded long-term predictions of PFS that were implausibly high according to the medical experts (Figure 17). In contrast, the base-case exponential function predicted that 8.8% of patients treated with first-line ceritinib would remain progression-free at five years, an estimate that experts found to be more credible than the 5-year PFS rates predicted by the Gompertz and log-normal functions (23.1% and 20.8%, respectively).

For ceritinib OS, the exponential function was chosen as the base-case model based on goodness-of-fit with the observed data (indicated by lowest AIC and BIC among all distributions), and clinical plausibility (Figure 18). The log-cumulative hazard plot for OS with ceritinib was approximately linear in shape and also supported the choice of an exponential OS distribution (Figure 15). As described in Appendix J, the use of exponential PFS and OS functions for ceritinib yielded estimates of post-progression survival that were nearly equivalent to the first-line ceritinib and crizotinib treatment arms in ASCEND-4 and PROFILE 1014, respectively.

In model validation meetings, the clinicians agreed with the choice of the exponential OS function for ceritinib in the base case, but noted that long-term survival predictions were higher than they expected to observe in clinical practice. Given the uncertainty surrounding long-term OS with first-line ALK inhibitor treatments, scenario analyses were conducted using alternative parametric distributions of OS (i.e. Weibull and Gompertz).

Table 30 Parametric estimates of PFS and OS for ceritinib

	Progression-free survival		Overall survival	
Parametric function	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	750.407	753.649	498.862	502.104
Log-logistic	748.552	755.036	499.449	505.933
Log-normal	743.773	750.257	501.126	507.610
Weibull	751.576	758.060	499.420	505.903
Gompertz	749.725	756.209	499.938	506.422

AIC, Akaike information criterion; BIC, Bayesian information criterion; SD, standard deviation

Figure 17 Observed and predicted PFS for ceritinib using different parametric functions

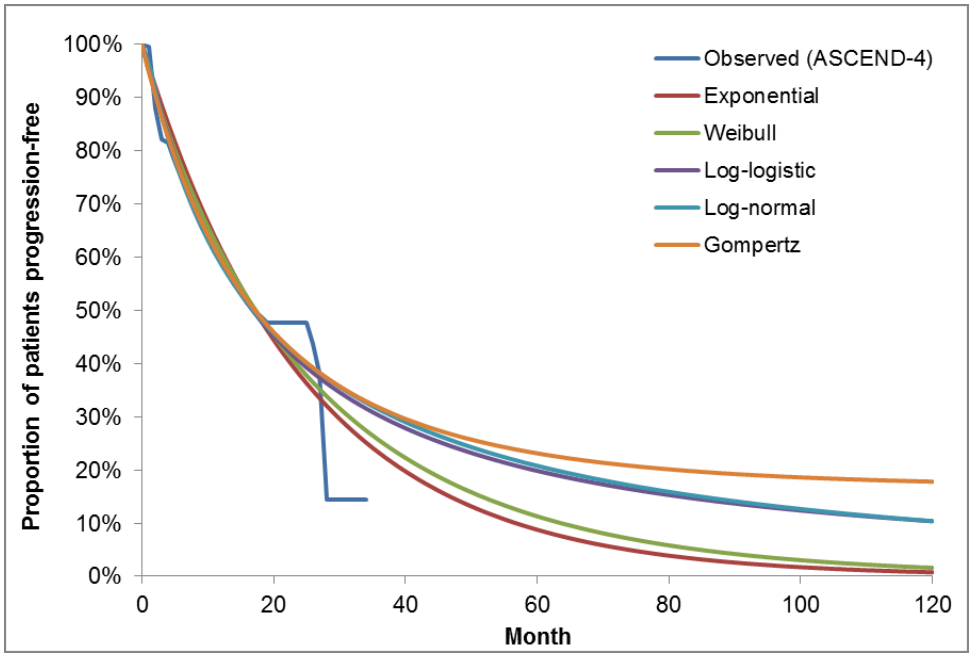
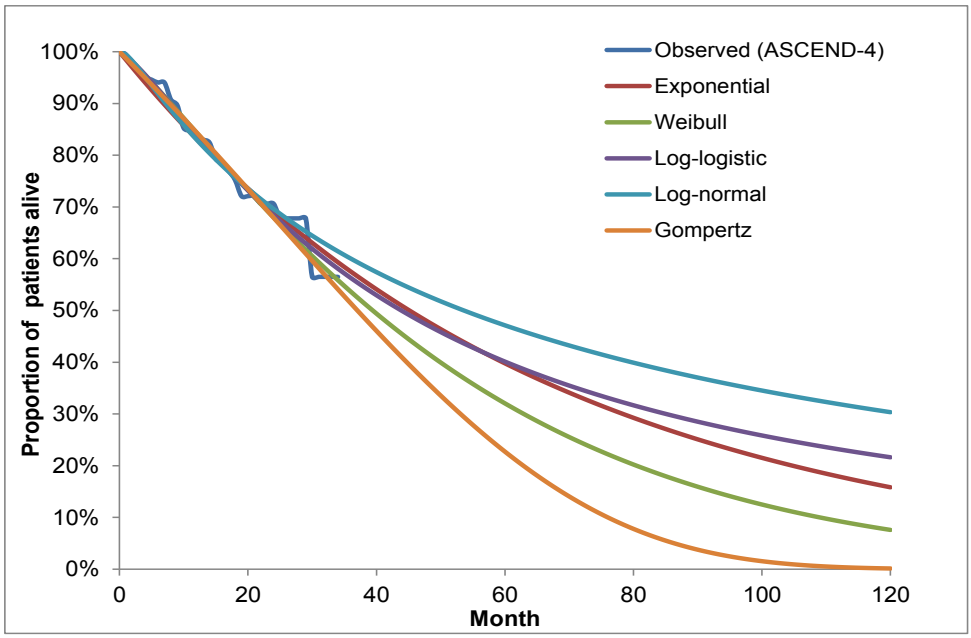


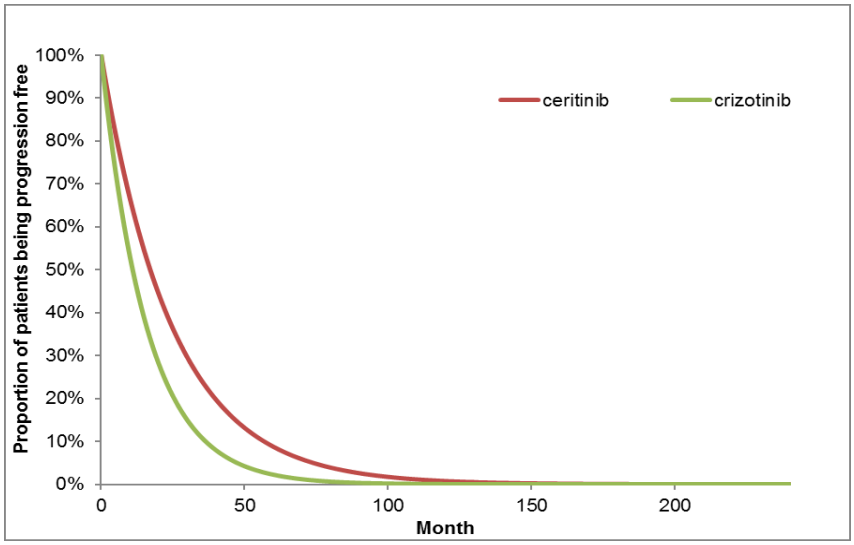
Figure 18 Observed and predicted OS for ceritinib using different parametric functions



Progression-free survival and overall survival for crizotinib

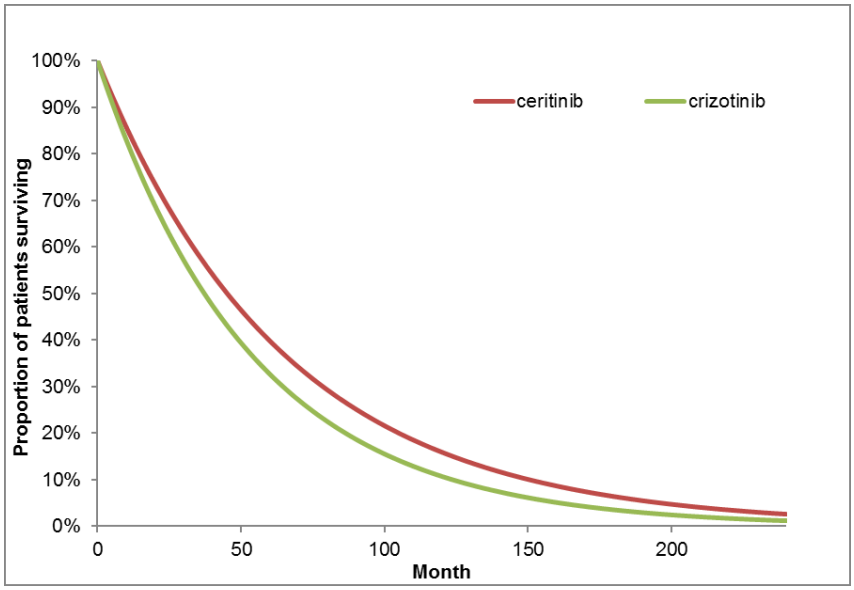
To generate PFS and OS curves for crizotinib in the base case analysis, the model applied the corresponding HR of crizotinib versus ceritinib to parametric models of ceritinib PFS (Figure 19) and OS (Figure 20). The HRs of PFS and OS for crizotinib versus ceritinib were estimated in the MAIC, as described in section B 2.9.

Figure 19 Predicted PFS for ceritinib and crizotinib



The predicted PFS curve for ceritinib is based on the exponential function. The PFS curve for crizotinib is derived by applying the HR vs. ceritinib to the exponential PFS curve for ceritinib.

Figure 20 Predicted OS for ceritinib and crizotinib



The predicted OS curve for ceritinib is based on the exponential function. The OS curve for crizotinib is derived by applying the HR vs. ceritinib to the exponential OS curve for ceritinib.

B 3.3.3 Adverse events

Treatment-related grade 3/4 AEs were included in the model if they affected ≥5% of patients receiving ceritinib or crizotinib in ASCEND-4 and PROFILE 1014, respectively, as summarised in Table 31.

Table 31 Treatment-related grade 3/4 adverse events included in the economic model

Adverse events, %	Ceritinib	Crizotinib
Neutropenia	0.5	11.1
Diarrhoea	5.3	2.3
Pulmonary embolism	0.0	6.4
Vomiting	5.3	1.8
Hyperglycaemia	6.3	0.0
Alanine transaminase (ALT) elevation	30.7	14.0
Aspartate aminotransferase (AST) elevation	16.9	0.0
Gamma-glutamyltransferase increased	28.6	0.0
Blood alkaline phosphatase increased	7.4	0.0

ASCEND-4 CSR[15]; Solomon *et al.,* 2014[39]

B 3.3.4 Treatment duration

Base case: Treatment until discontinuation

In the base case, patients were assumed to continue first-line treatment until discontinuation, based on treatment duration data reported from the ASCEND-4 and PROFILE 1014 trials. The proportion of

patients on treatment in each cycle was estimated using an exponential survival function for each treatment.

In the base case, the rate parameter (λ) of the exponential functions for ceritinib and crizotinib was estimated using the truncated median treatment durations reported in their respective clinical trials. This data approach was selected due to the unavailability of time-to-event data for crizotinib treatment discontinuation. During the preparation of this submission, requests were made to the manufacturer of crizotinib (Pfizer) (as advised by the NICE project team) for the Kaplan-Meier time to discontinuation curve from the PROFILE 1014 trial, but this could not be granted due to data confidentiality. Given this data limitation, estimating discontinuation rates based on the truncated median duration for both ceritinib and crizotinib was expected to yield a more balanced comparison of treatment duration than using patient-level time-to-event data for ceritinib (from ASCEND-4 trial) and the truncated median duration for crizotinib.

For ceritinib, the exponential rate of treatment discontinuation was estimated based on the truncated median duration of 15.3 months reported in the ASCEND-4 trial CSR, in which treatment duration was counted from the first ceritinib dosing date until the last ceritinib dosing date prior to the data cut-off. For crizotinib, the exponential rate of treatment discontinuation was estimated using the truncated median treatment duration of 10.9 months reported in the PROFILE-1014 trial.

In sensitivity analyses, several alternative treatment duration scenarios were tested. Each alternative scenario for treatment duration is described in more detail below. Table 32 summarises the mean duration of each first-line treatment under the base case and scenario analyses.

Table 32 Summary of mean treatment duration by treatment arm: base case and scenario analyses

Treatment duration assumption	Mean treatment duration (months)*	
	Ceritinib	Crizotinib
Base case: Treatment until discontinuation (based on truncated median duration for both ceritinib and crizotinib)	[redacted]	[redacted]
Scenario 1a: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on ASCEND-4)	[redacted]	[redacted]
Scenario 1b: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on PROFILE 1014)	[redacted]	[redacted]
Scenario 2: Treatment until progression	[redacted]	[redacted]
Scenario 3: Treatment until discontinuation or progression, whichever occurs first	[redacted]	[redacted]

*After applying a half-cycle correction

Alternative scenario 1a: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, based on ASCEND-4)

In this scenario, the exponential rate of ceritinib discontinuation was estimated using patient-level time-to-event data for treatment discontinuation in the ASCEND-4 trial. Patients were followed from the first ceritinib dosing date until treatment discontinuation, or until censoring (if patients remained on ceritinib treatment at the data cut-off). An exponential curve for time to ceritinib discontinuation was fitted to this patient-level data. The duration of treatment for crizotinib was assumed to be equivalent to that of ceritinib and was modelled based on patient-level time-to-event data for ceritinib treatment discontinuation in the ASCEND-4 trial.

Alternative scenario 1b: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, based on PROFILE 1014)

In this scenario, the duration of treatment for ceritinib was assumed to be equivalent to that of crizotinib. As in the base case, duration of crizotinib treatment was modelled based on the truncated median duration reported from the PROFILE 1014 trial.

Alternative scenario 2: Treatment until progression

For this scenario, the proportion of patients remaining on treatment at each model cycle was based on the predicted PFS curve for each treatment arm from the respective trials.

Alternative scenario 3: Treatment until discontinuation or progression (whichever occurs first)

In the last scenario analysis, patients were assumed to continue first-line treatment until discontinuation or progression, whichever occurs first. The clinical experts considered this assumption to be valid based on routine clinical practice, noting that they would consider switching therapies upon RECIST-defined progression, and that they may discontinue before progression if there is unacceptable drug toxicity. Under this rule, monthly drug costs in each treatment arm were adjusted with a time-varying proportion of patients on treatment to account for patients who discontinued treatment prior to progression. Specifically, the ratio between the proportion of patients who are both progression-free and on treatment and the proportion in PFS was estimated for each cycle. Both proportions were estimated using exponential functions fitted to patient-level data from the ASCEND-4 trial. For crizotinib, the ratio was assumed to be equal to that of ceritinib. In each treatment arm, the ratio was applied to the predicted PFS curve (as estimated based on the selected parametric function) to estimate the proportion of patients still on treatment in each month.

B 3.4 Measurement and valuation of health effects

B 3.4.1 Introduction

ASCEND-4 and PROFILE 1014[83] both included assessment of utilities using the EQ-5D for the period when patients were receiving study treatment, but not following treatment discontinuation. Utility values derived from the respective trials were therefore used in the base case for the PF health state. Neither study provides data that can be used to derive utility values for the PD health state. Thus, potentially relevant utility sources were identified through a systematic literature review, described in Appendix H. From this, a further publication was selected to provide utility values for the PD health state for both treatment groups in the model based on sample size, relevance of the study population (a multi-national real-world sample of patients with advanced NSCLC), and the inclusion of patients receiving any treatment for NSCLC.[111] [The other studies identified in the systematic literature review were subject to one or more of the following limitations and were therefore deemed less relevant to the present economic evaluation: used a valuation method other than EQ-5D (e.g., Doyle 2008,[112] Nafees 2008,[113] Nafees 2016,[114] Lewis 2010,[115] Chang 2016[116]); featured a relatively small sample size (e.g., Stewart 2015,[117] Balcik 2016[118]); were conducted in a patient population specific to a country other than the UK (e.g., Grutters 2010,[119] Lee 2011,[120] Labbe 2016,[121] Tramontano 2015[122]); did not adequately capture utility values of patients following progression on second-line therapy (e.g., Blackhall 2014,[123] Reck 2015[124]); or did not report utility values corresponding to PD health state (e.g., Yang 2014[125])].

B 3.4.2 Utility input for base case

Progression-free state utility

PF state utility values were obtained for each treatment arm based on EQ-5D data reported from the ASCEND-4 and PROFILE 1014 trials. In the ASCEND-4 trial, mean utility values were compared for ceritinib and CT using a repeated-measures regression model of EQ-5D index scores (based on the EQ-5D crosswalk value set for the UK using the time trade-off method).[15] Independent variables in the model included treatment, time, time by treatment interaction, strata, and baseline EQ-5D score. The least squares means of EQ-5D from this regression were used in the base case as the utility value for the PF health state for the ceritinib group. The PF utility value for crizotinib was taken from a repeated measures regression model comparing overall EQ-5D index scores for the treatment arms of PROFILE 1014, as reported by Felip et al. (2015).[83] This utility (0.81) was used as the utility value for the PF health state for the crizotinib treatment arm in the NICE crizotinib submission, and was agreed by the Committee to be appropriate for this patient population in the UK.[101]

Table 33 summarises the utility values used in the base case. As shown, the PF utility estimates were similar for ceritinib and crizotinib. In the model, no further adjustments for differential treatment

response rates were made to the base case PF health state utilities, with the rationale that these utilities already represent weighted averages of utility for patients with stable disease or those achieving objective responses to either first-line treatment. Additionally, because these PF state utility values are treatment-specific and already incorporate any disutility impact of AEs associated with each treatment, the base case did not separately apply AE-related disutilities to the treatment arms.

Table 33 Base case health state utilities

Health state	Utility value	Source
Ceritinib		
Progression free (stable disease or objective response)	0.81	ASCEND-4 CSR
Progressed disease	0.64	Chouaid *et al.,* 2013
Crizotinib		
Progression free (stable disease or objective response)	0.81	PROFILE 1014 (Felip *et al.,* 2015)
Progressed disease	0.64	Chouaid *et al.,* 2013

ASCEND-4 CSR[15]; Chouaid *et al.,* 2013[111]; Felip *et al.,* 2015[89]

Progressed disease state utility

Because EQ-5D scores were not collected systematically after disease progression in ASCEND-4 or PROFILE 1014, trial-based estimates of PD utility do not accurately reflect the health status of patients during the entire PD period before death. The utility estimates from ASCEND-4 only capture EQ-5D assessments within seven days of the last dose of study treatment before cross-over and before the start of any further anti-neoplastic therapies.[15] Given this limitation, the base-case utility value for PD state for both treatment arms was estimated based on the utility study by Chouaid *et al.,* (2013), a multi-national cross-sectional study among patients receiving any treatment for advanced NSCLC in real-world settings.[111] The NICE submission for first-line crizotinib similarly estimated PD utility based on external literature sources, an approach that was approved by the Committee.[101]

Chouaid *et al.,* (2013) administered the EQ-5D to 263 patients receiving any treatment for advanced NSCLC, and the scores were transformed into utility values using EQ-5D weights elicited from a UK population.[111] The utility scores associated with PF and PD health states for patients receiving first-, second-, and third/fourth-line therapies were reported.

The PD utility value of 0.64 used in the present model was derived using a weighted average of the utilities reported by Chouaid *et al.,* (2013) among patients in the following disease states: first-line disease progression (0.67; n=26), second-line progression-free (0.74; n=44) or disease progression (0.59; n=17), and third-/fourth-line progression-free (0.62; n=24) or disease progression (0.46; n=21). The sample size for each state was used as the weight for the post-progression utility estimate.

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

The model considered costs (correct as of 2016) associated with: the drug and drug administration, the management of AEs, PF medical input, PD medical care, second-line treatment, and other medical costs (e.g., terminal care).

B 3.5.1 Drug and drug administration

Monthly drug costs were calculated in the model as a function of unit drug costs, dosing, dose intensity (i.e. proportion of planned dose consumed) (Table 34), and drug administration costs.

Ceritinib and crizotinib unit drug costs (cost per package) were retrieved from the Monthly Index of Medical Specialties (MIMS).[126,127] Relative dose intensity accounted for the fact that patients may not take the full planned doses due to dose interruption or reduction associated with AEs or with non-compliance. Mean relative dose intensity for ceritinib was obtained from ASCEND-4. However, as the relative dose intensity was not reported in PROFILE 1014, the mean relative dose intensity for crizotinib was instead based on PROFILE 1007, a phase III open-label trial of crizotinib in previously treated patients.[128]

Table 34 Unit drug costs, doses, and dose intensity

Treatment	Cost per package, £	Package size	Strength, mg	Dosing schedule	Cost per mg, £	Dose per month, mg	Relative dose intensity (%)	Drug cost per month, £
Ceritinib	4,923.45	150 capsules	150	750 mg orally once daily	0.22	22,828	77.3	3,861.33
Crizotinib	4,689.00	60 capsules	250	250 mg orally twice daily	0.31	15,219	92.0	4,376.79

ASCEND-4 CSR;[15] Australian Department of Health;[128] MIMS[126,127]

Drug administration costs for ceritinib and crizotinib consisted of a monthly dispensing cost for oral therapies, based on the wages associated with 12 minutes of a pharmacist's time (including qualification costs).[129] This was calculated as £14.26 per month. This unit cost of administration for oral ALK-inhibitor therapy is consistent with the NICE submission for ceritinib among previously treated patients, in which the Committee accepted the use of a monthly pharmacy dispensing cost as a suitable estimate for ceritinib administration cost.[130]

B 3.5.2 Progression-free costs

Costs associated with the PF state included healthcare provider visit costs [i.e. cancer nurse visits, outpatient visits, general practitioner (GP) visits], and laboratory test and procedure costs (i.e. full blood count, computerised tomography scan, X-ray, and serum chemistry). Consistent with the NICE submission for crizotinib for untreated ALK+ advanced NSCLC, resource assumptions for routine medical management in the PF disease state were derived from previous NICE appraisals for erlotinib in EGFR-TK+ NSCLC (TA162 and TA258),[131,132] in which resource use frequencies were estimated by an expert panel. These estimates were viewed as the best available estimates in the literature, as they have been informed by expert opinions (five leading UK clinicians specialising in the treatment of NSCLC), they have been reviewed by the NICE Evidence Review Groups (ERGs) and appraisal committees on four previous occasions, and, although not specifically focusing on patients with ALK+ disease, they are applicable for patients with NSCLC receiving treatment with an oral agent. As in the first-line crizotinib submission, monthly frequencies of monitoring tests and visits were expected to be dependent on health state rather than the specific treatment received as first-line therapy.

The unit cost per GP visit (per patient contact lasting 9.22 minutes, including direct care staff costs, without qualification costs) was obtained from the Personal Social Services Research Unit (PSSRU) for 2016, the most recent source available.[133] Other unit costs associated with provider visits and tests/procedures were obtained from the most recent NHS Reference costs (2015–2016).[134] Finally, the monthly frequencies of resource use were based on expert panel opinion reported in TA296.[135] Total PF costs per patient per month were estimated to be £184.42 (Table 35).

Table 35 Monthly PF cost

Resource	Unit cost, £	Frequency of use	Cost per month, £	Reference
Healthcare provider visits				
Cancer nurse	69.20 per visit	20% of patients (1 visit)	13.84	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trust and NHS foundation trusts - Other Currencies Data, N10AF - Specialist Nursing - Cancer Related, Adult, Face to face (unit costs)
Outpatient visit	151.12 per visit	0.75 visits	113.34	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trusts and NHS foundation trusts - Outpatient Attendances Data, 370 - Medical Oncology (unit costs)
GP visit	31.00 per visit	10% of patients (1 visit)	3.10	Expert panel (resource use); PSSRU 2016 general practitioner unit cost per patient contact lasting 9.22 minutes, including direct care staff costs, without qualification costs (unit costs)
Tests and procedures				

Full blood count	3.10 per test	All patients, 0.75 per month	2.33	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trust and NHS foundation trusts - Other Currencies Data - DAPS05-Haematology (unit costs)
Computerised tomography scan	125.49 per scan	30% of patients, 0.75 per month	28.24	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trust and NHS foundation trusts - Diagnostic Imaging - Direct Access - total HRG data, RD26Z - Computerised Tomography Scan of three areas, with contrast (unit costs)
X-ray	30.26 per X-ray	All patients, 0.75 per month	22.70	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trust and NHS foundation trusts - total HRG data, DAPF - Direct Access Plain Film (unit costs)
Serum chemistry	1.18 per test	All patients, 0.75 per month	0.89	Expert panel (resource use); Schedule of Reference Costs (unit costs) 2015 to 2016, all NHS trust and NHS foundation trusts - Other Currencies Data - DAPS04 - Clinical Biochemistry
Total cost per month			**184.42**	

NHS Reference costs (2015–2016);[134] PSSRU for 2016;[133] TA296[135]

B 3.5.3 Progressed disease costs

Costs associated with the PD state included the costs of healthcare provider visits (i.e. cancer nurse visits, outpatient visits, and GP visits), medications [i.e. steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), morphine, bisphosphonate, and dietary supplements], and laboratory tests and procedures (i.e. full blood count, serum chemistry, computerised tomography scan, home oxygen, and X-ray). Resource utilisation assumptions for routine medical management in the PD state were derived from TA162 and TA258.[131,132] Unit costs per provider visit and per test/procedure were collected from the PSSRU 2016[133] and the NHS Reference costs 2015–2016.[134]

Based on TA162, this model considered several medications, including steroids, NSAIDs, morphine, bisphosphonate and dietary supplements, as components for PD costs.[131] The unit costs (cost per package) for these drugs were obtained from the electronic Market Information Tool (eMIT) from the Commercial Medicines Unit of the NHS, which provides mean product prices for generic medicines drawn from information from approximately 95% of NHS Trusts.[136] The frequency and unit cost of dietary supplements were based on the Tarceva (erlotinib) NICE submission (TA277).[137] Monthly frequencies for other categories of resource use were based on expert panel opinion reported in TA162.[131]

All PD costs were applied in each monthly cycle while patients remained in the PD state, regardless of the treatment received before progression. Total PD costs per patient per month amounted to £267.19 (Table 36).

Table 36 Monthly PD costs

Resource	Unit cost, £	Frequency of use	Cost per month, £	Reference
Healthcare provider visits				
Cancer nurse	69.20 per visit	10% of patients (1 visit)	6.92	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trust and NHS foundation trusts - Other Currencies Data, N10AF - Specialist Nursing - Cancer Related, Adult, Face to face (unit costs)
Outpatient visit	151.12 per visit	All patients (1 visit)	151.12	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trusts and NHS foundation trusts - Outpatient Attendances Data, 370 - Medical Oncology (unit costs)
GP visit	31.00 per visit	28% of patients (1 visit)	8.68	Expert panel (resource use); PSSRU 2016 general practitioner unit cost per patient contact lasting 9.22 minutes, including direct care staff costs, without qualification costs (unit costs)
Medications				
Steroids (dexamethasone)	0.146 per 0.5mg	50% of patients, 0.5mg x 160	11.68	Expert panel (resource use); eMIT 2016 (2mg tablets / pack size 100)
NSAIDS (ibuprofen)	0.006 per 200mg	30% of patients, 200mg x 60	0.11	Expert panel (resource use); eMIT 2016 (200mg tablets / pack size 84)
Morphine	0.710 per 60mg	75% of patients, 60mg x 7	3.73	Expert panel (resource use); eMIT 2016 (60mg/2ml / pack size 5)
Bisphosphonate (alendronate)	0.022 per 5mg	7.5% of patients, 5mg x 28	0.05	Expert panel (resource use); eMIT 2016 (10mg tablets / pack size 28)
Dietary supplement	3.54 per 350g	40% of patients, 350g x 20	28.34	Tarceva (erlotinib) NICE submission (TA277) (resource use and unit costs), inflation-adjusted to 2016 GBP
Tests and procedures				
Full blood count	3.10 per test	All patients, 1 per month	3.10	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trust and NHS foundation trusts - Other Currencies Data DAPS05- Hematology (unit costs)
Serum chemistry	1.18 per test	All patients, 1 per month	1.18	Expert panel (resource use); Schedule of Reference Costs (unit costs) 2015 to 2016, all NHS trust and NHS foundation trusts - Other Currencies Data - DAPS04 - Clinical Biochemistry
Computerised tomography scan	125.49 per scan	5% of patients, 0.75 per month	4.71	Expert panel (resource use); Schedule of Reference Costs 2015 to 2016, all NHS trust and NHS foundation trusts - Diagnostic Imaging - Direct Access - total HRG data, RD26Z - Computerised Tomography Scan of

				three areas, with contrast (unit costs)
Home oxygen	203.91 per event	20% of patients, 1 per month	40.78	Expert panel (resource use); Schedule of Reference Costs (unit costs) 2015 to 2016, all NHS trust and NHS foundation trusts -total HRG data, DZ33Z - Hyperbaric Oxygen Treatment
X-ray	30.26 per x-ray	30% of patients, 0.75 per month	6.81	Expert panel (resource use); Schedule of Reference Costs (unit costs) 2015 to 2016, all NHS trust and NHS foundation trusts -total HRG data, DAPF - Direct Access Plain Film (unit costs)
Total post-progression care costs, all patients			**267.19**	

NHS Reference costs (2015–2016);[134] PSSRU for 2016;[133] TA277;[137] TA162[131]

B 3.5.4 Second-line treatment costs

To more accurately capture the costs associated with disease progression on each treatment arm, patients with PD were assumed to incur the costs of second-line anti-neoplastic treatment. In the base case, data from the ASCEND-4 and PROFILE 1014 trials were used to estimate the proportions of patients in each treatment arm receiving different post-progression treatments. It was assumed that the clinical benefit of post-progression treatment was already represented in the efficacy parameters derived from the same trials.

Currently available post-progression treatments differ from those used in ASCEND-4 and PROFILE 1014. Thus a scenario analysis investigated the effects of using a distribution of second-line treatments that reflects current real-world practice, based on consultation with three medical experts.[3] This alternative scenario assumed that 60% of patients in the first-line ceritinib arm would receive second-line platinum doublet therapy, 60% of patients in the first-line crizotinib arm would receive second-line ceritinib, and (as in the base case), the remaining 40% of patients in both arms would receive no further systemic treatment (Table 40). (As noted in section B 1.3.5, crizotinib is not an appropriate treatment option following ceritinib.)

Second-line treatment options included ceritinib, crizotinib, docetaxel, single-agent pemetrexed, and pemetrexed plus platinum doublet chemotherapy. (Pembrolizumab and nivolumab were not included as second-line treatment options, as neither therapy was reported as a subsequent treatment in the ASCEND-4 and PROFILE 1014 trials. Clinicians also commented that immunotherapy agents would be an unlikely choice as second-line treatment in the target population.[3])

The cost of different second-line treatment regimens (reported in Table 37) was calculated based on monthly drug and drug administration costs (see Table 38), accounting for dose intensity and estimated mean duration of treatment. As the duration and dose intensity of post-progression treatments were not available from the ASCEND-4 and PROFILE 1014 trials, these parameters were collected from second-line clinical trials conducted in ALK+ or general NSCLC populations.[89,138-141] Body surface area (BSA) and glomerular filtration rate (GFR) were used to estimate the doses needed for chemotherapy. Mean BSA was 1.79/m^2, obtained from a UK study reporting the average BSA in adult cancer patients.[142] Mean GFR was 75 ml/min/1.73m^2, based on a prior NICE submission for pemetrexed as first-line treatment for NSCLC (TA181),)[143] which estimated that an AUC of 5 would require an average carboplatin dose of 500 mg, and implying a GFR of 75 based on the dosing equation of 500 = 5×(GFR+25). For intravenous drugs, the cost of initial chemotherapy administration (SB12Z), and the cost for subsequent administration (SB15Z) for total HRGs were also based on NHS Reference costs 2015-2016.[134] According to the European Medicines Agency license wording, dexamethasone, vitamin B12 and folic acid are required as pre-medicines for pemetrexed, and dexamethasone is a required pre-medicine for docetaxel.[144,145] The unit drug costs (costs per package) for pre-medicines were obtained from eMIT (and are summarised in Table 39).[136] Package sizes were selected based on their consistency with expected dosing amounts.[136]

Table 37 Costs of second-line treatment regimens

PD treatment	Relative dose intensity (%)	Drug cost per month[a], £	Drug administration costs per month, £		Treatment duration, months		Total drug + administration costs, £
			First month	Subsequent months	Median	Mean	
Ceritinib	80.9	4,041.16	14.26	14.26	8.00	11.54	46,805.89
Crizotinib	92.0	4,376.79	14.26	14.26	7.13	10.29	45,164.18
Docetaxel	92.6	28.09	403.75	495.66	2.09	3.02	1,489.42
Pemetrexed	98.6	2,046.49	395.67	486.09	4.14	5.97	15,034.72
Platinum doublet							
pemetrexed +	93.0	1,930.26	395.67	486.09	3.22	2.74	6,529.92
cisplatin, or	88.0	18.08	0.00[b]	0.00	3.22	2.74	49.54
carboplatin	88.0	29.52	0.00[b]	0.00	3.22	2.74	80.88

ASCEND-4 CSR;[15] Australian Department of Health;[128] Di Mario *et al.,* 2009;[139] Felip *et al.,;*[89] Herbst *et al.,* 2016;[140,141] MIMS[126,127] Smit *et al.,* 2009;[138] eMIT[136]

[a] The drug costs per month displayed above reflect drug costs after applying relative dose intensity.

[b] In platinum doublet regimens, drug administration costs for the platinum-based chemotherapy agents are bundled together with the administration cost for pemetrexed.

Table 38 Drug administration costs for second-line chemotherapy regimens

Type of administration	Detail	NHS reference code	Cost, £	Frequency

Intravenous infusion - Initial (first)	Deliver simple parenteral chemotherapy at first attendance	SB12Z	236.19	1 per cycle
Intravenous infusion - Subsequent	Deliver subsequent elements of a chemotherapy cycle	SB15Z	328.10	1 per cycle

NHS Reference costs 2015-2016[134]

Table 39 Costs of pre-medicines required for pemetrexed and docetaxel

Treatment	Package size	Strength (mg)	Cost per package, £	Dosing schedule
Dexamethasone (oral solution)	150 ml	2 mg/5 ml	17.34	Pemetrexed: 8 mg * 3 days per cycle Docetaxel: 16 mg * 3 days per cycle
Vitamin B12 (injection)	5 amp	1 mg/ml	4.44	Pemetrexed: 1000 micrograms * 2 for first cycle and 1 every 3 cycles thereafter
Folic acid (tablets)	28 tablets	5 mg	0.27	Pemetrexed: 350–1000 micrograms * 26 doses for first cycle and 21 doses for subsequent cycles

eMIT[136]

In each first-line treatment arm, the total cost of second-line treatment was estimated as a weighted average of the regimen-specific costs, given the distribution of second-line treatments in each arm (base case: Table 40; scenario analysis: Table 41). The total cost of second-line treatment was applied as a one-time cost among patients discontinuing first-line treatment in each model cycle. In alternative model scenarios that assumed first-line treatment until progression, or until progression or discontinuation (whichever occurs first), the cost of second-line treatment was instead applied as a one-time cost among patients exiting the PF health state in each model cycle.

Table 40 Base case: Trial-based distribution and total cost of second-line treatments, according to first-line treatment arm

Second-line treatment	Ceritinib (%)	Crizotinib (%)
Ceritinib	1.9	10.8
Crizotinib	9.4	1.5
Docetaxel	3.8	4.6
Pemetrexed	0.0	0.0
Platinum doublet	45.0	43.1
pemetrexed +	45.0	43.1
cisplatin, or	22.5	20.0
carboplatin	22.5	23.1
No active treatment	40.0	40.0
Total PD treatment cost, £	8,135.41	8,645.67

Table 41 Scenario analysis: Real-world distribution and total cost of second-line treatments, according to first-line treatment arm

Second-line treatment	Ceritinib (%)	Crizotinib (%)
Ceritinib	0.0	60.0
Crizotinib	0.0	0.0
Docetaxel	0.0	0.0
Pemetrexed	0.0	0.0
Platinum doublet	60.0	0.0
pemetrexed +	60.0	0.0
cisplatin, or	30.0	0.0
carboplatin	30.0	0.0
No active treatment	40.0	40.0
Total PD treatment cost, £	3,957.08	28,083.54

B 3.5.5 Adverse event costs

Patients incurred a one-time cost for the management of AEs. All unit costs were obtained from NHS Reference costs 2015 to 2016.[134] The cost of managing laboratory abnormalities was assumed to equal the cost of managing blood laboratory abnormalities (two blood tests and two outpatient visits). Table 42 presents the costs associated with AEs, and the total costs for each treatment are shown in Table 43.

Table 42 Costs associated with each AE included in the model

Grade 3/4 AEs	AE cost (2016 GBP)	Notes
Neutropenia	514.82	Non-Elective Inpatients (Short Stay), SA35A-E. Agranulocytosis
Diarrhoea	382.02	Day case, FZ36M, FZ36N, FZ36P, FZ36Q. Gastrointestinal infections without intervention, with CC score 0+)
Pulmonary embolism	1,485.76	Total HRG activity: DZ09J-Q. Pulmonary Embolus
Vomiting	754.13	Assumed same cost as nausea (Total HRG activity [weighted average]: FZ90A-B. Abdominal Pain)
Hyperglycaemia	308.44	The cost of all lab abnormalities was assumed to be equal to the cost of two blood tests (Directly Accessed Pathology Services, DAPS05: Haematology) and two outpatient visits (Outpatient Attendances, 370: Medical Oncology)
Alanine transaminase (ALT) elevation	308.44	
Aspartate aminotransferase (AST) elevation	308.44	
Gamma-glutamyltransferase increased	308.44	
Blood alkaline phosphatase increased	308.44	

NHS Reference costs 2015 to 2016[134]

Table 43 Total AE costs for each treatment

Treatment	AE costs, £
Ceritinib	340.27
Crizotinib	218.23

B 3.5.6 Terminal care costs

All patients who transition to death were assumed to incur terminal care costs. These were based on Georghiou & Bardsley (2014),[110] which reported hospital care costs during the last 90 days before death. Original cost values from this source were inflated to 2016 (Table 44).[146]

Table 44 Terminal care costs

Terminal care costs	Average cost, £
District nurse	298.40
Nursing and residential care	1,073.36
Hospice care – inpatient	590.35
Hospice care – final three months of life	4,830.14
Marie Curie nursing service	536.68
Total terminal care costs	7,328.93

Georghiou & Bardsley, 2014[110]

B 3.5.7 ALK testing costs

ALK testing is required to identify patients eligible to receive treatment with ALK inhibitors, such as ceritinib or crizotinib. However, the base-case analysis assumes that ALK testing is already routinely performed among patients with non-squamous NSCLC in the UK, as confirmed by all clinical experts consulted, and therefore omits the cost of ALK testing as an expense. Since the cost of ALK testing would have applied equally to both the ceritinib and crizotinib arms, the inclusion of this cost would have increased total costs in both arms, hence having no impact on the ICER.

B 3.6 Summary of base-case analysis inputs and assumptions

Table 45 summarises the key assumptions of the model and Table 46 summarises all variables included in the analysis.

Table 45 Key assumptions of the model

Parameter	Assumption
Treatment discontinuation rules (section B 3.3.4)	• Patients receive first-line treatment according to the following treatment discontinuation rules: o Base case: Treatment until discontinuation, based on reported median treatment duration (right-truncated at the data cut-off) for ceritinib in ASCEND-4 and crizotinib in PROFILE 1014

Parameter	Assumption
	○ Alternatives to the above scenario were tested as part of the sensitivity analysis, including: ▪ Based on patient-level time-to-event data in ASCEND-4 for ceritinib and reported truncated median treatment duration in PROFILE 1014 for crizotinib ▪ Assuming equivalent time on treatment for ceritinib and crizotinib, with both based on ASCEND-4 ▪ Assuming equivalent time on treatment for ceritinib and crizotinib, with both based on PROFILE 1014 ○ Other sensitivity analyses included: ▪ Treatment until progression ▪ Treatment until discontinuation or progression, whichever occurs first
Treatment costs: First-line treatment (section B 3.5.1)	• Patients incur costs for first-line drug acquisition and administration during the period of time that they remain on treatment
Treatment costs: second-line treatments (section B 3.5.4)	• Patients incur costs of second-line treatments upon discontinuation of the first-line treatment. In the base case, the second-line treatments reflected those observed in the respective trials (i.e. ASCEND-4 and PROFILE 1014). In a scenario analysis, second-line treatments instead reflected current real-world practice based on input from medical experts
Medical costs and AE costs (sections B 3.5.2, B 3.5.3, B 3.5.5 and B 3.5.6)	• Medical costs in the PF health state include monthly monitoring and other medical costs. In addition, the cost of treatment-associated AEs was applied as a one-time cost in the first model cycle • Medical costs in the PD health state include monthly monitoring and outpatient costs • All patients incur one-time terminal care costs before death
ALK testing costs (section B 3.5.7)	• ALK testing was assumed to be a routine diagnostic test, and was therefore not considered as a cost component in the model
Utility and disutility (section B 3.4)	• Base-case health utilities are dependent on health state; additionally, the utility value for PF health state depends on the first-line treatment received. PF utilities for ceritinib were obtained from the CSR for ASCEND-4; the PF utility for crizotinib was obtained from PROFILE 1014, and the PD utility (used for both the ceritinib and crizotinib treatment arms) was obtained from published literature.

Felip *et al.,* 2015[83]; Chouaid *et al.,* 2013[111]

Table 46 Summary of variables applied in the economic model

Variable		Value	Measurement of uncertainty: SE or 95% CI	Reference to section in submission
Model settings	Discount rate (costs)	3.5%	NA	Refer to CE Model
	Discount rate (benefits)	3.5%	NA	
	Time horizon	20 years	NA	
PFS and OS with ceritinib	Exponential rate parameter: PFS	0.041	SE=0.004	Refer to CE Model
	Exponential rate parameter: OS	0.015	SE=0.002	
Hazard ratios for PFS and OS with crizotinib vs. ceritinib	Hazard ratio: PFS	1.56	95% CI: 1.15-2.13	Refer to CE Model
	Hazard ratio: OS	1.21	95% CI: 0.79-1.85	
Drug costs: first-line treatments (list price per package)	Ceritinib	£4,923.45	NA	Section B3.5.1
	Crizotinib	£4,689.00	NA	
Relative dose intensity: first-line treatments	Ceritinib	77.3%	SE=1.4%	Section B3.5.1
	Crizotinib	92.0%	SE=1.0%	
Drug administration costs	Monthly cost of oral drug administration	£14.26	NR	Section B3.5.1
Exponential rate of first-line treatment discontinuation	Ceritinib	0.045	NR	Refer to CE Model
	Crizotinib	0.064	NR	
Health state utilities	Utility for PF: ceritinib	0.810	SE=0.015	section B 3.4.2
	Utility for PF: crizotinib	0.810	NR	
	Utility for PD	0.641	SE=0.024	
Health state costs	Medical costs per cycle in PF	£184.42	NR	Section B3.5.2
	Medical costs per cycle in PD	£267.19	NR	Section B3.5.3
	One-time terminal care cost	£7,328.93	NR	section B3.5.6
Cost of second-line treatment, by first-line treatment	Ceritinib	£8,135.41	NR	Section B3.5.4

Variable		Value	Measurement of uncertainty: SE or 95% CI	Reference to section in submission
	Crizotinib	£8,645.67	NR	
Cost of AEs, by first-line treatment	Ceritinib	£340.27	NR	Section 3.5.5
	Crizotinib	£218.23	NR	

CI, confidence interval; NA, not applicable; NR, not reported; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; SE, standard error

B 3.7 Base case results

Base case results (with 3.5% discounting of costs and effectiveness) are presented in Table 47. Over a 20-year time horizon, the total gain in QALYs was estimated to be 3.22 for first-line treatment with ceritinib and 2.68 for first-line treatment with crizotinib. Total LYs gained were estimated to be 4.51 and 3.85, respectively. Total costs over the 20-year time horizon were £106,954 for ceritinib and £91,970 for crizotinib. Thus the incremental cost per QALY gained over a 20-year time horizon was estimated to be £27,936 for ceritinib vs. crizotinib and the corresponding incremental cost per LY gained was estimated to be £22,599 (Table 47). These results indicate that ceritinib is a cost-effective treatment for the first-line treatment of ALK+ advanced NSCLC when based on the list price for both ceritinib and crizotinib.

When the agreed PAS price is applied to ceritinib, the total costs for ceritinib over the 20-year time horizon were [redacted], representing a cost-saving of [redacted] compared with crizotinib (total costs = £89,714). Thus, in this case, ceritinib is dominant versus crizotinib (Table 48).

The gain in QALYs for the two health states indicated that for ceritinib the gain was similar for the PF and PD health states (Table 49). Ceritinib was associated with a greater gain in QALYs in the PF health state compared with crizotinib, reflecting the longer period patients spend in this state on ceritinib before disease progression. This difference accounts for the greater gain in QALYs seen with ceritinib compared with crizotinib. Similarly, the gain in LYs in the PF health state was greater for ceritinib than for crizotinib and this accounted for the overall difference in LYs between the two treatments.

Drug and drug administration costs for the first-line treatment comprised 75% of total costs for ceritinib and 72% for crizotinib, and were £14,229 greater for ceritinib, largely reflecting the longer duration of therapy (Table 49). Total medical costs (excluding anti-cancer treatments) over 20 years were also higher for ceritinib (£18,655 vs £17,401), similarly reflecting the longer duration of remission achieved with ceritinib. Drug and drug administration costs for second-line treatment comprised 7% and 9% of total costs in the ceritinib and crizotinib arms, respectively, and were higher in the crizotinib group.

The higher overall costs for ceritinib thus largely reflect the longer duration of therapy with ceritinib, as this enables patients to remain in remission for longer.

Table 47 Base-case results using the list price for both ceritinib and crizotinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	106,954	4.51	3.22	14,985	0.66	0.54	27,936
Crizotinib	91,970	3.85	2.68	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 48 Base-case results with PAS for ceritinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Crizotinib	89,714	3.85	2.68	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 49 Base case disaggregated costs and effectiveness

	Ceritinib	Crizotinib	Ceritinib vs. Crizotinib
Costs, £			
Drug and drug administration costs, first-line treatment	80,325	66,097	14,229
Drug and drug administration costs, second-line treatment	7,641	8,261	-620
Treatment associated AE costs	333	211	122
Medical costs	18,655	17,401	1,254
PF costs	4,245	2,787	1,458
PD costs	8,320	8,307	13
Terminal care costs	6,089	6,307	-218
Total costs	106,954	91,970	14,985
Effectiveness			
Total QALYs	3.22	2.68	0.54
QALYs: PF	1.55	1.02	0.53
QALYs: PD	1.66	1.66	0.00
Total LYs	4.51	3.85	0.66
LYs: PF	1.92	1.26	0.66
LYs: PD	2.59	2.59	0.00

AE, adverse event; LY, life-year; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year

B 3.8 Sensitivity analyses

B 3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to estimate the probability for ceritinib to be cost-effective compared to comparator treatments, based on different willingness-to-pay (WTP) thresholds. A Monte-Carlo simulation with 1,000 iterations was conducted. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarised in Table 50. Uncertainty in the PFS and OS survival probabilities for ceritinib was represented using normal distributions for the exponential parameter estimates, as this distribution reasonably describes the sampling distribution of the mean for many variables. For crizotinib, uncertainty in the HRs of PFS and OS versus ceritinib was modelled using log-normal distributions, the probability distribution typically used for relative risk parameters.[147,148] Log-normal distributions were also assumed for relative dose intensity parameters, which are constrained to be non-negative. Gamma distributions were assumed for health state cost parameters that can range between zero and infinity. Beta distributions were assumed for utilities of health states to reflect their allowable range between zero and one.

Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the standard error for each cost parameter was assumed to be equal to the mean value divided by four.

Table 50 PSA inputs

Input Parameter		Distribution	Mean	Alpha	Beta	SE	Note
PFS	Ceritinib - exponential	normal	0.041	-	-	-	• For ceritinib, the uncertainty in the survival probabilities was represented through the joint variance-covariance matrix of the parameter estimates • For crizotinib, uncertainty in the HR vs. ceritinib was modelled using a log-normal distribution • For the HR parameter, the standard error column provides the standard error of LN(HR) from the matching-adjusted indirect comparison study
	Crizotinib - HR	log-normal	1.561	-	-	0.157	
OS	Ceritinib - exponential	normal	0.015	-	-	-	• For ceritinib, the uncertainty in the survival probabilities was represented through the joint variance-covariance matrix of parameter estimates • For crizotinib, uncertainty in the HR vs. ceritinib was modelled using a log-normal distribution • For the HR parameter, the standard error column provides the standard error of LN(HR) from the matching-adjusted indirect comparison study
	Crizotinib - HR	log-normal	1.214	-	-	0.218	
Utility for PF (i.e. stable disease or treatment response)[a]	Ceritinib	beta	0.810	567.537	133.126	0.015	• SEs were obtained from the selected utility source(s). Since base-case PF utilities were treatment-specific, a separate PSA input for PF utility was selected for each treatment in each iteration
	Crizotinib	beta	0.810	567.537	133.126	0.015	
Utility for progressed disease (PD)	Ceritinib	beta	0.641	246.057	137.807	0.024	• The SE was derived from the PD utility source (Chouaid *et al.,* 2013) • Utility for PD could not exceed the PF utility. PD utilities were assumed to be non-treatment-specific; the PSA input for PD utility was therefore the same for both treatments in each iteration
	Crizotinib	beta	0.641	-	-	-	
Relative dose intensity (%)	Ceritinib	lognormal	77.3	-	-	1.4	• SE was obtained from the ASCEND-4 trial for ceritinib and PROFILE 1007 for crizotinib
	Crizotinib	lognormal	92.0	-	-	1.0	

Input Parameter		Distribution	Mean	Alpha	Beta	SE	Note
Costs	PF medical costs	gamma	184.42	16.00	11.53	46.11	• SE was assumed to be equal to 1/4*Mean
	Post-progression medical costs	gamma	267.19	16.00	16.70	66.80	
	Terminal care costs (one time)	gamma	7328.93	16.00	458.06	1832.23	

PF, progression free; SE, standard error

[a]The SE for ceritinib was obtained from the PF utility source (ASCEND-4 CSR); because the PF utility source for crizotinib did not report any variance measure, the SE for crizotinib was assumed to be the same as that of ceritinib. Base-case PF utilities were treatment-specific; therefore, a separate PSA input for PF utility was selected for each treatment in each iteration.

Across the 1,000 iterations of the PSA, the average incremental cost was £14,978, and the average incremental QALY gain was 0.51 for ceritinib vs. crizotinib. The resulting probabilistic ICER per QALY for ceritinib vs. crizotinib was £29,239, similar to the deterministic base-case ICER.

Figure 21 presents the scatter plot of simulated incremental cost and QALY pairs for ceritinib vs. crizotinib. The cost-effectiveness acceptability curve in Figure 22 shows the probability that ceritinib is cost-effective vs. crizotinib at varying willingness-to-pay thresholds. Based on the scatter plot, ceritinib was associated with higher costs than crizotinib in all iterations, and higher QALYs than crizotinib in 87% of iterations. When ceritinib is provided at list price, ceritinib had a 53.2% probability of being cost-effective vs. crizotinib at a willingness-to-pay threshold of £30,000 per QALY gained. As this analysis was based on the list price for both ceritinib and crizotinib the results have limited value for decision-making purposes.

Figure 21. Incremental cost-effectiveness plane for ceritinib vs. crizotinib

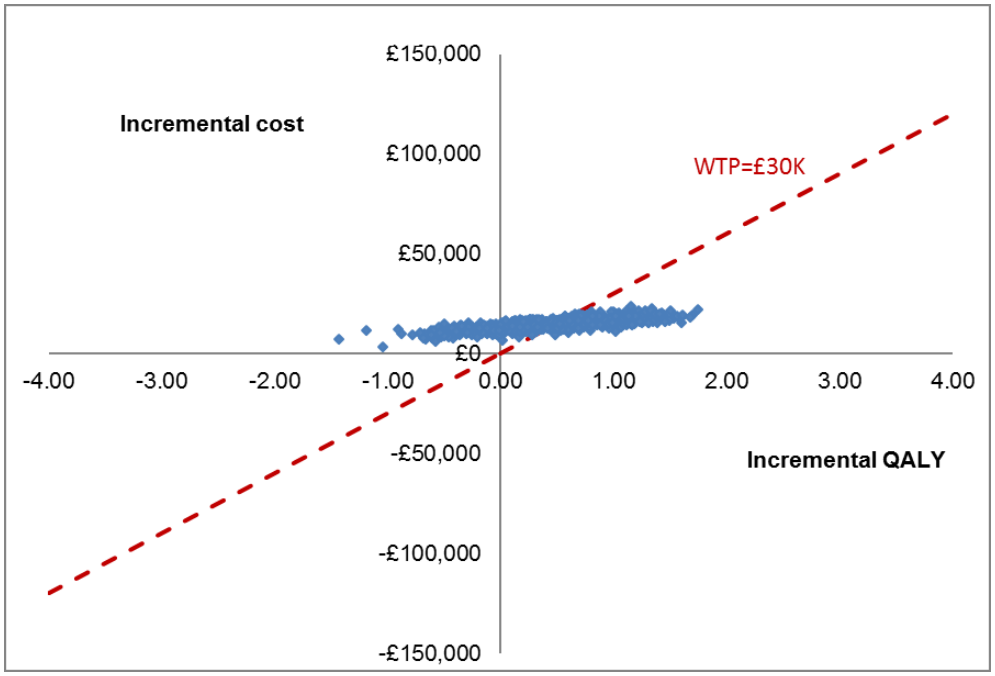
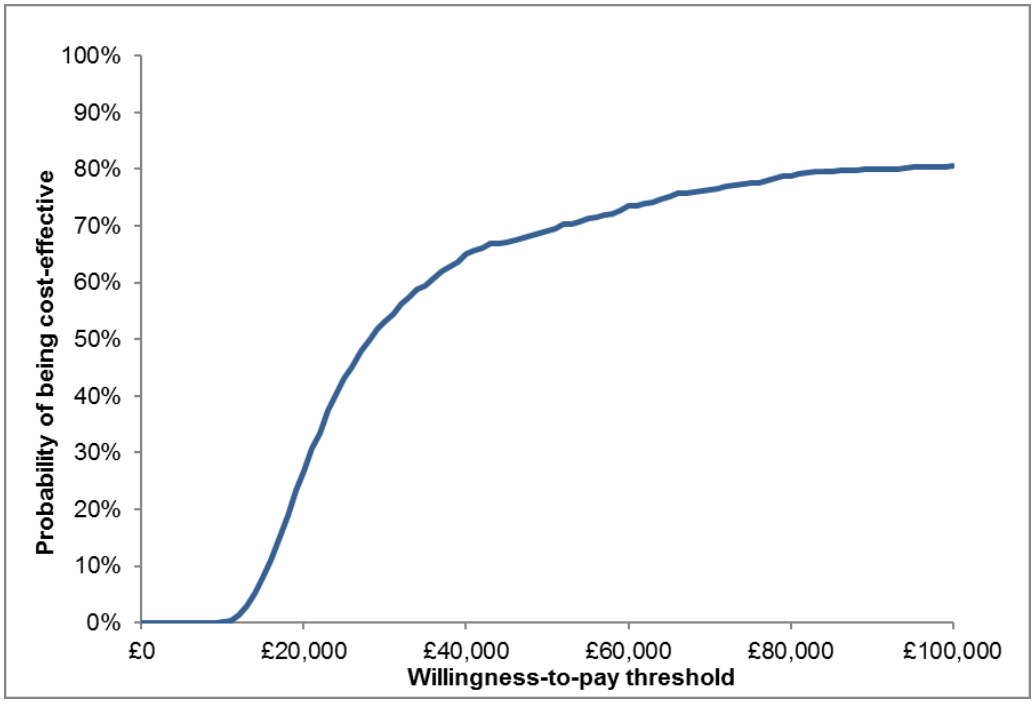


Figure 22. Cost-effectiveness acceptability curve for ceritinib vs. crizotinib



B 3.8.2 Deterministic sensitivity analysis

To assess the robustness of the model results, deterministic sensitivity analyses (DSAs) were conducted by varying one model input or assumption at a time. Table 51 summarises the variables assessed and the resulting ICERs, and the results are shown graphically in the tornado diagram (Figure 23). Sensitivity analyses are sorted from the widest to narrowest range of ICER values to highlight parameters with the strongest influence on the cost-effectiveness results.

Across the sensitivity analyses, ceritinib ranged from being a dominant strategy to having an incremental cost of £61,070 per QALY vs. crizotinib. The ICER was particularly sensitive to parameters related to OS (including the HR of OS for crizotinib vs. ceritinib and the choice of parametric function for modelling OS under ceritinib), as these parameters directly enter the calculation of expected QALYs for each treatment arm. In scenario analyses that tested alternative parametric functions of OS for ceritinib, the ICER was £44,060 per QALY gained versus crizotinib for the Gompertz OS function, and £33,215 per QALY gained for the Weibull OS function, respectively. These alternative parametric functions of OS were considered in sensitivity analyses only, as they demonstrated comparatively worse fit with the observed trial data than the base-case exponential OS function, based on AIC/BIC statistics and the shape of the log-cumulative hazard plot for ceritinib OS.

Other important drivers of cost-effectiveness included parameters related to drug costs – including relative dose intensity and the list prices of ceritinib and crizotinib – and assumptions about treatment duration. The ICER was higher than the base case for the scenario of treatment until progression (£43,921 per QALY), but was similar to the base case when assuming treatment until discontinuation or progression, whichever occurs first (£28,398 per QALY). In scenarios that assumed an equivalent duration of therapy between the two treatment arms, ceritinib was found to be a dominant strategy over crizotinib.

Compared to the base-case ICER (reflecting a 20-year time horizon), the ICER was similar when using a 15-year horizon (£29,440 per QALY), and was moderately higher (£33,593 per QALY) when using a 10-year horizon. The ICER for ceritinib vs. crizotinib showed small to moderate variation when changing PFS-related parameters, the discount rate for costs or effectiveness, or PF utility values (although the ICER was not sensitive to the use of treatment-non-specific PF utilities). The cost-effectiveness results were not sensitive to medical costs associated with PF or PD health states, terminal care costs, AE-related costs, or the PD utility value.

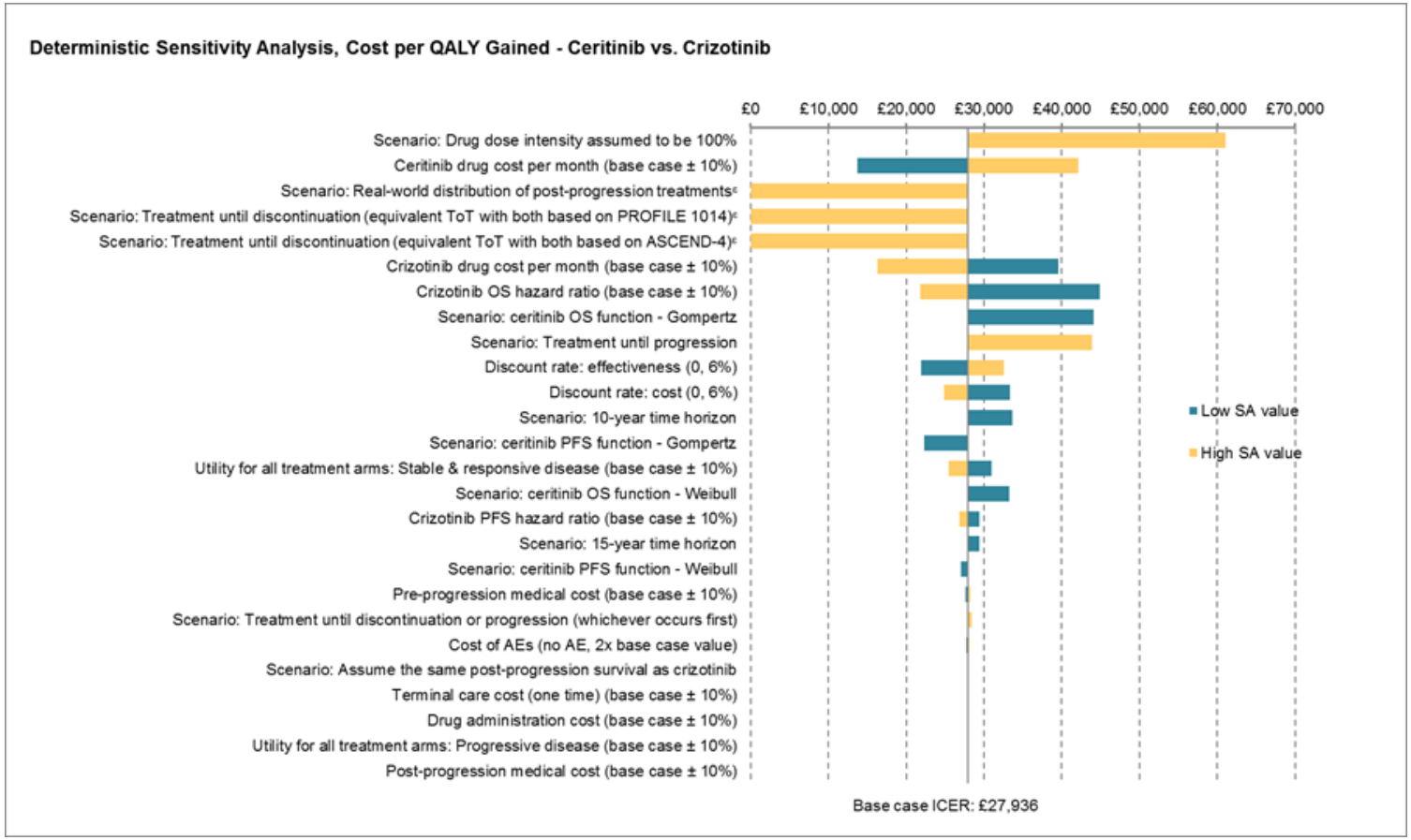
Table 51. Tabulated DSA results for ceritinib vs. crizotinib

Parameter	Incremental cost per QALY gained, £
Base case	27,936
Time Horizon	
Scenario: 10-year time horizon	33,593
Scenario: 15-year time horizon	29,440
Progression-free Survival	
Crizotinib PFS HR	
Base case + 10%	26,806
Base case - 10%	29,415
Scenario: ceritinib PFS function - Weibull	27,002
Scenario: ceritinib PFS function - Gompertz	22,279
Overall Survival	
Crizotinib OS HR	
Base case + 10%	21,763
Base case - 10%	44,925
Scenario: ceritinib OS function - Weibull	33,215
Scenario: ceritinib OS function - Gompertz	44,060
Scenario: assume the same PD survival as crizotinib	28,050
Drug costs	
Ceritinib drug cost per month	
Base case + 10%	42,114
Base case - 10%	13,758
Crizotinib drug cost per month	
Base case + 10%	16,269
Base case - 10%	39,603
Drug administration cost per month	
Base case + 10%	27,950
Base case - 10%	27,922
Scenario: drug dose intensity assumed to be 100%	61,070
Scenario: real-world distribution of second-line treatments	Dominant
Treatment duration	
Scenario: treatment until discontinuation (equivalent ToT with both based on ASCEND-4)	Dominant
Scenario: treatment until discontinuation (equivalent ToT with both based on PROFILE 1014)	Dominant
Scenario: treatment until progression	43,921
Scenario: treatment until discontinuation or progression whichever occurs first	28,398
Other medical costs	
PF medical costs	
Base case + 10%	28,208
Base case - 10%	27,664
PD medical costs	
Base case + 10%	27,938
Base case - 10%	27,934
Terminal care costs (one time)	
Base case + 10%	27,895

Base case - 10%	27,977
Cost of AEs	
Cost of AEs	
No AE cost	27,709
2x base case AE cost	28,163
Utilities	
PF utility for both treatment arms:	
Base case + 10%	25,408
Base case - 10%	31,023
PD utility for both treatment arms:	
Base case + 10%	27,922
Base case - 10%	27,950
Discount rate	
Discount rate: cost	
0%	33,358
6%	24,831
Discount rate: effectiveness	
0%	21,938
6%	32,552

AE, adverse event; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; ToT, time on treatment

Figure 23. Tornado diagram based on DSA results for ceritinib vs. crizotinib



AE, adverse event; OS, overall survival; PFS, progression-free survival; ToT, time on treatment
[ε] Ceritinib is dominant over crizotinib in this sensitivity analysis.

B 3.9 Subgroup analysis

Clinical data indicated that the benefits of ceritinib over chemotherapy were consistent across the entire patient population (see section B 2.7). Thus no subgroup analyses were performed.

B 3.10 Validation

B 3.10.1 Clinical expert validations

During model development, three expert clinicians were individually consulted to evaluate efficacy inputs and other key model parameters from a clinical perspective.[3] Details on the qualifications of each clinician are provided in Appendix K.

Based on feedback from these model validation meetings, efficacy inputs were not adjusted to the characteristics of a UK patient population. Experts commented that the ASCEND-4 and PROFILE 1014 trial populations were sufficiently representative of UK patients with ALK+ advanced NSCLC, and did not recommend adjustment of the efficacy data to a real-world patient cohort.

During the meetings, experts also validated the choice of base-case parametric functions for modelling PFS and OS in the ceritinib arm, affirmed the face validity of the MAIC-based HRs for disease progression and death with crizotinib vs. ceritinib, and evaluated the clinical plausibility of long-term outcome predictions. While experts agreed with the choice of the exponential OS function for ceritinib in the base case, they noted that long-term survival predictions in both treatment arms were higher than they expected to observe in clinical practice. Given the uncertainty surrounding long-term OS with first-line ALK inhibitor treatments, scenario analyses were conducted using alternative parametric distributions of OS.

B 3.10.2 Quality control

To verify the results of the *de novo* cost-effectiveness model, internal quality control procedures were first undertaken by the consulting group that developed the model on behalf of the manufacturer. The model was subsequently reviewed by a separate team of health economists, who evaluated the model from an overall health economics perspective, in addition to checking the accuracy of the programming to identify errors or omissions. Face validity of the model was assessed through individual consultations with three clinical experts, who provided feedback on the clinical plausibility of the model's efficacy extrapolations under different parametric assumptions.[3]

B 3.11 Interpretation and conclusions

B 3.11.1 Result summary

Over a 20-year time horizon, first-line ceritinib is expected to yield improvements in QALYs and LYs relative to crizotinib among untreated patients with ALK+ advanced NSCLC. Compared to crizotinib, ceritinib was predicted to provide a gain in QALYs of 0.54 and a gain in LYs of 0.66. The base case ICER for ceritinib vs. crizotinib was £27,936 per QALY. Results from the DSA supported the base case findings, with most variation being observed when parameters related to OS and drug costs were varied. In the PSA, the average ICER per QALY across all iterations was consistent with the base-case ICER. At the list price, ceritinib had a 53.2% probability of being cost-effective vs. crizotinib at a willingness-to-pay threshold of £30,000 per QALY gained.

B 3.11.2 Strengths of the economic evaluation

The partitioned survival analysis is a well-established approach in modelling of NSCLC, and has been used in many previous NICE submissions in the NSCLC arena.[109,130,132,137,141,149] Efficacy inputs for first-line ceritinib were based on patient-level data from the phase III, ASCEND-4 trial. The choice of parametric survival curves for PFS and OS for ceritinib was based on goodness of fit statistics and clinical plausibility according to the opinion of three clinical experts. PF state utility inputs for both first-line treatment arms were obtained directly from the ASCEND-4 and PROFILE 1014 trials, and were measured using the EQ-5D, as per the NICE reference case.

B 3.11.3 Limitations of the economic evaluation

As with any pharmacoeconomic evaluation, this model has limitations. The main limitation of this analysis was the lack of a head-to-head clinical trial comparing crizotinib and ceritinib in untreated patients with ALK+ advanced NSCLC. An indirect comparison method, the MAIC approach, was used to indirectly compare efficacy outcomes between crizotinib and ceritinib, while adjusting for cross-trial differences in observed patient characteristics.[150] The MAIC methodology is an extension of propensity score weighting, which has long been used in epidemiological studies for adjusted comparisons of non-randomised treatment groups.[151-153] Furthermore, MAIC are becoming widely used in Health Technology Assessments where data are not available for anchor-based indirect comparisons, including a number of recent NICE submissions.[84] The baseline characteristics of patients in the two pivotal trials used in the MAIC – ASCEND-4 and PROFILE 1014 – were relatively similar, such that the extent of weighting required to balance baseline patient characteristics was mild. However, there may have been residual systematic errors resulting from unobserved prognostic variables and effect modifiers, and some differences in study design such as differences in the definition used for CR and the use of radiotherapy for treatment of brain metastases prior to study entry may have affected treatment outcomes.

Another limitation of the model was the need to extrapolate long-term OS based on short-term trial data. Although the model incorporated the best available evidence on OS from the ASCEND-4 and PROFILE 1014 trials,[39] OS inputs are subject to uncertainty due to the lack of mature OS data for both ceritinib and crizotinib. This was addressed in a number of sensitivity analyses which considered alternative OS inputs.

PF utility state inputs were directly available from the first-line clinical trials of ceritinib and crizotinib. However, EQ-5D scores were not collected systematically after treatment discontinuation in ASCEND-4 or PROFILE 1014; therefore, utilities from the literature were applied for the PD health state.[111] Sensitivity analyses, however, showed that the ICER was not sensitive to the utility values used for the PD health state.

Finally, only limited information was available on time to discontinuation of crizotinib in the PROFILE 1014 trial. In the absence of patient-level time-on-treatment data for crizotinib, the duration of treatment for both agents was estimated based on the truncated median treatment durations reported in ASCEND-4 and PROFILE 1014. Although this is not ideal, it provides the most balanced comparison based on the available data regarding the treatment duration for crizotinib. Sensitivity analyses investigated the impact of this variable and found that the ICER was sensitive to treatment duration.

B 3.11.4 Conclusions

Currently, patients with ALK+ advanced NSCLC have limited treatment options. The established and approved treatment, crizotinib, is a first-generation ALK inhibitor and has significant limitations. Patients develop progressive disease after a median of less than 12 months and approximately 5% of patients show primary resistance. Furthermore, severe neutropenia has been noted in approximately 10% of patients and three-quarters of patients experience vision deterioration, while oedema is seen in approximately 40% of patients. There is thus a need for an alternative targeted therapy to improve the outlook for this specific subgroup of patients with advanced NSCLC.

Ceritinib is a highly selective, potent, second-generation ALK inhibitor that has greater affinity and specificity for ALK than crizotinib. Ceritinib has been shown to overcome resistance to crizotinib in preclinical and clinical (phase 1) studies, and has demonstrated superior efficacy to crizotinib as a first-line therapy for patients with ALK+ NSCLC. In particular, results of a MAIC have shown that, compared to crizotinib, ceritinib significantly reduces the risk of disease progression or death by 36% which corresponds to a clinically meaningful prolongation of disease remission. The clinical benefits reported for ceritinib therapy have been shown to translate into meaningful improvements in symptoms and HRQoL. Furthermore, ceritinib is associated with a prolonged duration of response and is generally well tolerated. AEs are largely manageable with dose reductions and treatment

interruptions with less than 5% of patients discontinuing from the pivotal trial due to treatment-related AEs. Thus, ceritinib fulfils a significant unmet need, extending the treatment options for patients with ALK+ advanced NSCLC, a subgroup having a particularly poor prognosis prior to the introduction of ALK inhibitors. Clinical experts consulted in the validation process confirmed that ceritinib would be an invaluable additional therapeutic option in this patient population.

A cost-effectiveness analysis from the perspective of the NHS has demonstrated ceritinib to be cost-effective over a 20-year time horizon compared to crizotinib, providing an incremental gain in LYs and QALYs of 0.66 and 0.54, respectively, and being associated with a minor incremental treatment cost of £ 14,985. This results in an incremental cost per QALY gained of £27,936 in the base case at the list price. When the agreed PAS for ceritinib of [redacted] is applied, the savings to the NHS are [redacted], and ceritinib is dominant versus crizotinib. Deterministic sensitivity analyses showed that the cost-effectiveness of ceritinib was robust in most scenarios but was sensitive to estimates of OS. (According a PSA based on the list price for both drugs, ceritinib has a 53.2% probability of being cost-effective at the willingness-to-pay threshold of £30,000, although this is of limited value for decision-making given that ceritinib and crizotinib are both provided at PAS prices.)

A budget impact analysis showed that the introduction of ceritinib for the treatment of patients with ALK+ advanced NSCLC will have a net budget impact to the NHS of [redacted] from year 3 onwards, based on the list price. This is based on an assumption that the market penetration for ceritinib will be [redacted] in the first year and [redacted] thereafter. However, this analysis is limited in its value in that a PAS is in place for both drugs.

In conclusion, the introduction of ceritinib as an alternative to crizotinib for first-line treatment of ALK+ advanced NSCLC addresses a current unmet need for the management of a group of patients with a poor prognosis in the absence of effective ALK inhibitor therapy. Ceritinib offers significant clinical benefits over crizotinib, including a more prolonged remission and an improved safety profile, as well as providing an alternative to crizotinib for patients with primary resistance. These clinical benefits mean ceritinib is associated with an increase in QALYs and LYs compared with crizotinib, and a minimal increase in cost when provided at the list price. The resulting ICER is £27,936 per QALY over a 20-year time horizon for ceritinib at the list price. Sensitivity analyses indicated the ICER is robust to plausible changes in most parameters considered, while a budget impact analysis suggests that the introduction of ceritinib in this indication will result in a net budget impact of approximately [redacted] from year 3 onwards. Thus ceritinib represents a clinically-effective and cost-effective option for NHS England and NHS Wales.

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Single technology appraisal

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

Dear Alex,

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have looked at the submission received on 25 July 2017 from Novartis. 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 **Friday 1 September 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sophie Cooper, Technical Lead (Sophie.Cooper@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

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Section A: Clarification on effectiveness data

A1. Figure 5 presents patient disposition in ASCEND-4 and includes reasons for discontinuation of treatment. For 12 and 9 patients in the ceritinib and crizotinib arms respectively, the reason is 'other'. Please can you provide details of these other reasons. The ERG notes that in the clinical study report (CSR) for 7 and 11 patients respectively the reason for discontinuation is 'Physician decision'. This is not a reason listed in Figure 5 of the submission. Furthermore, 2 'physical decision' reasons listed in Figure 5 do not appear in the CSR. Please can you explain the discrepancies.

A2. Section B 2.4.1 states that the full analysis set consisted of all randomised patients and was used for the primary efficacy analysis. However 12/187 (6.4%) randomised patients in the chemotherapy arm did not receive treatment. Please comment on this baseline imbalance and the impact on the interpretation of the trial results.

A3. On page 43 under 'Crossover and sensitivity analysis', it states that [redacted] patients were initially randomised to chemotherapy. This appears to be incorrect – 187 patients were randomised to chemotherapy. The submission does not provide any details of the RPSFT adjustment for crossover. Please can you check whether the apparent error in the number of patients randomised to chemotherapy has impacted on this analysis. If necessary please provide corrected results for this sensitivity analysis.

A4. **Priority question**: A number of different methods are available to adjust for crossover in the analysis of overall survival (ASCEND-4). Please provide the rationale for the selection of the RPSFT methodology for the present analysis. Please provide the results using alternative appropriate methods.

A5. Section B 2.6.6 states that ≥ 80% of patients completed the EQ-5D, EORTC QLQ-C30, EORTC QLQ-LC13 and LCSS questionnaires at most time points. Please can you provide the percentages for completions for all questionnaires at all time points.

A6. **Priority question**: Section D 1.1.7 lists 3 identified trials, but in Section 2.9 it states that study NCT0169001 was not considered to be relevant to the match adjusted indirect comparison (MAIC) as it included only Asian patients. Please can you provide further details of this trial: the baseline characteristics and progression-free survival (PFS) and overall survival (OS) results.

A7. **Priority question**: The inclusion criteria for the ASCEND-4 and PROFILE 1014 trials specified different methods for the determination of ALK status. Please comment on the implications of these differences. Which test for ALK status is used routinely or most commonly in the NHS?

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A8. **Priority question**: One of the patient characteristics used for matching in the MAIC analysis is 'baseline brain metastases status'. Can you clarify that by this you mean presence of brain metastases, yes or no? We note that the inclusion criteria for brain metastases differ between ASCEND-4 and PROFILE 1014, in particular only patients with treated brain metastases were allowed in PROFILE 1014. Please comment on the implications of this for the matching and interpretation of the results.

A9. There appear to be some discrepancies between the list of subsequent therapies listed for ceritinib in Table 40 and those described in Section 12.1.4 of the ASCEND-4 CSR. We note that those described in the CSR are only the 'first next treatment'; does table 40 include other additional treatments? Please clarify the reasons for the discrepancies. Also, please provide further details of the second-line therapies (post disease progression) for ASCEND-4 (We have not been sent Table 14.3-2.5B of the CSR).

A10. **Priority question**: The data cut analysed was on July 2016. Is a later cut of the data available? If so can the company provide us with this later data cut for OS and PFS (Kaplan Meier-plots and numbers at risk) and incorporate this new data into the economic model?

A11. In the company submission it is asserted that more than 90% of people currently receive crizotinib first-line. Going forward, are there any circumstances in which people would receive first-line pemetrexed-based therapy instead of crizotinib or ceritinib?

Section B: Clarification on cost-effectiveness data

Effectiveness

B1. **Priority question**: It is acknowledged that there is no direct evidence on the effectiveness of ceritinib and crizotinib, but the ERG has highlighted concern about the reliability of the effectiveness estimates from the MAIC analysis. In order for the ERG to fully explore the impact of different sources of data and assumptions, could the company please carry out the following alternative scenario analyses and incorporate them into the economic model:

a. The current base-case analysis models the population in the ASCEND-4 trial. Please present an alternative scenario in which data is adjusted to the PROFILE 1014 trial population. In this scenario, time on treatment will also need to be adjusted to the crizotinib population, as well as PFS and OS.

b. Using the analysis in part (a), please fit the parametric curves to the Kaplan Meier data independently i.e. not assuming proportional hazards. The

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presentation of this analysis should include the full set of distribution parameters estimates, AIC and BIC fits statistics, diagnostics (Q-Q plots for example) and plots.

B2. **Priority question**: We have identified a trial relevant to the comparison of ceritinib with crizotinib[1]. This trial presents further data on the effectiveness of crizotinib in untreated patients with ALK positive advanced NSCLC.

a. Can the company re-run the MAIC analysis using the clinical data on crizotinib from ALEX trial data rather than the crizotinib data from PROFILE 1014?

b. Can the ALEX and PROFILE trial be combined and incorporated into the MAIC analysis, i.e. is there a methodology to facilitate a meta-analysis of the crizotinib data to be the comparator?

B3. **Priority question**: To explore the impact of the analysis requested in question B2 on cost-effectiveness, can the company incorporate the analysis using the ALEX trial into the economic model. In the scenarios the ERG request that this analysis be carried out (i) modelling the population in the ASCEND-4 study as per the company's base-case, and (ii) modelling the population in the ALEX trial/(ALEX and PROFILE 1014) population similar to question B1a.

B4. **Priority question**: Section B 2.9.4 present the patients characteristics for ASCEND-4 and PROFILE 1014, demonstrating the similarities between the trial populations. It states that only mild weighting was required to match the individual patient data (IPD) from ASCEND-4 to PROFILE 1014. However, as shown in Table 20, the process of matching has a big impact on the median survival with ceritinib, which is increased from [redacted] months to [redacted] months. This does not appear to have face validity. Please explore this further and provide information on why such a large change happens; this should include regression analysis exploring the impact of base-line characteristics on PFS and OS.

B5. **Priority question**: Time on treatment is likely to be key driver of costs and hence cost-effectiveness, the ERG would like to understand how differences in base-line characteristics may impact on time on treatment. As per question B4, can the company present addition regression analysis exploring the impact of base-line characteristics on time on treatment.

[1] Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T, ALEX Trial Investigators. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med [Internet]. 2017.)

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B6. **Priority question**: The base-case analysis presented by the company uses data from the ASCEND-4 trial to estimate time on treatment for ceritinib and data from the PROFILE 1014 trial to estimate time on treatment for crizotinib. The populations in these two trials are, however, different and it is possible that this is influencing the estimated time on treatment. The ERG suggest that it is possible to present population-adjusted estimates of time on treatment using methods similar to those used to estimate PFS and OS in the base-case analysis. Details of the process are described below:

a. Using the MAIC, estimate time on treatment for people on ceritinib adjusted to the crizotinib population.

b. Using the median time on treatment from the adjusted analysis, estimate λ as per the base-case analysis and using λ estimate an exponential curve for time on treatment curves for ceritinib as per the base-case analysis.

c. Use the exponential curve estimated in part (b) along with the time on treatment curve for crizotinib to estimate a hazard ratio for time on treatment in the crizotinib population.

d. Apply this hazard ratio to the exponential curve estimated using the individual patient data (scenario 1a in the model).

B7. Please comment on whether we might expect the rates of adverse events for ceritinib and crizotinib to vary within different patient populations (e.g. whether people with brain metastases have a different safety profile on ceritinib compared to those without). If so, should these be included within the MAIC analysis and adjusted for differences in populations? How might the inclusion of the outcome of this analysis affect the results of the model?

B8. Some discrepancies between the data reported in the submission and model and the figures in the ASCEND-4 CSR were noted: the submission states that included adverse events are treatment-related (Table 12-9 in the CSR). The figures in the model correspond to those with any study drug relationship (Table 12-8 in the CSR). Can you also please define how treatment-related events are defined?

B9. The submission reports rates for “serious adverse events”, including those which are grades 3 to 4 (Table 25). Can you please describe how these are defined and how they differ to the grade 3 to 4 adverse events presented in Table 23, and why they were not selected for use in the economic analysis?

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B10. Can you please confirm the specific definition for the adverse event rates (i.e. that they correspond to the total number of patients experiencing each type of event). Did any patient experience multiple instances of a particular adverse event? If so, please provide the total number of events.

B11. **Priority question**: Please justify why the safety profile of each second-line therapy was not modelled. We would expect that the number of adverse events would differ in each arm, based on the different distributions of treatments provided after discontinuation. Please provide a scenario where this is included in the model, basing the rates of each event from appropriate sources (e.g. ceritinib or crizotinib given as second-line therapy).

Time on treatment

B12. Time on treatment for ceritinib as calculated from the exponential function with a rate parameter estimated from the truncated median appears to underestimate actual time on treatment (as calculated using the individual patient data in the ASCEND-4 trial).

i) Please provide information on the number of patients who continued ceritinib treatment after disease progression, the duration of treatment post-progression in these patients and the Kaplan-Meier curve for time on treatment for ceritinib. Please also provide further information on how well the exponential curve fit to the Kaplan-Meier curve, including which validation techniques were used.

ii) Were any other curves for time on treatment considered for the analysis? If so, please provide details of the fit and predicted mean time on treatment for these curves, and a justification for why they weren't selected for use in the model.

Quality of life

B13. Please comment on whether we might expect the quality of life for patients on ceritinib and crizotinib to vary within different patient populations (e.g. whether patients with brain metastases have a different quality of life on ceritinib compared to those without). If so, should these be included within the MAIC analysis and adjusted for differences in populations? How might the inclusion of the outcome of this analysis affect the results of the model?

B14. Please provide additional information on how EQ-5D data was collected for ceritinib patients in ASCEND-4, including:

i) When records were collected (the frequency of collection, when records ceased to be collected e.g. progression or discontinuation);

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ii) The number of records (where applicable) were collected in ceritinib patients who were: (a) pre-progressed and on first-line treatment, (b) pre-progressed and off treatment, (c) post-progressed and on treatment, and (d) post-progressed and off treatment;

i) The mean utility and other descriptive statistics in each of the four patient groups described above (where applicable).

Drug costs

B15. Please explain why the drug and administration costs and pre-progression costs were halved in the first cycle of the model.

Health state costs

B16. **Priority question:** The same per-cycle post-progression costs were applied in both the ceritinib and the crizotinib arms in the model. Given that it would be reasonable to assume that these may differ in each arm (e.g. because of the differential proportion of people on an ALK inhibitor or the potential different number of people on active treatment), please justify why these costs were applied in this way.

B17. The clinicians consulted by the company advised that whole brain radiotherapy be included in the post-progression health state costs. Further, it was stated that the utilisation of this resource was expect to be different in each arm. Please explain why radiotherapy was not included in the health state costs in the model.

Second-line treatment

B18. Please provide a justification as to why the same proportion of patients received active therapy post-discontinuation in each arm of the model? Is this likely to be reflective of clinical practice? The ASCEND-4 trial and the PROFILE 1014 trial report that 35% of people in ASCEND-4 and 43% in PROFILE 1014 received some systemic therapy. Why were the rates of second-line treatment in the trials not used in the model? The proportion of people receiving second-line systemic therapy were lower than those used in the model – please describe why this was and how it might impact on the overall survival estimates.

B19. **Priority question:** The same duration for each second-line therapy has been applied to each option regardless of the arm of the model it is applied in. People on ceritinib, who have been demonstrated to live longer post-progression than those on crizotinib, might be expected to receive second-line treatment for a longer duration than people treated with crizotinib. Please comment on whether the assumption made within the model is a realistic one.

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B20. **Priority question:** Please clarify whether the duration of second-line therapies was recorded in the ASCEND-4 trial? If so, please modify and include within the model as an additional scenario analysis in which time on secondary therapy is based on duration of second-line therapy recorded in the ASCEND-4 trial.

Single technology appraisal

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

A1. Figure 5 presents patient disposition in ASCEND-4 and includes reasons for discontinuation of treatment. For 12 and 9 patients in the ceritinib and crizotinib arms respectively, the reason is 'other'. Please can you provide details of these other reasons. The ERG notes that in the clinical study report (CSR) for 7 and 11 patients respectively the reason for discontinuation is 'Physician decision'. This is not a reason listed in Figure 5 of the submission. Furthermore, 2 'physical decision' reasons listed in Figure 5 do not appear in the CSR. Please can you explain the discrepancies.

Figure 5 from the submission has been revised and agrees with the relevant table from the CSR, Table 10-1, which is given on the following page. An explanation of the changes is given below.

Figure 1 Patient disposition in ASCEND-4

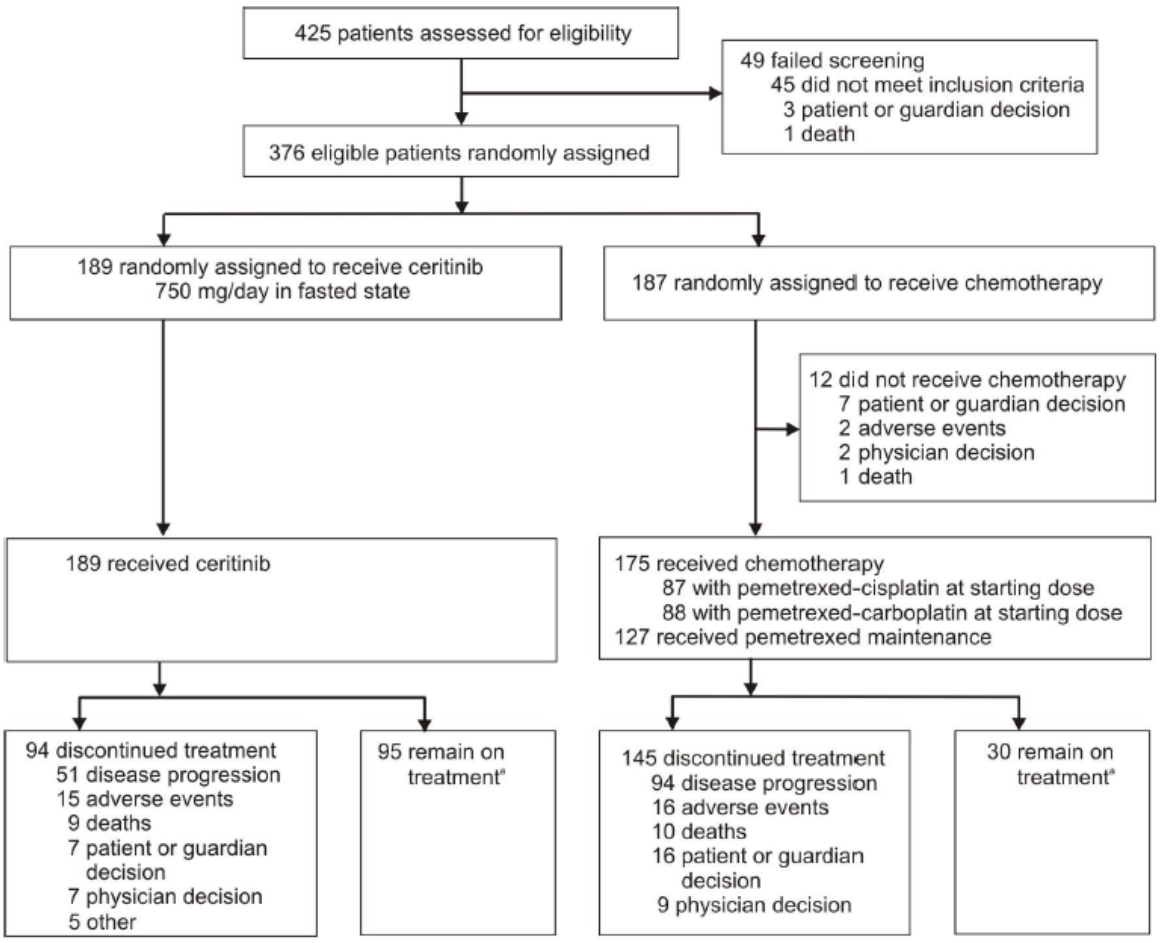

Table 10-1 Patient disposition by treatment arm (FAS)

Table 10-1 Patient disposition by treatment arm (FAS)

Disposition/ reason	Ceritinib 750 mg N=189 n (%)	Chemotherapy N=187 n (%)	All patients N=376 n (%)
Patients randomized			
Untreated	0	12(6.4)	12(3.2)
Treated	189(100)	175(93.6)	364(96.8)
Treatment phase			
Ongoing [a]	95(50.3)	30(16.0)	125(33.2)
Discontinued from treatment phase	94(49.7)	157(84.0)	251(66.8)
Entered extension-treatment phase	0	81(43.3)	81(21.5)
Entered post-treatment follow-up phase	10(5.3)	16(8.6)	26(6.9)
Entered survival follow-up phase	64(33.9)	31(16.6)	95(25.3)
Discontinued from study	20(10.6)	29(15.5)	49(13.0)
Primary reason for discontinuation from treatment phase			
Adverse event	15(7.9)	18(9.6)	33(8.8)
Death	9(4.8)	11(5.9)	20(5.3)
Lost to follow-up	2(1.1)	0	2(0.5)
Non-compliance with study treatment	2(1.1)	0	2(0.5)
Physician decision	7(3.7)	11(5.9)	18(4.8)
Progressive disease	51(27.0)	94(50.3)	145(38.6)
Protocol deviation	1(0.5)	0	1(0.3)
Subject/guardian decision	7(3.7)	23(12.3)	30(8.0)

Table 10-1 in the CSR lists together the primary reason for not starting treatment (row 5 of the patient disposition figure, Figure 5) or for discontinuing from the treatment phase (row 7 of the disposition figure).

In the ceritinib group, all patients started on treatment and reasons for discontinuation during the treatment phase are listed in row 7 of the disposition figure. The reasons given in Figure 5 and Table 10-1 are in agreement, given that “Other, n = 12” in the previous version of the disposition figure corresponds to the following reasons listed in the CSR: 2 patients who were lost to follow up, 2 patients who were non-compliant with study treatment, 7 patients who discontinued treatment on the basis of physician decision, and 1 patient who had a protocol deviation. Figure 5 has now been revised to show the 7 patients who discontinued on the basis of physician decision, and the 5 patients who discontinued for other reasons.

In the chemotherapy group, 12 patients randomised to chemotherapy did not receive any study drug, while a further 145 discontinued during the treatment phase. In Figure 5 the details are given in rows 5 and 7, respectively, while in Table 10-1, the reasons for all 157 discontinuations or reasons for not starting treatment are listed together. Of the 12 patients who were randomised to chemotherapy but did not receive study drug, 2 did so for physician decision. This was incorrectly recorded as “physical decision” in the patient disposition figure, and this has been corrected. The 9 patients recorded as discontinuing chemotherapy during the treatment phase (row 7) all did so for physician decision, making 11 in total discontinuing for this reason, as given in Table 10-1. This has now been changed from “other” to “physician decision”.

The numbers of patients discontinuing on the basis of physician decision are listed for both treatment groups in the revised Figure 5.

A2. Section B 2.4.1 states that the full analysis set consisted of all randomised patients and was used for the primary efficacy analysis. However 12/187 (6.4%) randomised patients in the chemotherapy arm did not receive treatment. Please comment on this baseline imbalance and the impact on the interpretation of the trial results.

The robustness and consistency of the positive treatment effect in favour of ceritinib in the primary analyses results was confirmed with multiple subgroup, supportive, and sensitivity analyses; the PFS results were similar to those obtained according to central assessment. Furthermore, central assessment PFS results for the per-protocol set (which included patients who had an adequate local tumour assessment at baseline, a follow-up local tumour assessment >5 weeks after starting, and who received study drug only from the treatment arm they were randomised to prior to cross-over) were consistent with those of the primary analysis results based on FAS. Thus, the fact that 12 patients in the chemotherapy group did not receive treatment is not expected to impact on the interpretation of the results for ASCEND-4. Furthermore, the focus for this submission and the economic evaluation is the outcomes for the ceritinib group, rather than the difference between treatment groups. This is due to the fact that chemotherapy is no longer considered a relevant treatment option in this patient population.[1]

A3. On page 43 under 'Crossover and sensitivity analysis', it states that 105 (72%) of 145 patients were initially randomised to chemotherapy. This appears to be incorrect – 187 patients were randomised to chemotherapy. The submission does not provide any details of the RPSFT adjustment for crossover. Please can you check whether the apparent error in the number of patients randomised to chemotherapy has impacted on this analysis. If necessary please provide corrected results for this sensitivity analysis.

The relevant sentence from the submission reads: "At the time of the OS analysis, 105 (72%) of 145 patients initially randomised to CT had received an ALK inhibitor after CT discontinuation". As per Figure 5, 145 patients initially randomised to chemotherapy **had discontinued treatment by the time** of the OS analysis, and of these 145, 105 received an ALK inhibitor after CT discontinuation. The original sentence in the submission is therefore correct. The value of 187 relates to the total number of patients randomised to CT (not those who had discontinued therapy); hence there is no need to correct the sensitivity analysis.

A4. Priority question: A number of different methods are available to adjust for crossover in the analysis of overall survival (ASCEND-4). Please provide the rationale for the selection of the RPSFT methodology for the present analysis. Please provide the results using alternative appropriate methods.

RPSFT methodology was specified in the protocol, and was performed in order to correct for confounding introduced by the change of treatment when patients crossed over from the chemotherapy to the ceritinib arm. After adjusting for crossover with the RPSFT model, the HR estimate was similar (HR 0.73, 95% CI 0.49, 1.10) to that of the primary OS analysis (HR 0.73, 95% CI 0.50, 1.08);[2] hence alternative methods to adjust for crossover were not conducted. Furthermore, the RPSFT was included in the protocol as a sensitivity analysis, and hence only one methodology was selected.

A further consideration is that the OS data for this study are immature. The OS data presented for ASCEND-4 relate to the second interim analysis for OS, at which stage only 107 OS events had occurred; this represents approximately 42.3% of the required events for the final OS analysis.[3] The study did not cross the efficacy stopping boundary for OS at this second interim analysis, thus other exploratory analyses were not investigated. The next planned interim analysis for OS is expected in [redacted] (based on approximately 215 deaths), followed by a final OS analysis in [redacted] (based on approximately 252 deaths).[3]

As discussed in this submission, chemotherapy is no longer considered an appropriate treatment option for first-line treatment of patients with ALK+ NSCLC.[1] Instead, the relevant comparator to ceritinib is crizotinib. A MAIC was therefore performed in order to compare the outcomes for ceritinib and crizotinib since there are no direct head-to-head data. Thus the only OS data of interest for the submission are those relating to treatment with ceritinib, not those for the chemotherapy arm. The MAIC is only based on data for the ceritinib group. Therefore, adjustment for crossover is not relevant to the focus of this submission or for the economic evaluation.

A5. Section B 2.6.6 states that ≥ 80% of patients completed the EQ-5D, EORTC QLQ-C30, EORTC QLQ-LC13 and LCSS questionnaires at most time points. Please can you provide the percentages for completions for all questionnaires at all time points.

The relevant percentage completion rates for the patient-reported outcome questionnaires are available in the extended version of the CSR (which has been provided along with the answers to these clarification questions). They may be found in the following Tables of the extended CSR: Table 14.2-4.24 (EORTC QLQ-C30), 14.2-4.25 (EORTC QLQ-LC13), 14.2-4.26 (LCSS), and 14.2-4.27 (EQ-5D).[3]

A6. Priority question: Section D 1.1.7 lists 3 identified trials, but in Section 2.9 it states that study NCT0169001 was not considered to be relevant to the match adjusted indirect comparison (MAIC) as it included only Asian patients. Please can you provide further details of this trial: the baseline characteristics and progression-free survival (PFS) and overall survival (OS) results.

The full manuscript for this study has not yet been published, however an abstract was presented at ASCO 2017 (http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.9058), and preliminary results are available in the entry on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01639001?sect=Xfedcba9871056). The following information is taken directly from the results available on the latter.[4,5]

Participants recruited to this study had a histologically or cytologically proven diagnosis of locally advanced, recurrent, or metastatic non-squamous non-small cell lung cancer, and those patients with measurable disease and a positive result for translocation or inversion of the ALK gene locus (as determined by an ALK break-apart FISH test) were enrolled. [4,5]

Patients were randomised to receive crizotinib or chemotherapy.[4,5] In the crizotinib group, patients received oral crizotinib 250 mg twice daily, at approximately the same time each day, on a continuous daily dosing schedule. Each treatment cycle was defined as 21 days, and participants could continue crizotinib treatment beyond RECIST-defined progressive disease (as determined by independent radiological review), at the discretion of the investigator, if the participant was perceived to be experiencing ongoing clinical benefit. In the chemotherapy arm, standard doses were administered intravenously every 3 weeks, for a maximum of 6 cycles. The three chemotherapy drugs were administered as follows:

- Pemetrexed (500 mg/m^2) was administered over 10 minutes (or according to institutional administration timing);
- Cisplatin (75 mg/m^2) was administered after adequate hydration, and approximately 30 minutes after the end of pemetrexed infusion;
- Carboplatin was administered on Day 1 of a 21-day cycle, at a dose calculated to produce an area under the concentration time curve of 5-6 mg/min/mL, and beginning approximately 30 minutes after the end of pemetrexed infusion.

Participant flow through the study is illustrated in the table below:[5]

	Crizotinib	Chemotherapy
STARTED	104	103
Treated	104	101
COMPLETED	0	0
NOT COMPLETED	104	103
Randomised but not treated	0	2
Ongoing at date of cut-off	65	60
Refused further follow-up	3	6
Lost to follow-up	1	0
Death	35	35

In the crizotinib and chemotherapy arms, respectively, the mean age was 48 and 49 years old, 91% and 93% were Han Chinese, 48% and 42% were male, 95% and 95% had ECOG PS 0/1, and 20% and 31% had brain metastases. [4,5]

The primary outcome was PFS, based on independent radiological review by treatment arm.[5] PFS was defined as the time from the date of randomisation to the date of first documentation of objective tumour progression (by independent radiological review), death on study due to any cause, or last tumour assessment without progression and before any additional anti-cancer therapy (whichever occurred first, and assessed up to 33 months). If tumour progression data included more than one date, the first date was used, and PFS (in months) was calculated as: (first event date- randomisation date +1)/30.44. Progression was defined using RECIST v1.1, as a least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of one or more new lesions. The full analysis population included all participants who were randomised, with study treatment assignment designated according to the initial randomisation.

The secondary endpoint was OS, defined as the time from randomisation due to the date of death (of any cause) or last known date at which the patient was alive (whichever occurred first, assessed up to 33 months).[5] OS (in months) was calculated as: (date of death – date of randomisation +1)/ 30.44.

Compared to chemotherapy, crizotinib significantly prolonged PFS (HR: 0.40; 95% CI: 0.29–0.57; 1-sided $P < 0.0001$). The median PFS was 11.1 months (95% CI: 8.3–12.6 months) for crizotinib and 6.8 months (5.7–7.0 months) for chemotherapy.[4,5] With only 35% of OS events, there was a numerical (not statistically significant) improvement in OS with crizotinib (HR: 0.90; 95% CI: 0.56–1.45; 1-sided $P = 0.33$). [4]

A7. Priority question: The inclusion criteria for the ASCEND-4 and PROFILE 1014 trials specified different methods for the determination of ALK status. Please comment on the implications of these differences. Which test for ALK status is used routinely or most commonly in the NHS?

In ASCEND-4,[2] ALK status was determined centrally using the VENTANA anti-ALK (D5F3) immunohistochemistry (IHC) assay, while in PROFILE 1014,[6] ALK status was evaluated centrally using the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular).

Implications for use of different ALK tests in ASCEND-4 and PROFILE 1014

At least 12 studies [7]have compared D5F3 IHC with FISH. Although there are some issues with false-positive and false-negative results, sensitivity ranged from 81-100% and specificity from 82-100%. The correlation between the results with these two tests is therefore excellent, and inter-observer concordance using D5F3 IHC in a series of lung adenocarcinoma with known ALK genotype (with a panel of international pathologists) was high. Given the above results, we have no reason to suspect that the use of different ALK testing methods in ASCEND-4 and PROFILE 1014 has any significant implications regarding the patient populations involved in these two studies, or the results reported for these studies.

ALK tests used in the NHS

According to the 9 UK oncologists who participated in an advisory board meeting to discuss first-line therapy for ALK+ NSCLC, the consensus was that most centres in the UK use IHC for first-line ALK testing, with FISH sometimes being used to confirm results.[1] Of the 9 centres represented, the responses were as follows:

- 2 centres use reflex IHC
- 1 centre uses routine IHC with confirmatory FISH in “difficult” cases
- 2 centres use IHC and FISH simultaneously (although 1 of these centres uses IHC alone in trial patients)
- 2 centres use reflex FISH (of which, 1 centre carries out NGS on squamous patients)
- 1 clinician also commented that it is his belief that the testing is slowly changing in the UK, from FISH, to IHC followed by confirmatory FISH

The D5F3 IHC assay has recently been validated, and guidelines (Marchetti et al.) now recommend ALK IHC for screening (with or without verification by means of FISH) to determine ALK inhibitor eligibility.[7] We therefore expect that UK centres will continue to adopt this method of testing as opposed to, or in conjunction with, FISH.

A8. Priority question: One of the patient characteristics used for matching in the MAIC analysis is 'baseline brain metastases status'. Can you clarify that by this you mean presence of brain metastases, yes or no? We note that the inclusion criteria for brain metastases differ between ASCEND-4 and PROFILE 1014, in particular only patients with treated brain metastases were allowed in PROFILE 1014. Please comment on the implications of this for the matching and interpretation of the results.

The presence of brain metastases was a binary variable with the values "yes" or "no".[2]

The inclusion criteria regarding brain metastases were comparable between the trials, with the exception that PROFILE 1014 required prior treatment of brain metastases. Specifically:

- In ASCEND-4, patients with brain metastases were eligible for inclusion if brain metastases were asymptomatic or neurologically stable, and any previous radiotherapy to the brain had been completed at least 2 weeks before study treatment initiation.[2]
- In PROFILE 1014, patients with brain metastases were only eligible if pre-treated with radiotherapy and neurologically stable, with no ongoing requirement for corticosteroids for at least 2 weeks before enrolment. Any prior radiation therapy must have been completed at least 2 weeks prior to the initiation of study medication.[6]

Based on the inclusion criteria, the ASCEND-4 trial contained only a subset of patients with brain metastases who had been previously treated with radiation before study drug initiation. Of the 61 patients with baseline brain metastases in the ceritinib arm, 24 patients, or 39%, had received prior radiation therapy to the brain.[3] In contrast, in PROFILE 1014, all patients with brain metastases were required to have been pre-treated with radiotherapy.[6] Although the MAIC adjusted for the baseline presence of brain metastases in the PROFILE 1014 population, this cross-trial difference in the inclusion criteria for patients with brain metastases was not adjusted for in the MAIC. If patients derived some lasting benefit from this prior radiation treatment, this could have created a bias against ceritinib versus crizotinib in the MAIC of PFS and OS outcomes.

A9. There appear to be some discrepancies between the list of subsequent therapies listed for ceritinib in Table 40 and those described in Section 12.1.4 of the ASCEND-4 CSR. We note that those described in the CSR are only the 'first next treatment'; does table 40 include other additional treatments? Please clarify the reasons for the discrepancies. Also, please provide further details of the second-line therapies (post disease progression) for ASCEND-4 (We have not been sent Table 14.3-2.5B of the CSR).

Table 14.3-2.5b can be found on pages 26217-26218 of the extended CSR (submitted with these clarification question responses).[3] It lists the anti-neoplastic therapies that patients received second-line (i.e. the first treatment after the study treatment to which they were randomised), as well as the numbers and percentages of patients who received these treatments – see table below.

Table A9.1 Antineoplastic therapies received second-line in ASCEND-4

ATC class Preferred term	LDK378 750 mg N=189 n (%)	Chemotherapy N=187 n (%)
-Any ATC class		
-Total	33 (17.5)	112 (59.9)
Folic Acid Analogues		
-Total	17 (9.0)	3 (1.6)
Pemetrexed	15 (7.9)	2 (1.1)
Pemetrexed disodium	2 (1.1)	1 (0.5)
Other Therapeutic Products		
-Total	2 (1.1)	0
Investigational drug	2 (1.1)	0
Platinum Compounds		
-Total	24 (12.7)	2 (1.1)
Carboplatin	14 (7.4)	2 (1.1)
Cisplatin	10 (5.3)	0
Protein Kinase Inhibitors		
-Total	4 (2.1)	107 (57.2)
Alectinib hydrochloride	0	1 (0.5)
Ceritinib	1 (0.5)	81 (43.3)
Crizotinib	3 (1.6)	24 (12.8)
Gefitinib	0	1 (0.5)

ATC class Preferred term	LDK378 750 mg N=189 n (%)	Chemotherapy N=187 n (%)
Pyrimidine Analogues		
-Total	3 (1.6)	0
Gemcitabine	3 (1.6)	0
Taxanes		
-Total	6 (3.2)	2 (1.1)
Docetaxel	0	2 (1.1)
Paclitaxel	6 (3.2)	0
Unspecified Herbal And Traditional Medicine		
-Total	1 (0.5)	0
Unspecified herbal	1 (0.5)	0

The distribution of second-line treatments in the cost-effectiveness model (presented in Table 40) was derived using a combination of clinical trial data and feedback from clinical validation meetings.[1] Specifically, the inputs in Table 40 reflect the following broad assumptions:

1. Based on feedback from three clinical experts, 60% of patients in both the ceritinib and crizotinib treatment arms were assumed to receive active second-line treatment following discontinuation of firstline therapy. The remaining 40% of patients were assumed to receive no further systemic therapy, due to rapid performance status deterioration or death.

2. Among the 60% of patients who receive active second-line therapy (based on the assumption above), the distribution of patients across second-line treatment options was estimated based on the relative frequency of different second-line treatments observed in the ASCEND-4 and PROFILE-1014 studies.

The first assumption was applied because, in both clinical trials, there was insufficient follow-up time available after progression to estimate the overall percent of progressed patients who received active second-line systemic therapy. We expected that a larger proportion of progressed patients would eventually transition to second-line treatment beyond the data cut-off. During independent consultations with three clinical experts, two of the experts estimated that 60% of patients would receive active second-line treatment after discontinuation of a first-line ALK inhibitor, while the third expert estimated that this percentage could be as high as 90%. Based on this feedback, 60% was selected as the base-case estimate.

Tables A9.2 and A9.3 below provide additional details on the calculation of the second-line treatment distribution for the first-line ceritinib and crizotinib arms, respectively. As shown, among those receiving an active second-line therapy, the distributions of patients across major second-line treatment options were calculated based on the relative numbers of patients who initiated those treatments, as reported in the trials. In both trials, the small percentage of patients who received other, uncommon second-line treatments were proportionally redistributed to the treatment options below.

Table A9.2: Proportion of patients receiving each second-line treatment regimen in the first-line ceritinib arm: Calculation details

Second-line treatment	Distribution of second-line treatments, conditional on receiving an active second-line treatment		Distribution of second-line treatments among all patients who discontinue first line
	Percentage (with formula) [1]	Notes/assumptions	Percentage (with formula)
ceritinib	3.1% (=1/(24+2+5+1))		1.9% (=3.1%*(100%-40%))
crizotinib	15.6% (=5/(24+2+5+1))	Based on reported use of ALK inhibitors other than ceritinib.	9.4% (=15.6%*(100%-40%))
docetaxel	6.3% (=2/(24+2+5+1))	Based on reported use of single-agent chemotherapy.	3.8% (=6.3%*(100%-40%))
pemetrexed	0.0%		0.0%
platinum doublet	75.0% (=24/(24+2+5+1))	Based on reported use of platinum-based doublet chemotherapy. Assumes equal proportions of cisplatin vs. carboplatin use as the platinum-based component.	45.0% (=75%*(100%-40%))
pemetrexed +	*75.0%*		*45.0%*
cisplatin, or	*37.5%*		*22.5%*
carboplatin	*37.5%*		*22.5%*
no active treatment	0.0%		40.0% [2]
Total:	***100%***		***100%***

Notes:

[1] Calculations are based on the reported number of patients receiving different second-line treatments after discontinuing first-line ceritinib (Section 12.1.4 of the ASCEND-4 CSR). The denominator of 32 (=24+2+5+1) includes patients in the first-line ceritinib arm who received an active second-line treatment (excluding 1 patient who received a Chinese patent medicine).

[2] Based on expert opinion during clinical validation meetings, 40% of patients were assumed to receive no further systemic therapy following disease progression.

Table A9.3: Proportion of patients receiving each second-line treatment regimen in the first-line crizotinib arm: Calculation details

Second-line treatment	Distribution of second-line treatments, conditional on receiving an active second-line treatment		Distribution of second-line treatments among all patients who discontinue first line
	Percentage (with formula) [1]	Notes/assumptions	Percentage (with formula)
ceritinib	17.9% (=(6+1)/(6+1+1+15+13+3))	Based on reported use of ALK inhibitors other than crizotinib.	10.8% (=17.9%*(100%-40%))
crizotinib	2.6% (=1/(6+1+1+15+13+3))	Based on reported use of ALK inhibitors other than ceritinib.	1.5% (=2.6%*(100%-40%))
docetaxel	7.7% (=3/(6+1+1+15+13+3))		4.6% (=7.7%*(100%-40%))
pemetrexed	0.0%	Based on the combined frequencies of cisplatin and carboplatin, it was assumed that all reported use of pemetrexed was in combination therapy (with no patients receiving single-agent pemetrexed).	0.0%
platinum doublet	71.8% (=(15+13)/(6+1+1+15+13+3))	Use of platinum doublet was inferred based on the combined frequencies of cisplatin and carboplatin.	43.1% (=71.8%*(100%-40%))
pemetrexed +	*71.8%*		*43.1%*
cisplatin, or	*33.3% (=13/(6+1+1+15+13+3))*		*20.0% (=33.3%*(100%-40%))*
carboplatin	*38.5% (=15/(6+1+1+15+13+3))*		*23.1% (=38.5%*(100%-40%))*
no active treatment	0.0%		40.0% [2]
Total:	***100%***		***100%***

Notes:

[1] Calculations are based on the reported number of patients receiving different post-progression treatments following first-line crizotinib (Supplemental Appendix, Table S2 of Solomon et al. (2014))[6]. The denominator of 39 (=6+1+1+15+13+3) reflects the sum of the reported numbers of patients in the first-line crizotinib arm who received an ALK inhibitor (ceritinib, alectinib, or crizotinib), cisplatin, carboplatin, and/or docetaxel following progression. Note that this denominator exceeds the total reported number of patients who received ≥1 active post-progression (n=38), as patients may have received more than one therapy.

[2] Based on expert opinion during clinical validation meetings, 40% of patients were assumed to receive no further systemic therapy following disease progression.

A10. Priority question: The data cut analysed was on July 2016. Is a later cut of the data available? If so can the company provide us with this later data cut for OS and PFS (Kaplan Meier-plots and numbers at risk) and incorporate this new data into the economic model?

We can confirm that there are no later data cuts available at this stage. Furthermore, there are no further planned analyses for PFS (since the final PFS analysis has already been presented in the ASCEND-4 primary paper, as per the study protocol).

Updated efficacy assessments for OS will be completed as per the protocol; the third interim analysis for OS is planned for when approximately 215 deaths are observed, and a final analysis will be conducted when approximately 253 deaths are observed.[3] Latest estimates indicate that these are likely to become available in [redacted], and [redacted], respectively.

A11. In the company submission it is asserted that more than 90% of people currently receive crizotinib first-line. Going forward, are there any circumstances in which people would receive first-line pemetrexed-based therapy instead of crizotinib or ceritinib?

At an advisory board, 9 UK oncologists were asked to comment on their treatment strategies in the ALK+ population, assuming that ceritinib received a first-line licence (since the advisory board pre-dated this licence being granted).[1] Specifically, they were asked if they would prescribe ceritinib in the first-line setting, and for their views regarding the role of immunotherapy and chemotherapy in this patient population. In response to these two questions, no clinician suggested that they would use chemotherapy in the first-line setting; the consensus was that they would prescribe ceritinib first-line over crizotinib for most patients (with the exception of some patients with a performance status of 2, for whom they would prescribe crizotinib). Furthermore, all of the clinicians who commented on the sequencing of ALK inhibitor therapy, chemotherapy, and immunotherapy indicated that ALK inhibitors would be their first approach, followed by either chemotherapy, immunotherapy, or chemotherapy followed by immunotherapy; again, no clinician suggested that chemotherapy would be an appropriate first-line option. Finally, there were discussions concerning the first-line treatments of choice in 3 and 5 years' time in which the clinicians focused solely on targeted ALK inhibitors, with no mention of chemotherapy as an option. We therefore believe, based on lengthy discussions with UK clinicians, and the superiority of ALK inhibitors in terms of outcome measures in phase 3 RCTs, that pemetrexed-based therapy is not considered an appropriate first-line treatment option in this population.

B1. Priority question: It is acknowledged that there is no direct evidence on the effectiveness of ceritinib and crizotinib, but the ERG has highlighted concern about the reliability of the effectiveness estimates from the MAIC analysis. In order for the ERG to fully explore the impact of different sources of data and assumptions, could the company please carry out the following alternative scenario analyses and incorporate them into the economic model:

a. The current base-case analysis models the population in the ASCEND-4 trial. Please present an alternative scenario in which data is adjusted to the PROFILE 1014 trial population. In this scenario, time on treatment will also need to be adjusted to the crizotinib population, as well as PFS and OS.

b. Using the analysis in part (a), please fit the parametric curves to the Kaplan Meier data independently i.e. not assuming proportional hazards. The presentation of this analysis should include the full set of distribution parameters estimates, AIC and BIC fits statistics, diagnostics (Q-Q plots for example) and plots.

Response to part (a):

To conduct the requested scenario analysis, we modified the current base-case analysis as follows:

- Parametric functions of PFS and OS for ceritinib were re-fitted using Kaplan-Meier curves from the ASCEND-4 trial after weighting the data to match the baseline characteristics of the PROFILE 1014 trial population; and

- Truncated median time on treatment was similarly re-calculated for ceritinib after weighting the ASCEND-4 data to match the PROFILE 1014 trial population.

Weighted parametric estimates of PFS and OS for ceritinib are summarised in Table B1.1 along with AIC/BIC fit statistics. Parametric curves are plotted alongside the weighted Kaplan-Meier curves for ceritinib PFS and OS in Figures B1.1 and B1.2, respectively.

As expected, weighting the ASCEND-4 data to match PROFILE 1014 patient characteristics caused a slight upward shift in the parametric functions of PFS and OS compared to the base case (base-case parametric functions are plotted in Figures 17 and 18 of the original submission). However, the shape of the different parametric functions, and their relative ranking in terms of fit with the observed data, was similar to the base-case parametric functions. We therefore selected the same functional forms to model PFS and OS for ceritinib as in the base case. Specifically, PFS was modelled using the exponential function; although the log-normal, log-logistic, and Gompertz functions demonstrated better fit with the observed data (based on AIC/BIC statistics), these functions yielded implausibly high estimates of PFS in the long term according to the clinical experts that we consulted. [1] OS was modelled using the exponential function, which demonstrated the best fit with the observed data based on AIC/BIC statistics and was supported by the shape of the cumulative hazard plot (shown in Figure 15 of the original submission both before and after weighting adjustment).

The truncated median duration of ceritinib increased slightly after weighting the ASCEND-4 data to match the PROFILE 1014 trial population (15.3 vs. [redacted] months, see Table B1.2). As a result, mean duration of first-line ceritinib treatment increased by [redacted] months ([redacted] vs. [redacted] months) over the model's timeframe.

Results from this scenario analysis (Table B1.3) show that the incremental cost per QALY increased to £29,149 (vs. £27,936 in the base case) when using weighting-adjusted estimates of PFS, OS, and time on treatment for ceritinib. The increase in the ICER was attributable to the longer duration of ceritinib treatment, and the resulting increase in ceritinib treatment costs under this scenario analysis.

Instructions to replicate the B1a scenario analysis in the Excel model:

1. In the "Effectiveness" tab, set the first dropdown menu to "Hazard ratio" and the second dropdown menu to "ASCEND-4 data reweighted to match PROFILE 1014 characteristics". Ensure that the selected parametric functions for modelling PFS and OS in the ceritinib arm are exponential.
2. In the "On Treatment" tab, set the first dropdown to "until discontinuation", the second dropdown to "ASCEND-4 data reweighted to match PROFILE 1014 characteristics", and the third dropdown to "Based on truncated median time on treatment from respective trials (ASCEND-4 for ceritinib, PROFILE 1014 for crizotinib)".

Table B1.1: Parametric estimates of PFS and OS for ceritinib after applying MAIC weights to match PROFILE 1014 baseline characteristics

Functional form	Progression-free survival (PFS), ceritinib[1]			
	A[2]	B[2]	AIC	BIC
Exponential	0.038	-	662.516	665.650
Weibull	27.750	0.921	663.804	670.073
Log-logistic	18.271	1.091	661.057	667.326
Log-normal	2.919	1.573	657.053	663.322
Gompertz	-0.029	0.048	662.018	668.286

Functional form	Overall survival (OS), ceritinib[1]			
	A[2]	B[2]	AIC	BIC
Exponential	0.014	-	428.343	431.478
Weibull	57.744	1.173	429.215	435.484
Log-logistic	47.293	1.268	429.140	435.409
Log-normal	4.082	1.597	430.637	436.906
Gompertz	0.018	0.012	429.731	435.999

Notes:

[1] Parameters for ceritinib were estimated based on data from ASCEND-4 trial (data cut-off date June 24, 2016), reweighted to match the reported distribution of baseline characteristics in the PROFILE-1014 patient sample. The weights were estimated in a matching-adjusted indirect comparison study.

[2] For the exponential distribution, A refers to the rate parameter (λ). For the Weibull and the log-logistic functions, A refers to the scale parameter, and B refers to the shape parameter. For the log-normal function, A refers to the log mean parameter and B refers to the log standard deviation parameter. For the Gompertz function, A refers to the shape parameter and B refers to the rate parameter.

AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure B1.1: Predicted PFS for ceritinib using different parametric functions (after applying MAIC weights to match PROFILE 1014 baseline characteristics)

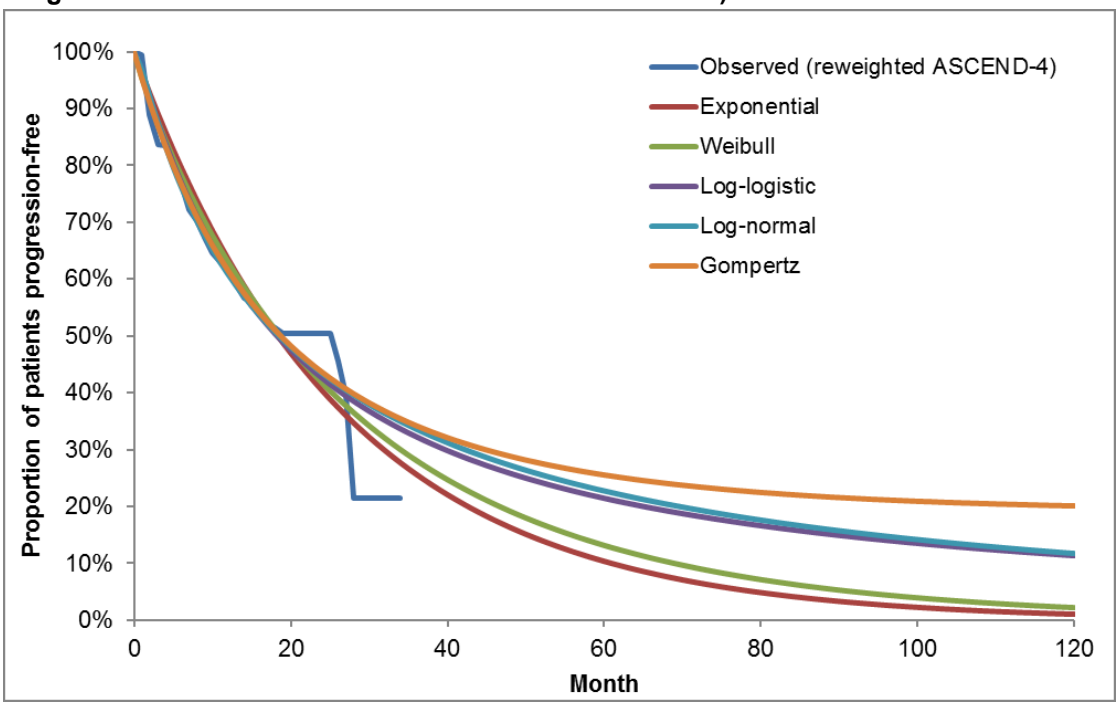

Figure B1.2: Predicted OS for ceritinib using different parametric functions (after applying MAIC weights to match PROFILE 1014 baseline characteristics)

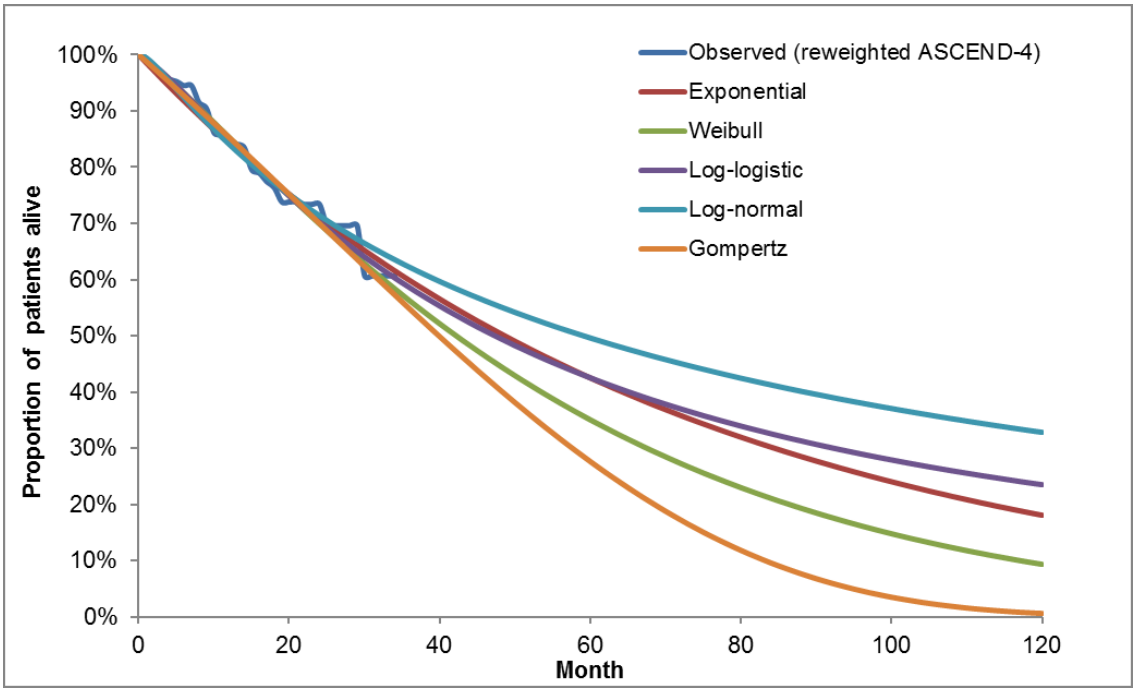

Table B1.2: Estimated duration of treatment with first-line ceritinib: base case vs. scenario analysis using the matching-adjusted median time on treatment

Treatment duration assumption	Median duration of ceritinib treatment (months)	Mean duration of ceritinib treatment (months)[1]
Base case: Treatment until discontinuation based on the truncated median time on treatment (as originally reported in ASCEND-4 and PROFILE 1014)	15.3	[redacted]
Scenario analysis: Treatment until discontinuation based on the truncated median time on treatment (after weighting ASCEND-4 data to match the PROFILE 1014 population)	[redacted]	[redacted]

Notes:

[1] A half-cycle correction was applied when calculating mean duration of treatment.

Table B1.3: Cost-effectiveness results in scenario analysis using weighted-adjusted estimates of PFS, OS, and time on treatment for ceritinib

	ceritinib	crizotinib	ceritinib vs. crizotinib
Costs (£)			
Drug and drug administration costs, initial treatment	81,656	66,097	15,559
Drug and drug administration costs, post-progression treatment	7,633	8,261	-628
Treatment associated adverse event costs	334	212	122
Medical costs	19,297	18,023	1,274
PF costs	4,542	2,987	1,555
PD costs	8,762	8,807	-45
Terminal care costs	5,993	6,229	-236
Indirect costs	0	0	0
Total costs	108,919	92,592	16,327
Effectiveness			
Total QALYs	3.41	2.85	0.56
QALYs: PF	1.66	1.09	0.57
QALYs: PD	1.75	1.76	-0.01
Total LYs	4.78	4.10	0.69
LYs: PF	2.05	1.35	0.70
LYs: PD	2.73	2.75	-0.01
Incremental cost-effectiveness ratio (ICER) (£)			
Incremental cost per QALY gained			29,149
Incremental cost per LY gained			23,711

LY, life-year; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year.

Response to part (b):

To conduct the requested scenario analysis, we further modified the scenario analysis in part (a) by separately fitting parametric functions of PFS and OS for the crizotinib arm. Specifically, patient-level time-to-event data for PFS and OS were re-created based on published KM curves from the PROFILE 1014 trial using digitization software. The Engauge digitization software (http://digitizer.sourceforge.net/) was used to extract survival probabilities at multiple time points from the published KM curve images. Based on the extracted survival curves, and on the reported numbers of patients at risk at various time points, approximate individual patient data were generated using the approach described by Guyot et al. (2012).[8] Parametric estimates of PFS and OS for crizotinib are provided in Table B1.4, and the resulting curves are plotted alongside observed Kaplan-Meier data for crizotinib in Figures B1.3 and B1.4.

For this scenario analysis, we continued to use the same MAIC-weighted parametric functions of PFS and OS for ceritinib as in part (a). For crizotinib, we selected the same functional forms to model PFS and OS as those used for ceritinib (i.e., exponential distributions for both outcomes). This approach is consistent with the NICE DSU Technical Support Document 14, which recommends that the same functional form should be selected for all treatment arms to prevent the extrapolated portion of the survival curves from following drastically different trajectories.[9] Based on AIC/BIC statistics, the relative ranking of the different parametric functions of PFS for crizotinib was similar to that observed for ceritinib (see Table B1.1), and the rationale for selecting the exponential PFS function for ceritinib also appeared to be applicable to crizotinib. Namely, while the log-normal, log-logistic, and Gompertz functions demonstrated better fit with the observed data (based on AIC and/or BIC statistics), these functions yielded estimates of PFS for crizotinib that appeared implausibly high in the long term. The best-fitting function of OS for crizotinib was log-normal (based on AIC) or exponential (based on BIC); however, long-term estimates of OS based on the log-normal curve (e.g., 16% survival at 20 years) had questionable face validity based on the poor prognosis of the model's target population. Moreover, the log-cumulative hazard plot for OS with crizotinib was approximately linear in shape and also supported the choice of an exponential OS distribution (see Figure 15 of the original submission).

Model output from this scenario analysis is summarised in Table B1.5. When using this alternative efficacy estimation approach, the incremental cost per QALY gained for ceritinib versus crizotinib moderately increased to £38,534 (vs. £27,936 in the base case).

Instructions to replicate the B1b scenario analysis in the Excel model:

1. In the "Effectiveness" tab, set the first dropdown menu to "Parametric model" and the second dropdown menu to "ASCEND-4 data reweighted to match PROFILE 1014 characteristics". Select exponential parametric functions for modelling PFS and OS in both the ceritinib and crizotinib arms.
2. Settings in the "On Treatment" tab should be the same as in the B1a scenario analysis.

Table B1.4: Parametric estimates of PFS and OS for crizotinib based on PROFILE 1014

Functional form	Progression-free survival (PFS), crizotinib[1]			
	A[2]	B[2]	AIC	BIC
Exponential	0.056	-	779.767	782.915
Weibull	17.843	1.035	781.592	787.887
Log-logistic	11.127	1.417	768.479	774.774
Log-normal	2.430	1.216	766.301	772.596
Gompertz	-0.028	0.070	777.861	784.156

Functional form	Overall survival (OS), crizotinib[1]			
	A[2]	B[2]	AIC	BIC
Exponential	0.016	-	462.679	465.827
Weibull	57.585	1.060	464.484	470.779
Log-logistic	43.287	1.188	462.897	469.192
Log-normal	3.888	1.569	461.242	467.537
Gompertz	-0.012	0.018	464.267	470.562

Notes:

[1] Parameters for crizotinib were estimated based on extracted Kaplan-Meier curve data from Solomon et al. (2014).[6]

[2] For exponential distribution, A refers to the rate parameter (λ). For the Weibull and the log-logistic functions, A refers to the scale parameter, and B refers to the shape parameter. For the log-normal function, A refers to the log mean parameter and B refers to the log standard deviation parameter. For the Gompertz function, A refers to the shape parameter and B refers to the rate parameter.

AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure B1.3: Predicted PFS for crizotinib using different parametric functions (separately estimated based on published Kaplan-Meier curves from PROFILE 1014)

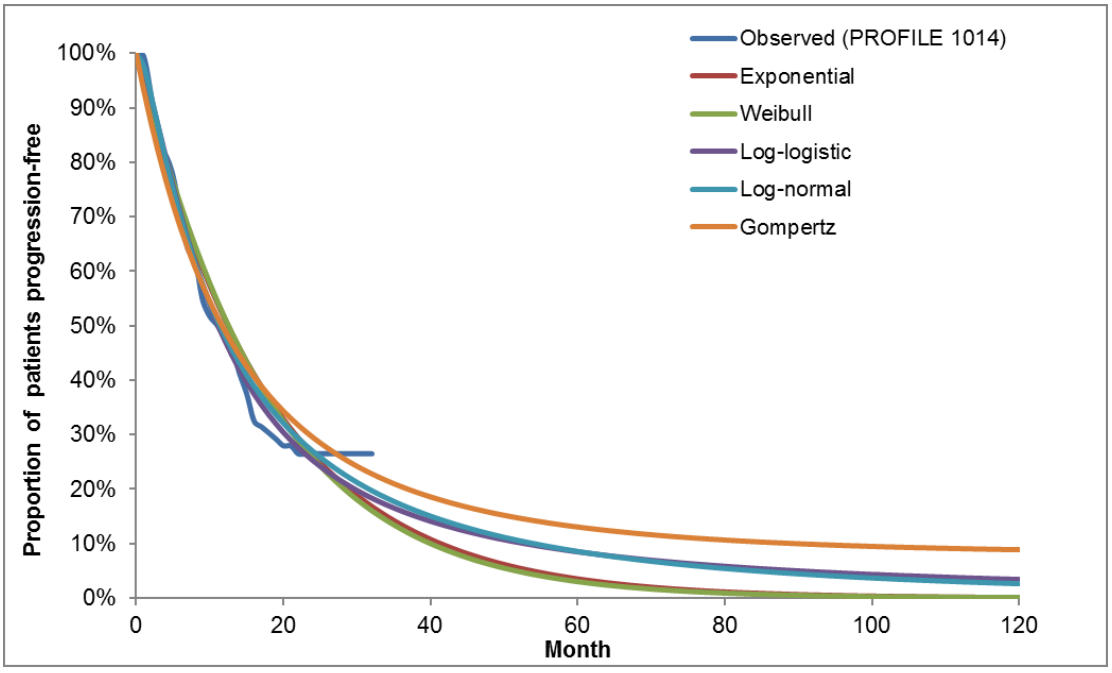

Figure B1.4: Predicted OS for crizotinib using different parametric functions (separately estimated based on published Kaplan-Meier curves from PROFILE 1014)

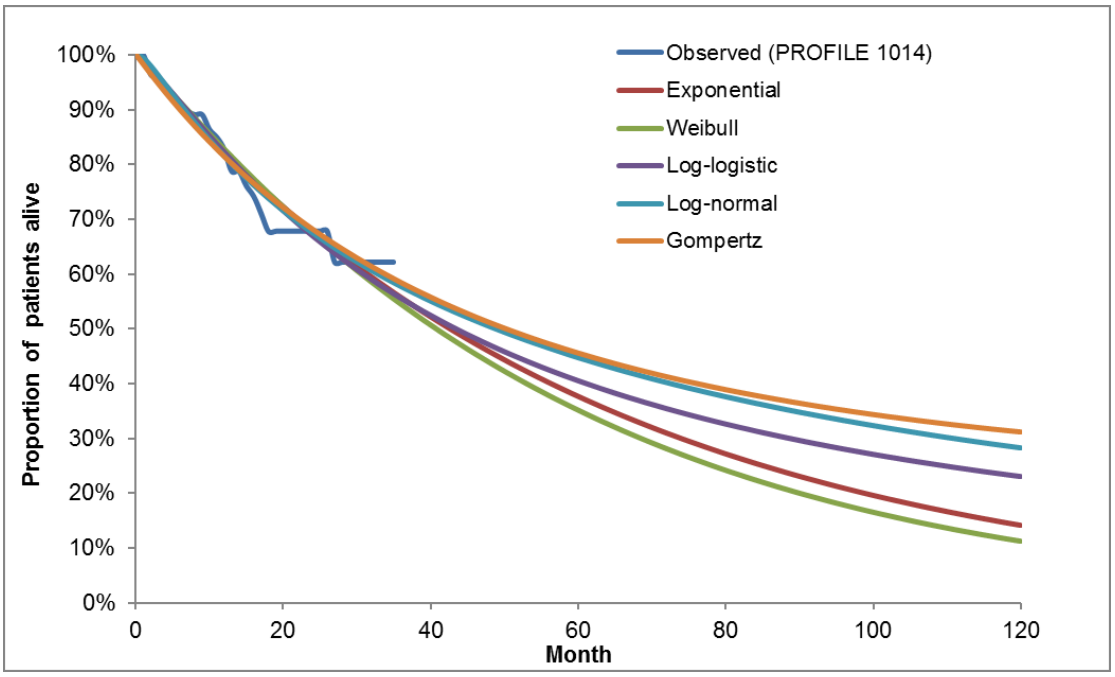

Table B1.5: Cost-effectiveness results in scenario analysis using: weighted-adjusted estimates of PFS, OS, and time on treatment for ceritinib; *and* separately estimated parametric functions of PFS and OS for crizotinib

	ceritinib	crizotinib	ceritinib vs. crizotinib
Costs (£)			
Drug and drug administration costs, initial treatment	81,656	66,097	15,559
Drug and drug administration costs, post-progression treatment	7,633	8,261	-628
Treatment associated adverse event costs	334	212	121
Medical costs	19,297	18,567	730
PF costs	4,542	3,153	1,389
PD costs	8,762	9,256	-494
Terminal care costs	5,993	6,158	-165
Indirect costs	0	0	0
Total costs	108,919	93,136	15,783
Effectiveness			
Total QALYs	3.41	3.00	0.41
QALYs: PF	1.66	1.15	0.51
QALYs: PD	1.75	1.85	-0.10
Total LYs	4.78	4.31	0.47

LYs: PF	2.05	1.42	0.63
LYs: PD	2.73	2.89	-0.15
Incremental cost-effectiveness ratio (ICER) (£)			
Incremental cost per QALY gained			38,534
Incremental cost per LY gained			33,332

LY, life-year; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year.

B2. Priority question: We have identified a trial relevant to the comparison of ceritinib with crizotinib[1]. This trial presents further data on the effectiveness of crizotinib in untreated patients with ALK positive advanced NSCLC.

a. Can the company re-run the MAIC analysis using the clinical data on crizotinib from ALEX trial data rather than the crizotinib data from PROFILE 1014?

b. Can the ALEX and PROFILE trial be combined and incorporated into the MAIC analysis, i.e. is there a methodology to facilitate a meta-analysis of the crizotinib data to be the comparator?

Response to follow by 8th September 2017

[1] Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T, ALEX Trial Investigators. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med [Internet]. 2017.)

B3. Priority question: To explore the impact of the analysis requested in question B2 on cost-effectiveness, can the company incorporate the analysis using the ALEX trial into the economic model. In the scenarios the ERG request that this analysis be carried out (i) modelling the population in the ASCEND-4 study as per the company's base-case, and (ii) modelling the population in the ALEX trial/(ALEX and PROFILE 1014) population similar to question B1a.

Response to follow by 8th September 2017

B4. Priority question: Section B 2.9.4 present the patients characteristics for ASCEND-4 and PROFILE 1014, demonstrating the similarities between the trial populations. It states that only mild weighting was required to match the individual patient data (IPD) from ASCEND-4 to PROFILE 1014. However, as shown in Table 20, the process of matching has a big impact on the median survival with ceritinib, which is increased from [redacted] months to [redacted] months. This does not appear to have face validity. Please explore this further and provide information on why such a large change happens; this should include regression analysis exploring the impact of base-line characteristics on PFS and OS.

While the median PFS for ceritinib increased from 16.6 months before matching to [redacted] months after matching, the 95% CI did not change substantially ([redacted])] before matching; [redacted]). As illustrated in Figure B4.1 below, the change in median PFS occurs due to the shift of an apparent plateau on the Kaplan-Meier curve that was below the median PFS before matching and above after matching. The impact of baseline matching on PFS can be illustrated using the 12-month PFS rate and HR of ceritinib vs. crizotinib, neither of which change substantially after matching ([redacted] before matching; [redacted] after matching).

Using the cost-effectiveness model, we further examined the overall impact of MAIC weighting on the estimated effectiveness of ceritinib. Specifically, Table B4.1 presents a comparison of mean QALYs and LYs in the ceritinib arm when using unweighted parametric estimates of ceritinib PFS and OS (base case) vs. MAIC-weighted parametric estimates (scenario analysis from Question B1). Over the 20-year model timeframe, mean OS ("LYs") with ceritinib differed by only 0.27 years (3.3 months) between the two scenarios. Mean PFS ("LYs: PF" in Table B4.1) differed by 0.13 years (1.6 months), a much smaller difference than the observed shift in the Kaplan-Meier median before vs. after matching.

This model output provides further confirmation that the large change in median PFS was an artefact of the specific Kaplan-Meier curve shape, rather than indicative of a truly large shift in the PFS curve overall. Consequently, no further regression analyses were conducted to explain this result.

Figure B4.1: Kaplan-Meier curves of PFS for crizotinib before vs. after weighting ASCEND-4 data to match the PROFILE 1014 trial population

Table B4.1: Comparison of mean QALYs and LYs in the ceritinib arm when using unweighted vs. MAIC-weighted parametric functions of PFS and OS

Outcome	Effectiveness in the ceritinib arm over 20-year model timeframe		Difference [B] - [A]
	Base case: Parametric functions of PFS and OS fitted to unweighted ASCEND-4 data [A]	**Scenario: Parametric functions of PFS and OS fitted to MAIC-weighted ASCEND-4 data [B]**	
Total QALYs	3.22	3.41	0.20
QALYs: PF	1.55	1.66	0.11
QALYs: PD	1.66	1.75	0.09
Total LYs	4.51	4.78	0.27
LYs: PF	1.92	2.05	0.13
LYs: PD	2.59	2.73	0.14

LY, life-year; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year.

B5. Priority question: Time on treatment is likely to be key driver of costs and hence cost-effectiveness, the ERG would like to understand how differences in base-line characteristics may impact on time on treatment. As per question B4, can the company present addition regression analysis exploring the impact of base-line characteristics on time on treatment.

To address the potential impact of cross-trial differences on treatment duration, we have conducted additional scenario analyses using MAIC-adjusted time on treatment estimates for ceritinib. Details on these scenario analyses are included in our responses to Questions B1 and B6.

Since the time on treatment parameters in these scenario analyses were estimated based on PROFILE 1014 patient characteristics for both ceritinib and crizotinib, no further regression analyses were conducted to explore the impact of baseline characteristics on time on treatment. However, given the likely correlation between PFS and time on treatment in the ceritinib arm, the pre-specified subgroup analyses of PFS in the ASCEND-4 trial (Figure B5.1)[2] provide indirect evidence on baseline characteristics that are likely to predict longer duration of treatment.

For example, results from the subgroup analyses of PFS show that, in the ceritinib arm, median PFS was numerically shorter among current/former smokers compared to never smokers. Before matching, the ASCEND-4 population included a significantly higher proportion of current smokers than the PROFILE 1014 population. Weighting the ASCEND-4 population to match PROFILE 1014 baseline characteristics reduced the proportion of current smokers, which may have contributed to the small increase in both PFS and time on treatment after matching adjustment. Although the proportion of current smokers was the only statistically significant difference in baseline characteristics between the ASCEND-4 and PROFILE 1014 populations, slight changes in other characteristics after MAIC weighting (e.g., proportion with brain metastases) may have similarly contributed to the small increase in these outcomes.

Figure B5.1: Subgroup analysis of PFS in the ASCEND-4 trial ([2]

	Number of patients (%)	HR (95% CI)	Median PFS (95% CI; months)	
			Ceritinib (n=189)	Chemotherapy (n=187)
Geographic region				
South America	18 (5%)	0.65 (0.17-2.54)	7.0 (11.1-NE)	5.0 (1.4-11.2)
Europe	199 (53%)	0.54 (0.37-0.80)	17.1 (11.7-27.7)	7.1 (4.8-11.1)
Asia Pacific	159 (42%)	0.60 (0.38-0.96)	26.3 (11.0-NE)	9.7 (5.8-13.9)
Age (years)				
<65 years	295 (78%)	0.58 (0.42-0.80)	17.1 (12.5-27.7)	8.1 (5.8-12.4)
≥65 years	81 (22%)	0.45 (0.24-0.86)	14.0 (8.3-NE)	6.8 (4.2-12.8)
Sex				
Male	160 (43%)	0.41 (0.27-0.63)	15.2 (11.0-NE)	4.3 (3.3-7.1)
Female	216 (57%)	0.63 (0.43-0.93)	25.2 (11.0-27.7)	10.6 (7.6-14.5)
Race				
Caucasian	202 (54%)	0.44 (0.30-0.66)	16.4 (12.1-27.7)	7.0 (4.3-8.5)
Asian	158 (42%)	0.66 (041-1.06)	26.3 (8.6-NE)	10.6 (6.7-15.0)
Brain metastases at screening				
Absence	255 (68%)	0.48 (034-0.69)	26.3 (15.4-27.7)	8.3 (6.0-13.7)
Presence	121 (32%)	0.70 (0.44-1.12)	10.7 (8.1-16.4)	6.7 (4.1-10.6)
WHO status				
0	139 (37%)	0.59 (0.37-0.96)	17.1 (11.3-NE)	9.7 (7.0-14.2)
>1	236 (63%)	0.52 (0.37-0.74)	16.6 (10.9-27.7)	6.7 (4.3-8.5)
Previous adjuvant chemotherapy				
Yes	19 (5%)	1.41 (0.12-15.84)	NE (6.9-NE)	NE (14.5-NE)
No	357 (95%)	0.55 (0.41-0.73)	16.4 (12.1-27.2)	7.5 (5.7-9.7)
Disease burden per central assessment				
Baseline SOD for target lesions <median SOD for target lesions	177 (47%)	0.51 (0.32-0.80)	26.3 (14.0-NE)	10.6 (7.0-14.5)
Baseline SOD for target lesions <median SOD for target lesions	184 (49%)	0.53 (0.36-0.79)	13.9 (9.5-27.2)	5.6 (4.1-8.1)
Smoking history				
Never smoked	230 (61%)	0.56 (0.38-0.80)	16.6(11.7-27.7)	8.3 (7.0-12.5)
Ex-smoker or current smoker	146 (39%)	0.48 (0.30-0.77)	15.7 (9.7-26.3)	5.8 (4.1-12.4)
All patients	**376**	**0.55 (0.42-0.73)**	**16.6 (12.6-27.2)**	**8.1 (5.8-11.1)**

B6. Priority question: The base-case analysis presented by the company uses data from the ASCEND-4 trial to estimate time on treatment for ceritinib and data from the PROFILE 1014 trial to estimate time on treatment for crizotinib. The populations in these two trials are, however, different and it is possible that this is influencing the estimated time on treatment. The ERG suggest that it is possible to present population-adjusted estimates of time on treatment using methods similar to those used to estimate PFS and OS in the base-case analysis. Details of the process are described below:

a. Using the MAIC, estimate time on treatment for people on ceritinib adjusted to the crizotinib population.

b. Using the median time on treatment from the adjusted analysis, estimate λ as per the base-case analysis and using λ estimate an exponential curve for time on treatment curves for ceritinib as per the base-case analysis.

c. Use the exponential curve estimated in part (b) along with the time on treatment curve for crizotinib to estimate a hazard ratio for time on treatment in the crizotinib population.

d. Apply this hazard ratio to the exponential curve estimated using the individual patient data (scenario 1a in the model).

Response to parts (a)-(c):
As shown below, Table B6.1 reports the intermediate results requested in parts (a) to (c). Based on the MAIC-adjusted comparison of truncated median time on treatment, we obtained a hazard ratio of [redacted] for discontinuation with crizotinib vs. ceritinib.

Table B6.1: Calculation of a matching-adjusted hazard ratio of treatment discontinuation for crizotinib vs. ceritinib

Treatment	Truncated median time on treatment in months (estimated based on PROFILE 1014 characteristics)[1]	Exponential rate (λ) of treatment discontinuation, based on median time on treatment[2]	Hazard ratio of discontinuation with crizotinib vs. ceritinib
Ceritinib	[redacted]	[redacted]	-
Crizotinib	[redacted]	[redacted]	[redacted]

Notes:
[1] The truncated median time on treatment for ceritinib was calculated using MAIC-weighted ASCEND-4 data to match patient characteristics in PROFILE 1014 (see response to Question B1). The truncated median time on treatment for crizotinib was obtained from Solomon et al. (2014).[6]
[2] As in the base case from the original submission, the exponential rate parameter for each treatment was calculated based on the truncated median, assuming a constant hazard rate.

Response to part (d):
Table B6.2 summarises the exponential rates of ceritinib and crizotinib discontinuation that we obtained using the requested hazard ratio approach. Two scenarios are presented:

i) As requested in Question B6, the first scenario uses the exponential rate of ceritinib discontinuation from scenario 1a in Table 32 of the original submission; this rate parameter was fitted to unweighted patient-level data from ASCEND-4. Under this scenario, parametric functions

of PFS and OS for ceritinib were similarly fitted to unweighted patient-level data from ASCEND-4 (as in the base case).

ii) Based on feedback in Question B1, we tested an additional scenario in which the exponential curve for time to ceritinib discontinuation was instead fitted using patient-level ASCEND-4 data weighted to match PROFILE 1014 baseline characteristics. Under this scenario, parametric functions of PFS and OS for ceritinib were similarly fitted to weighted patient-level data from ASCEND-4 (as in the scenario analyses from Question B1).

Under both of these scenarios, the exponential rate of crizotinib discontinuation was estimated by applying the MAIC-adjusted hazard ratio of [redacted] (Table B6.1) to the exponential rate of ceritinib discontinuation. Analogously, PFS and OS curves for crizotinib were estimated by applying the MAIC-adjusted hazard ratios of PFS and OS to the corresponding curves for ceritinib.

Mean treatment durations from these scenarios are reported in Table B6.3. The incremental cost per QALY for ceritinib vs. crizotinib moderately increased under these scenarios (£36,135 or £37,344 vs. the base-case of £27,936); this increase is due to the larger difference in treatment duration between the two arms when using the hazard ratio approach for discontinuation.

Instructions to replicate the B5 scenario analyses in the Excel model:

(i) Scenario based on original, unweighted patient-level data from ASCEND-4 for ceritinib

1. In the "Effectiveness" tab, set the first dropdown menu to "Hazard ratio" and the second dropdown menu to "ASCEND-4 data". Ensure that the selected parametric functions for modelling PFS and OS in the ceritinib arm are exponential.
2. In the "On Treatment" tab, set the first dropdown to "until discontinuation", the second dropdown to "ASCEND-4 data", and the third dropdown to "Based on patient-level ASCEND-4 data for ceritinib and hazard ratio approach for crizotinib".

(ii) Scenario based on MAIC-weighted patient-level data from ASCEND-4 for ceritinib

1. In the "Effectiveness" tab, set the second dropdown menu to "ASCEND-4 data reweighted to match PROFILE 1014 characteristics". Otherwise, select the same settings in this tab as in scenario (i) above.
2. In the "On Treatment" tab, set the second dropdown to "ASCEND-4 data reweighted to match PROFILE 1014 characteristics". Otherwise, select the same settings in this tab as in scenario (i) above.

Table B6.2: Exponential rate of treatment discontinuation based on individual patient data from ASCEND-4 (ceritinib) and the hazard ratio approach (crizotinib): two scenarios

Scenario	Exponential rate (λ) of treatment discontinuation for ceritinib, based on individual patient data	Exponential rate (λ) of treatment discontinuation for crizotinib, based on hazard ratio of [redacted]
(i) Based on original, unweighted patient-level data from ASCEND-4 for ceritinib[1]	[redacted]	[redacted]
(ii) Based on MAIC-weighted patient-level data from ASCEND-4 for ceritinib[2]	[redacted]	[redacted]

Notes:

[1] Under this scenario, the exponential rate of ceritinib discontinuation is that same as in scenario 1a (Table 32) from the original submission, and was estimated based on unweighted patient-level data from ASCEND-4.
[2] Under this scenario, the exponential rate of ceritinib discontinuation was instead fitted to patient-level data from ASCEND-4 after MAIC weighting to match PROFILE 1014 baseline characteristics.

Table B6.3: Estimated duration of treatment based on individual patient data from ASCEND-4 (ceritinib) and the hazard ratio approach (crizotinib): two scenarios

Treatment duration assumption	Mean duration of ceritinib treatment (months)	Mean duration of crizotinib treatment (months)
(i) Based on original, unweighted patient-level data from ASCEND-4 for ceritinib[1]	[redacted]	[redacted]
(ii) Based on MAIC-weighted patient-level data from ASCEND-4 for ceritinib[2]	[redacted]	[redacted]

Notes:
[1] Under this scenario, the exponential rate of ceritinib discontinuation is that same as in scenario 1a (Table 32) from the original submission, and was estimated based on unweighted patient-level data from ASCEND-4.
[2] Under this scenario, the exponential rate of ceritinib discontinuation was instead fitted to patient-level data from ASCEND-4 after MAIC weighting to match PROFILE 1014 baseline characteristics.

Table B6.4: Cost-effectiveness results in scenario analyses using: treatment discontinuation rates based on individual patient data from ASCEND-4 (ceritinib) and the hazard ratio approach (crizotinib)

(i) Scenario using original, unweighted patient-level data from ASCEND-4 for ceritinib discontinuation, PFS, and OS

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	126,164	4.51	3.22	19,383	0.66	0.54	36,135
Crizotinib	106,782	3.85	2.68	-	-	-	-

(ii) Scenario using MAIC-weighted patient-level data from ASCEND-4 for ceritinib discontinuation, PFS, and OS

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	135,931	4.78	3.41	20,918	0.69	0.56	37,344
Crizotinib	115,014	4.10	2.85	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYs, life years; MAIC, matching-adjusted indirect comparison; QALYs, quality-adjusted life years.

B7. Please comment on whether we might expect the rates of adverse events for ceritinib and crizotinib to vary within different patient populations (e.g. whether people with brain metastases have a different safety profile on ceritinib compared to those without). If so, should these be included within the MAIC analysis and adjusted for differences in populations? How might the inclusion of the outcome of this analysis affect the results of the model?

As noted in Section 12.5.2.2 of the ASCEND-4 CSR, subgroup analysis of safety by region, age, gender, race, presence or absence of brain metastases, prior adjuvant chemotherapy (yes vs. no), and WHO PS (0 vs. 1-2) at baseline showed that the proportion of patients with AEs was generally consistent across subgroups.

Because the proportion of patients with AEs was similar across subgroups, no MAIC adjustment of the AE rates was performed. Additionally, because deterministic sensitivity analyses found that the cost-effectiveness results were not sensitive when varying the costs of AEs from zero to twice their base-case values, we expect that the use of MAIC-weighted AE rates for ceritinib would have minimal impact on the ICER.

B8. Some discrepancies between the data reported in the submission and model and the figures in the ASCEND-4 CSR were noted: the submission states that included adverse events are treatment-related (Table 12-9 in the CSR). The figures in the model correspond to those with any study drug relationship (Table 12-8 in the CSR). Can you also please define how treatment-related events are defined?

We confirm that adverse event (AE) costs for ceritinib were modelled based on any-cause AEs (as reported in Table 12-8 of the CSR), and not the treatment-related AEs from Table 12-9 of the CSR. AE costs for crizotinib were similarly modelled based on any-case AE data, which were obtained from Solomon et al. 2014[6]. The term "treatment-related" in Table 31 of the original submission referred to the fact that AE rates are specific to each treatment arm in the model, rather than treatment-related AEs as defined in the ASCEND-4 trial protocol. Treatment-related AEs were defined in the ASCEND-4 protocol as AEs suspected to be study drug related, as determined by the investigator.

B9. The submission reports rates for "serious adverse events", including those which are grades 3 to 4 (Table 25). Can you please describe how these are defined and how they differ to the grade 3 to 4 adverse events presented in Table 23, and why they were not selected for use in the economic analysis?

Additional information on serious adverse events (SAEs) and adverse event (AE) grading in the ASCEND-4 trial are provided in Table B9.1 below. In general, SAEs are defined according to general criteria that are applicable to any adverse event (AE), whereas the definition of grade 3 and grade 4 AEs are independently defined for specific AE types.

The inclusion of costs from grade 3/4 AEs with or without the serious designation is consistent with convention in prior cost-effectiveness models in NSCLC, including the NICE submission for crizotinib for previously untreated advanced ALK+ NSCLC. Additionally, because SAEs were not reported in the publication for the PROFILE 1014 trial, it would not have been possible to draw a balanced comparison of safety between ceritinib and crizotinib based on SAEs or grade 3/4 SAEs.

Deterministic sensitivity analyses in the original submission showed that the cost-effectiveness results were not sensitive to changes in AE costs, which were varied from zero to twice their base-case values. We expect that modelling adverse event costs based on SAEs or grade 3/4 SAEs would have had minimal impact on the ICER (base-case ICER £27,936 per QALY gained; sensitivity analysis for no AE costs: £27,709 per QALY gained; sensitivity analysis for 2 x AE costs: £28,163 per QALY gained).

Table B9.1: Definitions and source information on serious adverse events and grading of adverse events

Serious adverse events (SAEs)	The ASCEND-4 protocol defines an SAE as an AE that is one of the following: • Is fatal or life-threatening • Results in persistent or significant disability/incapacity • Constitutes a congenital anomaly/birth defect • Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above • Requires inpatient hospitalization or prolongation of existing hospitalization, • Note that hospitalizations for the following reasons should not be reported as serious adverse events: • Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition • Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent • Social reasons and respite care in the absence of any deterioration in the patient's general condition • Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
Grade	Grade refers to the severity of an AE. In the ASCEND-4 trial, AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. (Source: Common Terminology Criteria for Adverse Events (CTCAE). v4.03.

	Published June 14, 2010. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.)

B10. Can you please confirm the specific definition for the adverse event rates (i.e. that they correspond to the total number of patients experiencing each type of event). Did any patient experience multiple instances of a particular adverse event? If so, please provide the total number of events.

As detailed in the footers of Tables 12-6, 12-7, and 12-8 of the CSR, there were patients who experienced multiple adverse events. Those patients with multiple events in the same, or more than one category were counted only once in the relevant category. Similarly, patients with multiple adverse events within a primary system organ class were only counted once in the total row. It is also important to note that the event with maximum severity was recorded for patients who experienced multiple episodes of a particular event. For the reasons stated above, we do not have the total number of events.

B11. Priority question: Please justify why the safety profile of each second-line therapy was not modelled. We would expect that the number of adverse events would differ in each arm, based on the different distributions of treatments provided after discontinuation. Please provide a scenario where this is included in the model, basing the rates of each event from appropriate sources (e.g. ceritinib or crizotinib given as second-line therapy).

Second-line adverse event costs were not modelled, as the consideration of this cost component was expected to have limited impact on the cost-effectiveness results. In the deterministic sensitivity analysis (described in Section B 3.8.2 of the original submission), the incremental cost per QALY for ceritinib versus crizotinib ranged from £27,709 to £28,163 when varying first-line adverse event costs from zero to twice their base-case value, respectively. The inclusion of second-line adverse event costs was expected to have an even smaller impact on the ICER, given that there was a large degree of overlap between the distributions of second-line treatments across the two arms. Similar proportions of patients in the ceritinib and crizotinib arms were estimated to receive second-line docetaxel (3.8% vs. 4.6%) or platinum doublet (45% vs. 43.1%). Additionally, 40% of patients in both arms were projected to receive no further systemic treatment, and would therefore incur zero second-line adverse event costs.

Consequently, there would have limited potential for differences in second-line adverse event rates between the two arms. As noted, the consideration of first-line adverse event costs had little influence on the ICER, even though (by definition) there was no overlap between the first-line therapy received in the ceritinib arm versus the crizotinib arm.

B12. Time on treatment for ceritinib as calculated from the exponential function with a rate parameter estimated from the truncated median appears to underestimate actual time on treatment (as calculated using the individual patient data in the ASCEND-4 trial).

i) Please provide information on the number of patients who continued ceritinib treatment after disease progression, the duration of treatment post-progression in these patients and the Kaplan-Meier curve for time on treatment for ceritinib. Please also provide further information on how well the exponential curve fit to the Kaplan-Meier curve, including which validation techniques were used.

ii) Were any other curves for time on treatment considered for the analysis? If so, please provide details of the fit and predicted mean time on treatment for these curves, and a justification for why they weren't selected for use in the model.

Response to part (i):

The number of patients who continued ceritinib treatment after disease progression, and the duration of this treatment is provided in Table 14.3-1.9 below. The Kaplan-Meier curve for time on treatment is also below (Figure B12.1).

We present the following figures to validate the exponential parametric curves fitted to patient-level ASCEND-4 data for time to ceritinib discontinuation, before and after MAIC weighting to match PROFILE 1014 population characteristics:

- In Figures B12.1 and B12.2, the Kaplan-Meier curves for time to ceritinib discontinuation (before and after MAIC weighting, respectively) are plotted against the exponential functions fitted to these curves.

- Figures B12.3 and B12.4 present the log-cumulative hazard plots for time to discontinuation of ceritinib in ASCEND-4 (before and after MAIC weighting, respectively). The approximately linear shape of both plots is consistent with the assumption of a constant hazard rate of discontinuation, and supports the use of an exponential function to model time on treatment for ceritinib.

Table 14.3-1.9 Duration of exposure to treatment following BIRC confirmed disease progression by treatment arm (part1 of 2).

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Table 14.3-1.9 (Page 1 of 2)
Duration of exposure to treatment following BIRC-confirmed disease progression, by treatment arm
(Safety set)

	LDK378 750 mg N=189	Chemotherapy N=175
Patients who had BIRC-confirmed RECIST-defined disease progression	73	97
Patients who did not continue treatment beyond BIRC-confirmed RECIST-defined disease progression	12	69
Patients who continued treatment beyond BIRC-confirmed RECIST-defined disease progression	61	28
Exposure categories (weeks) - n (%)		
< 1	5 (6.8)	19 (19.6)
1 - < 3	11 (15.1)	2 (2.1)
3 - < 6	9 (12.3)	4 (4.1)
6 - < 12	8 (11.0)	0
12 - < 18	8 (11.0)	1 (1.0)
18 - < 24	5 (6.8)	1 (1.0)
24 - < 30	3 (4.1)	0
30 - < 36	3 (4.1)	1 (1.0)
36 - < 42	1 (1.4)	0
42 - < 48	4 (5.5)	0
48 - < 54	1 (1.4)	0
>= 54	3 (4.1)	0

A patient is counted in only one duration range, per treatment.
Duration of exposure is calculated based on the last dosing date to study treatment - date of first BIRC-confirmed RECIST-defined disease progression.
Date of first BIRC-confirmed RECIST-defined disease progression is the date of first progression by BIRC assessment on or following the date of progression by Investigator assessment.
Percentage to calculate exposure categories (weeks) is based on the number of patients who had BIRC-confirmed RECIST-defined disease progression.

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Table 14.3-1.9 Duration of exposure to treatment following BIRC confirmed disease progression by treatment arm (part 2 of 2).

CLDK378A2301 - Cut-off date: 24JUN2016

Table 14.3-1.9 (Page 2 of 2)
Duration of exposure to treatment following BIRC-confirmed disease progression, by treatment arm
(Safety set)

	LDK378 750 mg N=189	Chemotherapy N=175
Duration of exposure (weeks)		
n	61	28
Mean	16.0	3.5
SD	17.08	7.30
Median	9.6	0.7
Minimum	0.1	0.1
Maximum	68.4	30.0

A patient is counted in only one duration range, per treatment.
Duration of exposure is calculated based on the last dosing date to study treatment - date of first BIRC-confirmed RECIST-defined disease progression.
Date of first BIRC-confirmed RECIST-defined disease progression is the date of first progression by BIRC assessment on or following the date of progression by Investigator assessment.
Percentage to calculate exposure categories (weeks) is based on the number of patients who had BIRC-confirmed RECIST-defined disease progression.

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Figure B12.1: Validation of exponential function to time to discontinuation of ceritinib (based on patient-level data from ASCEND-4)

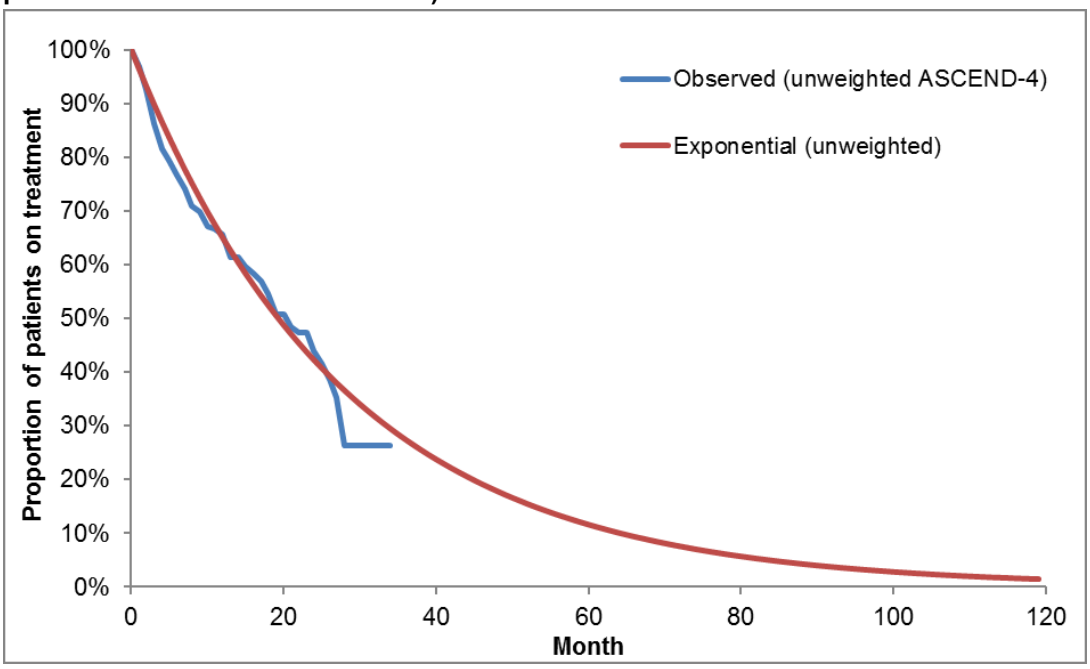

Figure B12.2: Validation of exponential function to time to discontinuation of ceritinib (based on patient-level data from ASCEND-4 weighted to match PROFILE 1014 baseline characteristics)

[redacted]

Figure B12.3: Log-cumulative hazard plot: Time to discontinuation of ceritinib (based on unweighted patient-level data from ASCEND-4)

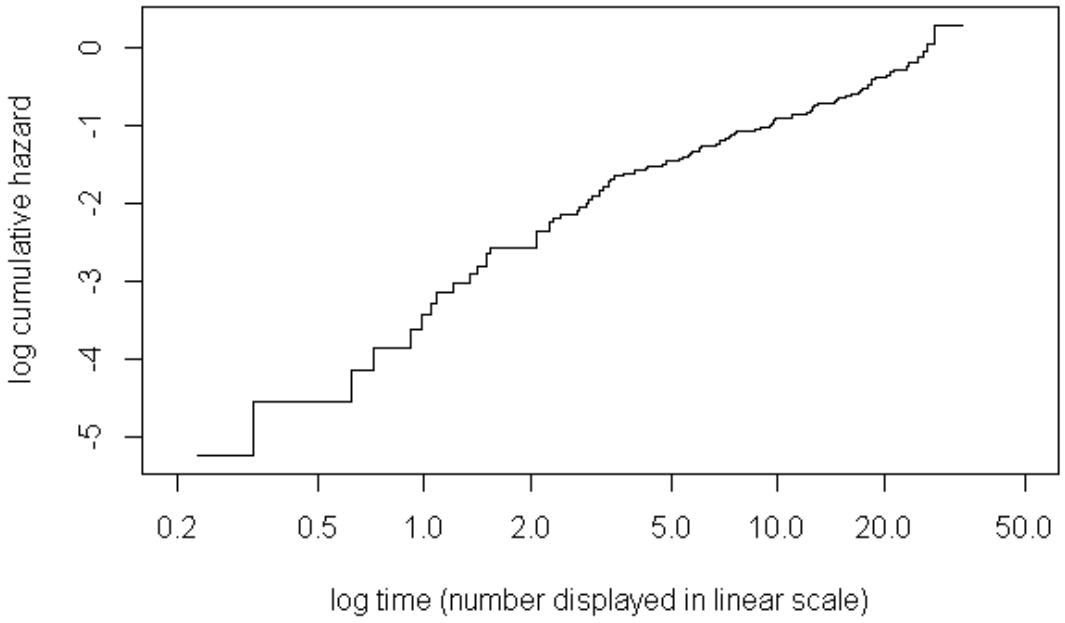

Figure B12.4: Log-cumulative hazard plot: Time to discontinuation of ceritinib (based on patient-level data from ASCEND-4 reweighted to match the PROFILE 1014 population)

Response to part (ii):

The exponential function was used to model time on treatment because it is a one-parameter survival function that could be estimated using a single data point (e.g., the reported median treatment duration). Because the Kaplan-Meier curve for time to crizotinib discontinuation in PROFILE 1014 has not been published, we were unable to fit two-parameter survival functions for crizotinib with the available data. We therefore did not consider alternative parametric functions for time to treatment discontinuation.

As noted by the ERG, one potential approach might have been to fit other proportional hazards models of ceritinib time on treatment using patient-level data, and apply the hazard ratio of discontinuation (calculated in response to Question B6) to estimate time on treatment for crizotinib. However, without additional data on the duration of crizotinib treatment, we are unable to assess the fit of different parametric functions within the crizotinib arm.

B13. Please comment on whether we might expect the quality of life for patients on ceritinib and crizotinib to vary within different patient populations (e.g. whether patients with brain metastases have a different quality of life on ceritinib compared to those without). If so, should these be included within the MAIC analysis and adjusted for differences in populations? How might the inclusion of the outcome of this analysis affect the results of the model?

In a regression analysis of EQ-5D-5L data from the ASCEND-4 trial (Table 14.2-4.19 of the CSR), presence/absence of brain metastases was not found to have a statistically significant correlation with utility. This finding suggests that utility while on first-line treatment with ceritinib may be comparable between patients with and without baseline presence of brain metastases. (Analyses of EQ-5D-5L in the ASCEND-4 CSR included utility assessments only up to 7 days following ceritinib discontinuation before the start of any further anti-neoplastic therapies, and therefore captured patients' utility values while on first-line treatment).

Within the model, patients' utility in a given cycle was linked to their concurrent health state (progression-free, progressive disease, or death). The health state distribution of patients in each cycle was determined by our estimation of PFS and OS over time in each treatment arm. Hazard ratios of PFS and OS in the model were derived based on the MAIC of these outcomes, in which ASCEND-4 data was reweighted to match PROFILE 1014 patient characteristics. Therefore, the comparison of QALYs between the two arms should already be adjusted for cross-trial differences (which should encompass differences in QoL for those patients with or without brain metastases) in the baseline prevalence of brain metastases and other characteristics included in the MAIC.

Table 14.2-4.19 Mixed effect model for EQ-5D.

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Table 14.2-4.19 (Page 1 of 2)
Mixed effect model for EQ-5D, comparison of LDK378 750 mg with chemotherapy
(Full analysis set)

Scale: EQ-5D-5L Index Value UK

Effect		Estimate	Standard Error
Treatment	LDK378 750 mg	0.513	0.0355
	Chemotherapy	0.507	0.0366
Brain metastases	Absence	0.007	0.0129
	Presence	0.000	
WHO status	0	0.009	0.0123
	1-2	0.000	
Prior adjuvant chemotherapy	No	-0.037	0.0281
	Yes	0.000	
Baseline		0.370	0.0280
Time		0.000	0.0000
Time*Treatment	LDK378 750 mg	0.000	0.0001
	Chemotherapy	0.000	

The randomization strata factors are WHO status, presence or absence of brain metastases and prior adjuvant chemotherapy.

B14. Please provide additional information on how EQ-5D data was collected for ceritinib patients in ASCEND-4, including:

i) When records were collected (the frequency of collection, when records ceased to be collected e.g. progression or discontinuation);

ii) The number of records (where applicable) were collected in ceritinib patients who were: (a) pre-progressed and on first-line treatment, (b) pre-progressed and off treatment, (c) post-progressed and on treatment, and (d) post-progressed and off treatment;

iii) The mean utility and other descriptive statistics in each of the four patient groups described above (where applicable).

Response to part (i):
In the ASCEND-4 trial protocol, the timing of patient-reported outcome (PRO) assessments was defined in terms of 21-day treatment cycles. EQ-5D and other PRO assessments took place at the beginning of Cycle 1 and Cycle 2, followed by every 2nd cycle (i.e., every 6 weeks) until Month 33, every 3rd cycle (i.e., every 9 weeks) after Month 33, and at the End of Treatment (EOT) visit.
Patients who permanently discontinued study treatment before BIRC-confirmed disease progression continued PRO assessments according to the protocol. The assessment ended upon BIRC-confirmed disease progression, withdrawal of consent for further assessments, lost to follow-up, death, pregnancy or study is terminated by the sponsor. These patients completed the EOT visit when they discontinued study treatment during the treatment phase and potentially had multiple PRO assessments before disease progression.
For patients in the ceritinib arm who had disease progression but continued to receive ceritinib, PRO assessments ended in the treatment phase when patients progressed. Therefore, these patients only completed the PRO at the EOT visit after permanent discontinuation of ceritinib.
All analyses of PROs reported in the CSR were conducted using non-missing post-baseline questionnaire assessments within 7 days of last dose of study treatment before the start of any further anti-neoplastic therapies.

Response to parts (ii) and (iii):
The requested analyses of EQ-5D data by health state and treatment status were not among the pre-specified analyses reported in the ASCEND-4 trial CSR, and could not be conducted within the allotted timeframe for this response. However, based on the protocol-defined PRO assessment schedule, we expect that EQ-5D measurements after disease progression and/or first-line treatment discontinuation would be largely limited to the EOT visit, and would constitute a small proportion of all collected assessments.

B15. Please explain why the drug and administration costs and pre-progression costs were halved in the first cycle of the model.

A half-cycle correction was applied to all cost components and effectiveness outcomes within the trace for each treatment arm. To apply the half-cycle correction, we subtracted half of the costs and effectiveness at the start of the first cycle and added back half of the costs and effectiveness at the end of the last cycle. For example, when using a 20-year time horizon, the Excel model will sum half of the outcomes at t=0 months, all outcomes at t=1, 2, 3,**…,** 239 months, and half of the outcomes at t=240 months. (As an exception, because AE costs are included as a one-time cost in the first model cycle, this cost component is modelled by summing half of the costs at t=0 months and half at t=1 month.)

B16. Priority question: The same per-cycle post-progression costs were applied in both the ceritinib and the crizotinib arms in the model. Given that it would be reasonable to assume that these may differ in each arm (e.g. because of the differential proportion of people on an ALK inhibitor or the potential different number of people on active treatment), please justify why these costs were applied in this way.

The per-cycle costs of routine medical management and supportive medications in the progressive disease state were assumed to be equivalent between the two treatment arms. As described in Section B 3.5.3 of the original submission, the monthly frequency of each resource was obtained from previous NICE appraisals for erlotinib in EGFR-TK+ NSCLC (TA162 and TA258), consistent with NICE submission for crizotinib for untreated ALK+ advanced NSCLC. These estimates were viewed as the best available evidence in the literature, as they have been informed by expert opinions (five leading UK clinicians specialising in the treatment of NSCLC), and have been reviewed by the NICE Evidence Review Groups (ERGs) and appraisal committees on four previous occasions. The clinical experts that we consulted also agreed with our use of these inputs for the current model.[1] To our knowledge, there is no alternative source in the literature that would have enabled us to distinguish monthly post-progression resource use by treatment arm.

As a clarification, the cost of post-progression treatment for NSCLC was considered as a separate cost component and was assumed to differ between the first-line ceritinib and crizotinib arms. Based on feedback from clinical experts and the reported frequencies of different post-progression treatments in the ASCEND-4 and PROFILE 1014 trials, we found that there was sufficient data available to differentiate post-progression treatment costs between the two arms. Further details on the estimation of post-progression treatment distributions and costs are provided in Section B 3.5.4 of the original submission, and in our responses to Questions A9 and B18.

B17. The clinicians consulted by the company advised that whole brain radiotherapy be included in the post-progression health state costs. Further, it was stated that the utilisation of this resource was expect to be different in each arm. Please explain why radiotherapy was not included in the health state costs in the model.

In clinical validation meetings, clinical experts agreed with the hypothesis that whole brain radiotherapy would likely be more common in patients treated with crizotinib than those treated with ceritinib.[1] Nevertheless, experts were unable to provide specific utilisation estimates for brain radiotherapy due to the high degree of uncertainty around this parameter. In the absence of concrete data to differentiate use of brain radiotherapy between the treatment arms, we omitted this cost component from the model. This was a conservative decision given our expectation that radiotherapy costs would be higher in the crizotinib arm.

B18. Please provide a justification as to why the same proportion of patients received active therapy post-discontinuation in each arm of the model? Is this likely to be reflective of clinical practice? The ASCEND-4 trial and the PROFILE 1014 trial report that 35% of people in ASCEND-4 and 43% in PROFILE 1014 received some systemic therapy. Why were the rates of second-line treatment in the trials not used in the model? The proportion of people receiving second-line systemic therapy were lower than those used in the model – please describe why this was and how it might impact on the overall survival estimates.

Based on feedback from clinical validation meetings, the model assumed that 60% of patients would receive second-line systemic treatment following progression on first-line ceritinib or crizotinib. (Additional details on the derivation of second-line treatment distributions are included in our response to Question A9.) Limited post-progression follow-up time was available in both the ASCEND-4 and PROFILE 1014 trials, and we expected that a larger proportion of progressed patients would eventually initiate second-line treatment beyond the data cut-off. We therefore sought input from clinical experts to obtain a reasonable extrapolation for the final percentage of progressed patients who would receive second-line systemic therapy.

Since the 60% figure represents an extrapolation of second-line treatment initiations that we would expect to observe in both trials with additional follow-up data, we consider this input to be internally consistent with the trial-based OS extrapolations used in the model. Nevertheless, we acknowledge that this parameter is subject to some uncertainty and have therefore tested two alternative scenarios in which: (i) 40% of patients receive second-line systemic therapy following progression in both arms; or (ii) 35% and 43% receive second-line systemic therapy in the ceritinib and crizotinib arms, respectively, in accordance with the truncated percentages observed in ASCEND-4 and PROFILE 1014 up to the data cutoff. (In both of these scenarios, usage of specific second-line treatment regimens was proportionally adjusted according to the overall percent of patients assumed to receive active second-line therapy.)

Results from these additional scenario analyses (presented in Table B18.1) demonstrate that the ICER for ceritinib vs. crizotinib is not sensitive to alternative assumptions regarding the overall use of second-line systemic therapy. The ICER nominally increased by £385 (see table B18.1)after reducing the utilisation of second-line treatment to 40% in both arms, and decreased by £1,572 GBP (see table B18.1) when assuming that 35% and 43% received second-line therapy in the ceritinib and crizotinib arms, respectively.

Table B18.1: Scenario analyses: Utilization of second-line systemic therapy after progression

Percentage of patients who receive second-line systemic therapy after progression	ICER of ceritinib vs. crizotinib (£/QALY)
Base case: 60% in both arms	27,936
Alternative scenario: 40% in both arms	28,321
Alternative scenario: 35% in the ceritinib arm, 43% in the crizotinib arm	26,364

B19. Priority question: The same duration for each second-line therapy has been applied to each option regardless of the arm of the model it is applied in. People on ceritinib, who have been demonstrated to live longer post-progression than those on crizotinib, might be expected to receive second-line treatment for a longer duration than people treated with crizotinib. Please comment on whether the assumption made within the model is a realistic one.

Based on the model's extrapolations of PFS and OS in each treatment arm, post-progression survival ("LYs: PD" in Table B19.1 below) was nearly equivalent between the ceritinib and crizotinib arms in the base case. The estimated survival advantage of ceritinib occurred in the progression-free health state, prior to the initiation of second-line therapy. The model therefore assumed that the mean duration of each second-line treatment option was equivalent between the ceritinib and crizotinib arms.

Table B19.1: Effectiveness outcomes in the base-case analysis (from Table 49 of the original submission)

Outcome	Ceritinib	Crizotinib	Ceritinib vs. Crizotinib
Total QALYs	3.22	2.68	0.54
QALYs: PF	1.55	1.02	0.53
QALYs: PD	1.66	1.66	0.00
Total LYs	4.51	3.85	0.66
LYs: PF	1.92	1.26	0.66
LYs: PD	2.59	2.59	0.00

LY, life-year; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year

B20. Priority question: Please clarify whether the duration of second-line therapies was recorded in the ASCEND-4 trial? If so, please modify and include within the model as an additional scenario analysis in which time on secondary therapy is based on duration of second-line therapy recorded in the ASCEND-4 trial.

No data on second-line treatment duration was collected.
Moreover, in the event that this data had been collected, there would not have been sufficient follow-up time and sample size to reliably extrapolate the mean duration of each specific second-line treatment regimen.

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Single technology appraisal

Ceritinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer [ID1117]

ERG clarification responses

8 Sept 2017

B2. Priority question: We have identified a trial relevant to the comparison of ceritinib with crizotinib.[1] This trial presents further data on the effectiveness of crizotinib in untreated patients with ALK positive advanced NSCLC.

a. Can the company re-run the MAIC analysis using the clinical data on crizotinib from ALEX trial data rather than the crizotinib data from PROFILE 1014?

b. Can the ALEX and PROFILE trial be combined and incorporated into the MAIC analysis, i.e. is there a methodology to facilitate a meta-analysis of the crizotinib data to be the comparator?

Response to a:

A matching adjusted indirect comparison (MAIC) analysis using data on crizotinib from the ALEX trial[1] was conducted using the same approach that was used in the previous MAIC using data on crizotinib from PROFILE 1014.[2] ALEX (NCT02075840) is a randomized, open-label phase III trial comparing alectinib (600 mg twice daily) and crizotinib (250 mg twice daily) as first-line treatment in patients with previously untreated, advanced ALK positive NSCLC.[1] Aggregate data for baseline characteristics and efficacy outcomes in patients treated with crizotinib in this trial were obtained from the primary publication. As in the previous MAIC, patient-level data was used for ceritinib patients from the ASCEND-4 trial.

The same patient baseline characteristics that were included in the MAIC vs. PROFILE 1014 in the original submission were matched between the two trials in the current study (Table B2.1). As ALEX only reported the presence of central nervous system (CNS) metastases instead of brain metastases, ceritinib-treated patients with brain metastases in ASCEND-4 were re-weighted to match the proportion of crizotinib-treated patients with CNS metastases from ALEX.

The efficacy outcomes compared were progression-free survival (PFS) and overall survival (OS). The definition of each outcome measure is detailed below:

- PFS: The time from randomization to progression or death due to any cause, assessed by central review. Disease progression was assessed using RECIST v.1.1. ASCEND-4 included PFS assessed by blinded independent review committee (BIRC) as a primary endpoint, while ALEX included investigator-assessed PFS as a primary endpoint and independent review committee (IRC)-assessed PFS as a secondary endpoint. In this analysis, IRC-assessed PFS from the ALEX trial was compared with BIRC-assessed PFS from the ASCEND-4 trial
- OS: The time from randomization to death due to any cause

The results of the baseline characteristics comparison between the ceritinib arm of the ASCEND-4 trial and the crizotinib arm of the ALEX trial are shown in Table B2.1. Prior to matching, the ceritinib patients had a numerically higher proportion of current smokers compared to the crizotinib patients (7.9% vs.

3.3%). After applying weights to ceritinib patients in ASCEND-4, all baseline characteristics were exactly balanced between the two patient populations.

Table B2.1: Comparison of baseline characteristics before and after matching[1] [2]

	Before matching			After matching		
	ASCEND-4 (Ceritinib)	ALEX (Crizotinib)		ASCEND-4 (Ceritinib)	ALEX (Crizotinib)	
	N = 189	N = 151	P-value	N = 189 (ESS = 174)	N = 151	P-value
Age < 54 years[3], %	46.6	50.0	0.528	50.0	50.0	1.000
Female, %	54.0	57.6	0.501	57.6	57.6	1.000
Race - Asian[4], %	40.2	45.7	0.310	45.7	45.7	1.000
Current smoker, %	7.9	3.3	0.072	3.3	3.3	1.000
Former smoker, %	34.9	31.8	0.543	31.8	31.8	1.000
Adenocarcinoma[5] , %	95.2	94.0	0.624	94.0	94.0	1.000
ECOG performance score 0 or 1[6], %	93.1	93.4	0.926	93.4	93.4	1.000
Metastatic disease[7] , %	95.2	96.0	0.725	96.0	96.0	1.000
Brain/CNS metastases[8] , %	31.2	38.4	0.165	38.4	38.4	1.000

* P-values < 0.05 were considered significant; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size after weighting; WHO: World Health Organization.
[1] The matching-adjusted indirect comparison (MAIC) was implemented to balance baseline patient and disease characteristics. All variables are categorical variables and were matched on proportions only.
[2] Chi-squared tests were used to compare baseline characteristics between ceritinib and crizotinib before matching. Weighted chi-square tests were used to compare baseline characteristics after matching.
[3] The median age for crizotinib patients in ALEX was 54 years old.
[4] In ASCEND-4, other race included Black, Caucasian, Native American, and other. In ALEX, other races were referred to as "non-Asian".
[5] In ASCEND-4, other histologic types included adenosquamous cell carcinoma, large cell carcinoma, undifferentiated carcinoma, and other types and were reported in 4.8% of ceritinib patients. In ALEX, other histologic types included large-cell carcinoma, mixed with predominantly adenocarcinoma component, squamous-cell carcinoma, and other types and were reported in 6.0% of crizotinib patients.
[6] In ASCEND-4, the ECOG performance status was referred to as WHO performance status. 6.9% of ceritinib patients in ASCEND-4 and 6.6% of crizotinib patients in ALEX had an ECOG performance score of 2 at baseline.
[7] 4.8% of ceritinib patients in ASCEND-4 and 4.0% of crizotinib patients in ALEX had a locally advanced disease (stage IIIB).
[8] Ceritinib-treated patients with brain metastases in ASCEND-4 were re-weighted to match the proportion of crizotinib-treated patients with CNS metastases from ALEX.

The MAIC results using the crizotinib data from ALEX were similar to those produced using the crizotinib data from PROFILE 1014 (see the MAIC study report for full details[2]). Compared to crizotinib in ALEX, ceritinib was associated with a significantly longer PFS before matching (median: 16.6 vs. 10.4 months; [redacted], Figure 1). After adjustment, the HR of ceritinib vs. crizotinib was [redacted]); the median PFS was [redacted] months for ceritinib (vs. [redacted] months for crizotinib, weighted log-rank p=[redacted]). The adjustment [redacted] the 95% CI for ceritinib ([redacted] before matching; [redacted] after

matching). In terms of OS, there was no significant difference between ceritinib and crizotinib in ALEX before ([redacted]) or after matching (weighted log-rank [redacted]), as would be expected given the immaturity of the data (Figure 1).

Figure 1: KM curves for PFS and OS before and after matching - ceritinib vs. crizotinib

[redacted]

Response to b:

We are not aware of a methodology to facilitate such meta-analysis. Considering similar MAIC results were obtained using crizotinib data, respectively from ALEX and PROFILE 1014, we expect a meta-analysis combining both trials would generate similar results.

B3. Priority question: To explore the impact of the analysis requested in question B2 on cost-effectiveness, can the company incorporate the analysis using the ALEX trial into the economic model. In the scenarios the ERG request that this analysis be carried out (i) modelling the population in the ASCEND-4 study as per the company's base-case, and (ii) modelling the population in the ALEX trial/(ALEX and PROFILE 1014) population similar to question B1a.

Based on the MAIC between the ceritinib arm from ASCEND-4 versus the crizotinib arm from ALEX, the following two additional scenarios were tested in the cost-effectiveness model:

- Scenario B3.i: Under this scenario, the original base case was modified by replacing the PFS and OS hazard ratios for ceritinib vs. crizotinib with those obtained from the MAIC with the ALEX trial. Additionally, the truncated median duration of crizotinib treatment was based on that reported in the ALEX trial (i.e., 10.7 months) rather than the PROFILE 1014 trial (i.e., 10.9 months). (As in the base case, parametric functions of PFS and OS for ceritinib were based on original, unweighted ASCEND-4 data. The truncated median duration of ceritinib treatment was also based on unweighted ASCEND-4 data as in the base case).
- Scenario B3.ii: Scenario B3.i was further modified by re-fitting parametric functions of ceritinib PFS and OS after weighting the ASCEND-4 data to match baseline characteristics from the ALEX trial population. Truncated median time on treatment was similarly re-calculated for ceritinib after weighting the ASCEND-4 data to match the ALEX trial population. (Scenario B3.ii is analogous to the scenario analysis conducted in response to Question B1a, but applies ALEX-based rather than PROFILE 1014-based weights to the ASCEND-4 data).

Note about testing Scenarios B3.i & B3.ii in the Excel model:

Within the time constraints, it was not possible to formally incorporate these scenario analyses as pre-programmed options within the Excel model. However, these scenarios can be tested within the model by manually plugging in the parameter values provided in Tables B3.1, B3.3, and B3.4.

Please note that the parameter values in these tables are reported to fewer decimal places than were used to generate the results in Tables B3.2 and B3.5. Thus, model users may obtain slightly different incremental cost-effectiveness ratios using the rounded parameter values from Tables B3.1, B3.3, and B3.4.

Model inputs and results under Scenario B3.i:

Table B3.1 summarizes the three model parameters that are modified under Scenario B3.i compared to the base-case analysis. As reported in Table B3.2., the incremental cost per QALY gained for ceritinib vs. crizotinib was £32,386 under this scenario analysis (compared to £27,936 in the base case).

Table B3.1: Hazard ratios of PFS and OS and truncated median duration of crizotinib treatment under Scenario B3.i

Parameter	Parameter value under Scenario B3.i
Hazard ratio of PFS with crizotinib vs. ceritinib	[redacted]
Hazard ratio of OS with crizotinib vs. ceritinib	[redacted]
Truncated median time on treatment for crizotinib	10.7 months[2]

Notes:
[1] Based on the MAIC with the ALEX trial.
[2] From Peters et al. (2017).

Table B3.2: Cost-effectiveness results: Scenario B3.i

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	106,954	4.51	3.22	16,124	0.63	0.50	32,386
Crizotinib	90,830	3.89	2.72	-	-	-	-

Model inputs and results under Scenario B3.ii:

Under Scenario B3.ii, the hazard ratios and truncated median duration of crizotinib treatment are the same as in Scenario B3.i (see Table B3.1). Parametric estimates of PFS and OS for ceritinib were similarly re-fitted after weighting the ASCEND-4 data to match the ALEX population (Table B3.3). The same parametric distributions were selected to model PFS and OS as in the base case (i.e., exponential for both), based on the same rationale described in Section B 3.3.2 of the original submission. Additionally, the truncated median duration of ceritinib treatment was recalculated after weighting ASCEND-4 data to match baseline characteristics in ALEX (Table B3.4); [redacted].

As reported in Table B3.5, the incremental cost per QALY gained was £31,766 under this scenario analysis.

Table B3.3: Parametric estimates of PFS and OS for ceritinib after applying MAIC weights to match ALEX baseline characteristics

Functional form	Progression-free survival (PFS), ceritinib[1]			
	A[2]	B[2]	AIC	BIC
Exponential	0.041	-	597.775	600.793
Weibull	25.540	0.919	599.097	605.131
Log-logistic	16.624	1.099	596.341	602.375
Log-normal	2.820	1.552	592.438	598.472
Gompertz	-0.031	0.052	597.292	603.326

Functional form	Overall survival (OS), ceritinib[1]			
	A[2]	B[2]	AIC	BIC
Exponential	0.015	-	381.481	384.498
Weibull	56.018	1.187	382.314	388.349
Log-logistic	46.148	1.281	382.396	388.430
Log-normal	4.054	1.582	383.826	389.861
Gompertz	0.023	0.012	382.639	388.674

Notes:
[1] Parameters for ceritinib were estimated based on data from ASCEND-4 trial (data cut-off date June 24, 2016), reweighted to match the reported distribution of baseline characteristics in the ALEX trial. The weights were estimated in a matching-adjusted indirect comparison study.
[2] For the exponential distribution, A refers to the rate parameter (λ). For the Weibull and the log-logistic functions, A refers to the scale parameter, and B refers to the shape parameter. For the log-normal function, A refers to the log mean parameter and B refers to the log standard deviation parameter. For the Gompertz function, A refers to the shape parameter and B refers to the rate parameter.
AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table B3.4: Truncated median duration of ceritinib treatment under Scenario B3.ii

Parameter	Value under Scenario B3.ii
Truncated median time on treatment for ceritinib	[redacted][1]

Notes:
[1] [redacted].

Table B3.5: Cost-effectiveness results: Scenario B3.ii

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
Ceritinib	107,561	4.72	3.35	16,174	0.65	0.51	31,766
Crizotinib	91,387	4.08	2.84	-	-	-	-

References

1. Peters S, Camidge DR, Shaw AT, al. e. Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. *New England Journal of Medicine* 2017;377:829-38.
2. Novartis. Data on file. Matching-Adjusted Indirect Comparison of Efficacy Outcomes of First-Line Ceritinib (ASCEND-4) and Crizotinib (ALEX) for the Treatment of Advanced or Metastatic Anaplastic Lymphoma Kinase-Positive (ALK+) Non-Small Cell Lung Cancer. 6 September 2017.

Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Ceritinib for untreated anaplastic lymphoma kinase positive non-small cell lung cancer [ID1117]

Submitting Organisation

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

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

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

General Points

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

2. The relatively recent addition of targeted therapies and immunotherapy, in the treatment of nsclc, has ensured active therapy options for many with nsclc. However, overall outcomes for many of this patient population remains poor. The availability of new targets and therapy choices being of key future importance.

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

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

This Product

1. Well tolerated
   Oral therapy - therefore, ease of administration.

   Ceritinib has been available for the treatment of ALK positive nclc, after Crizotinib therapy, for some months. As such, experience in use and side effect management is now commonplace. We understand that common side effects associated with Ceritinib include diarrhea, nausea, vomiting, tiredness, abdominal pain, cough and decreased appetite. Ceritinib may also cause more serious side effects, such as hepatotoxicity, lung toxicity and cardiac problems including bradycardia. In the anecdotal patient experience available to us, it appears to be generally well tolerated – in particular, when compared with current standard cytotoxic therapy for nsclc.

2. Very targeted population.

   The ALK gene rearrangement is found in about 2% to 7% of patients with nsclc. Crizotinib has previously been approved by NICE for untreated ALK positive nsclc patients. Ceritinib currently has NICE approval for this patient group, in second line, after Crizotinib treatment.

3. Outcome of treatment

   We do not have any additional data, beyond that publically available.

   We note, however, the results of the Phase 111 ASCEND-4 Study. All patients in the study we untreated and all had evidence of ALK rearrangement, identified by laboratory testing. Ceritinib was compared with standard platinum/pemetrexed chemotherapy (with pemetrexed maintenance. The median progression free survival (PFS) was 16.6 months in the Ceritinib arm, compared with 8.1 months in the chemotherapy arm. Confirmed ORR of 73% and 27% in the Ceritinib and chemotherapy arms respectively.
   Also, we note with interest, brain metastasis data in this study. In patients with measurable brain metastasis, the confirmed overall intracranial response rate was 57% in the Ceritinib arm, compared with 22% in the chemotherapy arm.

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

In summary

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

ALK gene rearrangement is found in a very small number of lung cancer patients. Ceritinib offers a further therapy option for this defined patient group.

[redacted].

August 2017.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Thoracic Society – a multidisciplinary professional society which aims to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The British Thoracic Society supports the proposed appraisal. There is an urgent need more treatment options for patients with lung cancer given the very poor prognosis.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example,	

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients	

or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA406, TA181, TA190, TA402]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, and Royal College of Radiologists.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	The treatment is not curative but aims to control advanced ALK + ve NSCLC extend life and by improving symptoms improve quality of life.

disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in progression free survival of > 3 months with an associated improvement in quality of life.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes patients with advance NSCLC have a very poor prognosis and more effective systemic treatment are badly needed.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Locally advanced / metastatic non-small cell lung cancer (NSCLC) has a number of NICE approved systemic treatment options for patients. In general these options are of limited effectiveness which will mean there is variation of practice across the UK particular as this area was not reviewed in the updated Management of Lung Cancer guideline 2011. Treatment is delivered by Oncologists in Teaching and District General Hospitals is increasing based on the molecular genotype using drugs that target specific mutational abnormalities (EGFR, ALK). When these mutations are present 'targeted' systemic drugs form the backbone of treatment strategies, however, most

	patients are 'negative' for these mutations and are considered systemic chemotherapy, immunotherapy or best supportive care. The choice of treatment will primarily be dictated by patient fitness (performance status PS).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Management of Lung Cancer guideline 2011. The anaplastic lymphoma kinase (ALK) re-arrangement occurs in approximately 3 – 7% of patients with NSCLC and there is good clinical data that has shown that targeted therapy with ALK tyrosine kinase inhibitors (ALK-TKI) is effective. Recent NICE assessment of crizotinib (TA422) and ceritinib (TA395) have concluded they offer a cost effective treatment on progression following first line system treatment. In addition NICE has reviewed crizotinib as first line treatment (TA406) and supported its use for patients the ALK rearrangement in that setting. Therefore, these ALK-TKIs are established as a standard of care in the UK for patients fit enough to receive them. Ceritinib has very recently received an EMA license for the first line treatment of ALK mutation positive NSCLC which means there no current guidelines in place within the EU recommending the place of ceritinib used within those licensed indication
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, ALK mutation testing at diagnosis is now a routine part of clinical practice in England and the majority those patients who test positive would receive first line treatment with crizotinib. The alternative option would be cisplatin-pemetrexed chemotherapy (the ALK mutation is only seen in the non-squamous population). When relapse occurs these patients would be considered for second line systemic treatment with crizotinib if not used in the first line setting or ceritinib if progression has occurred on crizotinib. Chemotherapy would again be the alternative, platinum based or docetaxel/nintendinib if the patients had received platinum chemotherapy previously. In both the first and second line setting entry into clinical trials may be considered or in patients with poor performance status best supportive care, which may include radiotherapy.

• What impact would the technology have on the current pathway of care?	Ceritinib is a second generation ALK-TKI and clinical trial data indicates that this class of drug is an innovative and effective systemic treatment option for patients with the ALK mutation. Internationally it is expected that the 2nd generation ALK-TKIs will be offered as a treatment option, and in due course are likely to replace crizotinib as an internationally recognised standard of care.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Ceritinib is an oral medication taken once daily that would be taken until disease. Treatment would be supervised though the specialist lung cancer oncology clinics / chemotherapy units that are operating across the UK. It is likely that ceritinib would be used in place of crizotinib or cisplatin / pemetrexed chemotherapy
• How does healthcare resource use differ between the technology and current care?	See above
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	See above
• What investment is needed to introduce the technology? (For	See above

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The clinical trials of ceritinib in the ALK mutation positive NSCLC population are consistent with our current standard NHS practice and the complexity of treatment delivery will be similar to the current standard chemotherapy treatments. Those trails report improvements in response and survival for ceritinib when compared to standard platinum/pemetrexed treatment (with pemetrexed maintenance) and there were associated improvements in quality of life. The side effect profile is different to standard chemotherapy treatment and generally gastro-intestinal but did require dose interruptions or modifications in the majority of patients. Therefore, some (relatively minor) modifications will be required for treatment assessment and follow up with a training requirement so that staff becomes familiar with the management of the side effect profile. This is currently occurring as other drugs in this class have been introduced into clinical practice. Oral home administration of ceritinib will not exacerbate the capacity pressures on oncology day-units though as the drug is given until time of progression, significant toxicity, or clinician/patient decision there will be pressures on chemotherapy outpatient clinics.
• Do you expect the technology to increase length of life more than current care?	Yes, there is no current data from studies comparing crizotinib and ceritinib directly as first line systemic treatment. Adjusted comparisons have been performed that suggest outcomes comparable to crizotinib and and other second generation ALK TKI inhibitors are reporting phase III study results that are superior to crizotinib.
• Do you expect the technology to increase	Trial data reports improved quality of life compared with chemotherapy, this data and personal experience suggest similar side effect profile and quality of life when compared to crizotinib.

health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	With the population limited to ALK +ve NSCLC there are no identified subgroups for whom the treatment appears less effective.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional	No practical implications, ceritinib requires the same clinical facilities / set up as crizotinib to deliver which is one of the current standards of care.

tests or monitoring needed.)	
4. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	ALK mutation testing as indicated above.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Ceritinib is a second generation ALK-TKI and clinical trial data indicates that this class of drug is an innovative and effective systemic treatment option for patients with the ALK mutation. Internationally it is expected that the 2nd generation ALK-TKIs will be offered as a treatment option, and in due course are likely to replace crizotinib as an internationally recognised standard of care.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, see above
• Does the use of the technology address any particular unmet need of the patient population?	Yes the 2nd generation ALK TKIs offer a more effective treatment option than those currently available.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of ceritinib are similar to other tyrosine Kinase inhibitors routinely managed in specialist lung oncology clinics.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Survival and quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TA406, TA181, TA190, TA402]	
21. How do data on real-world experience compare with the trial data?	Experience in the second line setting indicate a toxicity / effect profile as reported in the first line studies. Not aware of any 'real world' outcome data reported for first line treatment.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Innovative 2nd generation Alk tyrosine kinase inhibitor
- Trial data to support activity in the first line treatment setting.
- Outcomes would be equivalent / superior to current standards of care (crizotinib or cytotoxic chemotherapy)
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission on the NICE appraisal of 1st line ceritinib in the treatment of locally advanced/metastatic ALK mutation positive non small cell lung cancer

This statement contains information that is academic-in-confidence and commercial-in-confidence (underlined and highlighted in yellow/blue)

1. The correct comparator for ceritinib is crizotinib as 1st line treatment of ALK positive NSCLC. If NICE recommends ceritinib as 1st line use, then the use of crizotinib in the treatment of ALK pos NSCLC will cease (unless patients cannot tolerate ceritinib).
2. NHS England observes that the median duration of follow-up in the ceritinib phase III trial is 19.7 mo, not much longer than the median progression free survival (PFS) of 16.6 mo in the ceritinib arm. Follow-up is therefore still short and results immature from the point of assessing longer term outcomes.
3. NHS England notes that the matched indirect comparison delivers a PFS of [redacted] mo for ceritinib vs [redacted] mo for crizotinib after weighting, as opposed to the crude individual phase III trial figures of 16.6 and 10.9 months, respectively. NHS England would wish for reassurance from the ERG and the Technology Appraisal Committee that the matching and weighting in this indirect comparison were appropriate given that the control (chemotherapy) arms in these 2 phase III trials were similar (8 and 7 months, respectively).
4. NHS England notes the sensitivity of the ICER to the hazard ratio for overall survival which in turn is based on the indirect comparison involving arms of 2 trials with modest follow-up durations and which incorporated cross over in design. The uncertainty of this hazard ratio has to therefore be regarded as being substantial.
5. NHS England notes that the drug administration cost per cycle assumed for ceritinib/crizotinib by the company was £14. These drugs are high cost chemotherapy drugs and thus the oral chemotherapy administration tariff should be used. The ERG used the 2015/16 figure of £181. This is incorrect in 2017/18 and should be £120.
6. As reported follow-up is relatively short in both ceritinib and crizotinib 1st line trials, modest percentages of patients went on to 2nd line therapies. This is unlikely in clinical practice in NHS England. Though brain metastases are common in ALK pos NSCLC and thus this type of secondary spread does reduce numbers of patients proceeding to further treatments, patients with ALK pos NSCLC are closely monitored whilst on ceritinib/crizotinib and thus the majority will proceed to further active systemic therapy. The figure of 60% used in one of the scenario analyses is likely to be a little conservative.

[redacted]

[redacted]

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

October 2017

NICE National Institute for Health and Care Excellence

Clinical expert statement

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Matthew Hatton**
2. Name of organisation	**Weston Park Hospital**

3. Job title or position	**Consultant and Honorary Professor in Clinical Oncology**
4. Are you (please tick all that apply):	an employee or representative of a healthcare professional organisation that represents clinicians a specialist in the treatment of people with this condition
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	yes, I agree with it
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes In addition I have been asked to address the following questions - 1. Are NSCLC tumours routinely tested for the ALK mutation in current NHS practice? ALK mutation status is routinely in NSCLC patients with non-squamous histology only. 2. Different methods for the determination of ALK status were specified in the trials of ceritinib (Ventana immunohistochemistry test) and crizotinib (Vysis ALK Break Apart FISH Probe Kit [Abbott Molecular]).

a. Which of these 2 tests for ALK status is used routinely or most commonly in the NHS? Or are other tests more common?

This question is really outside my area of clinical expertise, I know that in North Trent the Vysis probe kit is used. I suspect this may be true nationally as testing became widespread when crizotinib was NICE approved but I have no personal experience to back that suspicion up.

b. Do the different testing methods differ in diagnostic accuracy?

This is not my area of expertise

c. We understand that the majority of people with ALK-positive advanced NSCLC in England receive crizotinib first-line.

Following NICE approval for first line treatment crizotinib has being increasingly used and I think that will be captured by the national SCAT (systemic anti-cancer therapy) chemotherapy database.

d. Are there any circumstances in which people would receive first-line pemetrexed-based therapy instead of crizotinib (or ceritinib)?

Yes there can be a delay in getting the ALK testing results and a decision may be taken to start treatment in symptomatic patients before the ALK mutation status is known. These patients would receive a platinum / pemetrexed doublet.

3. The Summary of Product Characteristics for ceritinib advises that treatment should continue "*as long as clinical benefit is observed*". That is, treatment could continue beyond disease progression (as per the clinical trial protocol).
   a. How is clinical benefit defined in clinical practice?

I think this would refer to situation where symptomatic improvement is maintained despite progression on imaging and may cover a slight worsening of disease that doesn't meet the RECIST criteria definitions for progression. I believe that those meeting RECIST criteria for progression would be offered alternative treatment rather than continue beyond progression and if there are any patients who do

	continue this would very short term as worsening symptoms are likely to occur within weeks of a RECIST documented progression. b. When would it be clinically appropriate to stop treatment with ceritinib? How would the decision to stop treatment be made? The scenarios would be progressive disease (RECIST criteria), significant toxicity (side effects) and deteriorating patient fitness (performance status). 4. The Summary of Product Characteristics for ceritinib does not limit its use to non-squamous ALK-positive NSCLC, although it states that "there is limited information for ceritinib in ALK-positive tumours with non-adenocarcinoma histology" (96.5% of patients in the pivotal trial had adenocarcinoma). Do you expect ceritinib to be used in people with ALK-positive non-adenocarcinoma histology? Squamous cell NSCLC patients will not be routinely tested for the ALK mutation so I do not think ceritinib will be in this category. However, there other histology groups (large cell neuroendocrine, NSCLC NOS) who will be have their ALK status routinely checked and may be positive. As the mutation will be a driver of the disease I think it would be reasonable to consider targeted treatments in this scenario. 5. Could 2nd line crizotinib be used after failure of 1st line ceritinib? I am not aware of any trials testing this approach or evidence / rationale that this might be an effective strategy.
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve	The treatment is not curative but aims to control advanced ALK + ve NSCLC extend life and by improving symptoms improve quality of life.

mobility, to cure the condition, or prevent progression or disability.)	
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in progression free survival of > 3 months with an associated improvement in quality of life.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, patients with advance NSCLC have a very poor prognosis and more effective systemic treatment are badly needed.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Locally advanced / metastatic non-small cell lung cancer (NSCLC) has a number of NICE approved systemic treatment options for patients. In general these options are of limited effectiveness which will mean there is variation of practice across the UK particular as this area was not reviewed in the updated Management of Lung Cancer guideline 2011. Treatment is delivered by Oncologists in Teaching and District General Hospitals is increasing based on the molecular genotype using drugs that target specific mutational abnormalities (EGFR, ALK). When these mutations are present 'targeted' systemic drugs form the backbone of treatment strategies, however, most patients are "negative" for these

	mutations and are considered systemic chemotherapy, immunotherapy or best supportive care. The choice of treatment will primarily be dictated by patient fitness (performance status PS).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Management of Lung Cancer guideline 2011. The anaplastic lymphoma kinase (ALK) re-arrangement occurs in approximately 3 – 7% of patients with NSCLC and there is good clinical data that has shown that targeted therapy with ALK tyrosine kinase inhibitors (ALK-TKI) is effective. Recent NICE assessment of crizotinib (TA422) and ceritinib (TA395) have concluded they offer a cost effective treatment on progression following first line system treatment. In addition NICE has reviewed crizotinib as first line treatment (TA406) and supported its use for patients the ALK rearrangement in that setting. Therefore, these ALK-TKIs are established as a standard of care in the UK for patients fit enough to receive them. Ceritinib has very recently received an EMA license for the first line treatment of ALK mutation positive NSCLC which means there no current guidelines in place within the EU recommending the place of ceritinib used within those licensed indication
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, ALK mutation testing at diagnosis is now a routine part of clinical practice in England and the majority those patients who test positive would receive first line treatment with crizotinib. The alternative option would be cisplatin-pemetrexed chemotherapy (the ALK mutation is only seen in the non-squamous population). When relapse occurs these patients would be considered for second line systemic treatment with crizotinib if not used in the first line setting or ceritinib if progression has occurred on crizotinib. Chemotherapy would

	again be the alternative, platinum based or docetaxel / nintendinib if the patients had received platinum chemotherapy previously. In both the first and second line setting entry into clinical trials may be considered or in patients with poor performance status best supportive care, which may include radiotherapy.
• What impact would the technology have on the current pathway of care?	Ceritinib is a second generation ALK-TKI and clinical trial data indicates that this class of drug is an innovative and effective systemic treatment option for patients with the ALK mutation. Internationally it is expected that the 2nd generation ALK-TKIs will be offered as a treatment option, and in due course are likely to replace crizotinib as an internationally recognised standard of care.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Ceritinib is an oral medication taken once daily that would be taken until disease progression. Treatment would be supervised though the specialist lung cancer oncology clinics / chemotherapy units that are operating across the UK. It is likely that ceritinib would be used in place of crizotinib or cisplatin / pemetrexed chemotherapy
• How does healthcare resource use differ between the technology and current care?	Ceritinib would require the same healthcare resources as crizotinib so there would be difference in delivery of this technology and current care would be nminimal.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care through the established Lung Oncology clinics in teaching and general hospitals.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities and equipment are in place through the established lung oncology clinics to deliver this treatment. A little training will be required to familiarise staff to the differences that might be present in the side effect profiles etc when compared to the other targeted drugs in current use.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The clinical trials of ceritinib in the ALK mutation positive NSCLC population are consistent with our current standard NHS practice and the complexity of treatment delivery will be similar to the current standard chemotherapy treatments. Those trails report improvements in response and survival for ceritinib when compared to standard platinum / pemetrexed treatment (with pemetrexed maintenance) and there were associated improvements in quality of life. The side effect profile is different to standard chemotherapy treatment, generally gastro-intestinal, and did require dose interruptions or modifications in the majority of patients. Therefore, some (relatively minor) modifications will be required for treatment assessment and follow up with a training requirement so that staff becomes familiar with the management of the side effect profile. This is currently occurring as other drugs in this class have been introduced into clinical practice.
	Oral home administration of ceritinib will not exacerbate the capacity pressures on oncology day-units though as the drug is given until time of progression, significant toxicity, or clinician/patient decision there will be pressures on chemotherapy outpatient clinics.
• Do you expect the technology to increase length of life more than current care?	Yes, there is no current data from studies comparing crizotinib and ceritinib directly as first line systemic treatment. Adjusted comparisons have been performed that suggest outcomes comparable to crizotinib and for other second generation ALK TKI inhibitors there are phase III study results showing superior outcomes to crizotinib
• Do you expect the technology to increase health-related quality of	Trial data reports improved quality of life compared with chemotherapy, this data and personal experience suggest similar side effect profile and quality of life when compared to crizotinib.

life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Within the population limited to ALK + ve NSCLC there are no identified subgroups for whom the treatment appears less effective.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	No practical implications, ceritinib requires the same clinical facilities / set up as crizotinib to deliver which is one of the current standards of care.

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	ALK mutation testing as indicated above.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Ceritinib is a second generation ALK-TKI and clinical trial data indicates that this class of drug is an innovative and effective systemic treatment option for patients with the ALK mutation. Internationally it is expected that the 2nd generation ALK-TKIs will be offered as a treatment option, and in due course are likely to replace crizotinib as an internationally recognised standard of care.

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, see above
• Does the use of the technology address any particular unmet need of the patient population?	Yes the 2nd generation ALK TKIs offer a more effective treatment option than those currently available.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of ceritinib are similar to other tyrosine kinase inhibitors routinely managed in specialist lung oncology clinics.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Survival and quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TA406, TA181, TA190, TA402]	
22. How do data on real-world experience compare with the trial data?	Experience in the second line setting indicate a toxicity / effect profile as reported in the first line studies. Not aware of any 'real world' outcome data reported for first line treatment.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Innovative 2nd generation Alk tyrosine kinase inhibitor
- Trial data to support activity in the first line treatment setting.
- Outcomes would be equivalent / superior to current standards of care (crizotinib or cytotoxic chemotherapy)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Yvonne Summers**

2. Name of organisation	**The Christie and University Hospital South Manchester** Clinical expert
3. Job title or position	**Consultant Medical Oncologist (Lung Cancer)**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? **x**☐ other (please specify): on this occasion I am not representing BTOG/RCP/RCR/NCRI but have been asked to participate as a clinical expert involved in trials in this area
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not	☐ yes

have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• shrink cancer • prevent progression of disease • help symptoms related to condition • maintain quality of life • improve survival.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in symptoms accompanied by objective response or disease stablisation is clinically meaningful, as is a delay in developing disease progression or worsening symptoms. Clinical benefit can also also seen in patients who do not meet response by RECIST criteria (ie reduction in target lesion measurements of >30%). There is no absolute tumour measurement which can adequately define this.

<table>
<tr><td>9. In your view, is there an unmet need for patients and healthcare professionals in this condition?</td><td>This is a rare subtype of lung cancer (approximately 3% of non-squamous NSCLC).
Although new treatments mean that outcomes are improving, recent UK audit data (Smith M, Yip K, Doherty G et al 2016 NCRI conference abstracts) demonstrate that median OS for ALK positive patients remains poor at 27 months. Retrospective data demonstrates that patients receiving ALK TKI therapy live longer than those who don’t (Shaw A, Yeap BY, Solomon B, et al Lancet Oncology 2011; doi.org/10.1016/s1470-2045(11)70232-7).
More effective therapies are needed.</td></tr>
<tr><td colspan="2">What is the expected place of the technology in current practice?</td></tr>
<tr><td>10. How is the condition currently treated in the NHS?</td><td>Treatment setting is oncology outpatient clinic. This relatively rare group of patients are treated within the context of clinical trials where possible.
First line therapy is with Crizotinib. Rarely patients may receive chemotherapy first line if the ALK gene rearrangement has not been identified (eg insufficient biopsy material)
Second line treatment is with Ceritinib (TA395), or crizotinib if not received first line or a clinical trial
Third line treatment is with platinum pemetrexed chemotherapy or a clinical trial or pembrolizumab
Forth line treatment is a clinical trial or docetaxel +/- nintedanib chemotherapy or a trial or pembrolizumab
Although PD-1 and PD-L1 inhibitors can be used in this setting the data is poor in comparison to chemotherapy. ASCO guidelines state “cannot recommend for or against immune checkpoint inhibitors vs single agent chemotherapy”</td></tr>
<tr><td>• Are any clinical guidelines used in the treatment of the condition, and if so, which?</td><td>Yes ESMO (updated Sept 2016), NCCN (updated July 2017), ASCO (updated Aug 2017)
<table>
<tr><td>Guideline</td><td>1st line</td><td>2nd line</td><td>3rd line</td></tr>
<tr><td>ESMO</td><td>Crizotinib</td><td>Ceritinib, Alectinib</td><td>Chemo/immunotherapy</td></tr>
<tr><td>ASCO</td><td>Crizotinib</td><td>Ceritinib
No recommendations</td><td>Chemo +/- ramicirumab
No recommendations about other ALK TKIs yet</td></tr>
</table></td></tr>
</table>

			about other ALK TKIs yet Platinum doublet chemo +/- bevacizumab		
	NCCN	Alectinib (preferred) Crizotinib Ceritinib Chemo if ALK not known	Consider local ablative therapy and continuing current TKI. Ceritinib Alectinib or Brigatinib	Refer back to standard NSCLC guide lines ie chemo/trials/immunotherapy	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Clinical opinion is consistent: ALK positive patients are best treated with an ALK TKI which is more effective in terms of improved response rates, PFS and OS, than chemotherapy (Profile 1014 of crizotinib vs chemotherapy was updated at ESMO 2017 with 46 months follow up and median OS was not reached in the crizotinib arm and 47.5 months in the chemotherapy arm, HR 0.76, p=0.0978, 4 year OS was 56.6% and 49.1%)				
• What impact would the technology have on the current pathway of care?	Crizotinib would be replaced by ceritinib in the first line setting. The second line treatment would change to chemotherapy (or other 2nd third generation ALK TKI's through trials)				
11. Will the technology be used (or is it already used) in	It would be used in the same way (oral therapy managed through out-patient clinics) and would replace crizotinib				

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	No significant change, both are oral therapies managed in out-patient clinic setting. Similar blood and radiology monitoring is required.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist lung oncology clinics (secondary and tertiary care).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Expertise already exists in managing TKIs. Experience with Ceritinib already exists in the 2nd line setting. No impact on chemotherapy suites.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. PFS for Ceritinib is 16.6 months from Ascend 4 whereas PFS for crizotinib from Profile 1014 is 10.9 months. Data from Ascend 4 is not mature enough to comment on OS.
• Do you expect the technology to increase	PFS will be longer, however overall survival is complex and is affected by subsequent therapies. As newer 3rd generation ALK TKI's become available to patients through trials, patient access schemes and NHS

length of life more than current care?	commissioning, survival will improve further. We will need to demonstrate these changes in survival by participating in repeat audits. Anecdotally, I have already seen these improvements in clinical practice: when I first started identifying ALK patients in my practice, the average survival time was 18-24months, now my current cohort or patients has a survival of >2years despite at least 50% having brain metastases.
• Do you expect the technology to increase health-related quality of life more than current care?	There are 2 aspects to consider: 1. The improved PFS compared to chemotherapy and crizotinib brings with it, increased duration of time with a lesser burden of disease related symptoms (less fatigue, pain, dyspnoea,cough and appetite loss) 2. The different toxicity profile compared to chemotherapy and crizotinib. a. Compared to chemotherapy there is less neutropaenia, anaemia and constipation, but more diarrhoea, nausea and vomiting and elevated transaminases. However only 5% or patients need to discontinue therapy with Ceritinib. b. Indirect comparisons with crizotinib suggest less oedema, visual disturbance and constipation, similar reduced appetite and abdominal pain and more diarrhoea, nausea, vomiting and elevated transaminases. The toxicity can be managed as an outpatient with dose reductions and supportive medication.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Poor PS (3-4) patients were not included in the trials and so data for this population is scarce. Brain metastases are common in this group on patients and a poor prognostic factor. In the ASCEND-4 study 32% of patients had brain metastases, and most patients with baseline brain metastases did not receive previous brain radiotherapy (59%). In this group of patients the PFS was 10.7 vs 6.7 months (hazard ratio 0.70). The incidence of patients with brain metastases was 23% in Profile 1014 (HR 0.57)
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)

The technology is an oral therapy similar to the current standard of care (Crizotinib).

QoL in Ascend 4 demonstrates improvement in all functional domains and symptom domains compared to chemotherapy except with regard to diarrhoea and nausea and vomiting.

Reviewing the adverse event reporting from ASCEND 4 and PROFILE 1014, there is a higher incidence of the following AE's, which is manageable:

AE	Profile 1014		Ascend 4	
	All grades	Grade 3-4	All grades	Grade 3-4
Diarrhoea	61%	2%	85%	5%
Vomiting	46%	2%	66%	5%
Elevated transaminases	36%	14%	60%	31%
Nausea	56%	1%	69%	3%

15. Will any rules (informal or formal) be used to start or stop treatment with the technology?

Treatment will be stopped on clinically significant PD, intolerable toxicity or patient choice.

No time cut off or additional testing applies.

Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Current QoL tools are poor at assessing symptom burden related to CNS disease.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Ceritinib is a more effective 2nd generation ALK TKI. It will delay progression of disease and increase time to progression of symptoms and deterioration in QoL

• Is the technology a 'step-change' in the management of the condition?	Crizotinib was a step change in the treatment of ALK positive NSCLC, in that it was a move away from chemotherapy to a better tolerated more effective treatment. Ceritinib is a further improvement on this path.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, outcomes remain very poor for this population of lung cancer patients, who are younger and fitter than the average NSCLC patient. Oral TKI therapy often allows patients to continue working or looking after their families.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ceritinib is generally better tolerated than chemotherapy. QoL assessment in patients from ASCEND 4 demonstrated improved symptom domains compared to chemotherapy in all areas except diarrhoea and nausea and vomiting. Unsurprisingly chemotherapy caused more anaemia and neutropaenia. Most adverse events can be managed with supportive medication and dose modification and overall only 5% of patients stopped Ceritinib due to adverse events.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The ideal study would have been a head to head of crizotinib vs ceritinib, but this is not planned and research has moved onto 3rd generation TKIs. The ALK studies have recruited patients in the UK and did reflect clinical practice at the time in which they were recruiting.

• If not, how could the results be extrapolated to the UK setting?	Although it is not advisable to compare studies, cross trial comparisons can be made between ASCEND 4 and PROFILE 1014 (Crizotinib vs Chemo)
• What, in your view, are the most important outcomes, and were they measured in the trials?	As crossover is a confounding factor, OS is less reliable than previously in NSCLC trials and PFS is therefore an important outcome. Response rate also has clinical relevance for this group of patients as they tend to respond quickly, and symptom improvement usually correlates with response. QoL measures are important, although the currently used questionnaires are not as discriminatory as one would like, particularly with regard to CNS disease.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Very large differences in PFS may still translate to OS, however much of this is driven by differences in subsequent therapy. Long term OS from PROFILE 1014 after 46 months follow up was presented at ESMO 2017 (LBA50 T Mok et al) demonstrating a non-statistically significant improvement for crizotinib compared to chemotherapy (HR 0.760; CI 0.548-1.053). Patients who did not receive an ALK TKI had the worst survival of all compared to those who receive another ALK TKI having the longest survival.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA406, TA181, TA190, TA402]	As detailed above Mok T et al, LBA50 ESMO 2017
22. How do data on real-world experience compare with the trial data?	UK audit data reported in 2017 on 99 patients treated with crizotinib between Jan 2013 and Aug 2017, demonstrated shorter PFS and OS than trial data (9.76 and 13.5 months respectively), however, outcomes were measured from start of crizotinib treatment, most patients received crizotinib post chemotherapy and <20% patients received a 2nd or 3rd generation ALK TKI (Yip K, et al, Lung Cancer doi.org/10.1016/s0169-5002(17)30112-5.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None identified

23b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Ceritinib improves PFS from 8.1 months to 16.6 months compared to chemotherapy in previously untreated ALK positive NSCLC patients
- Ceritinib improves RR from 58% to 70% compared to chemotherapy in previously untreated ALK positive NSCLC patients
- Ceritinib is a well tolerated oral therapy which demonstrates improvement in all functional domains of QoL assessment and the majority of symptom domains compared to chemotherapy.
- There is no head to head study of the current UK standard 1st line therapy, Crizotinib, however PFS for Ceritinib in ASCEND 4 was 16.6 months and PFS in PROFILE 1014 was 10.9 months

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Single Technology Appraisal:

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

Dear Dr Summers,

Further to the attached email, we look forward to receiving your expert statement by 11 September 2017. In addition, the technical team have some specific questions relevant to this appraisal. We would be grateful to receive a response to these at the same time:

1. Are NSCLC tumours routinely tested for the ALK mutation in current NHS practice?
    a. Are all tumours routinely tested, or only those with non-squamous histology?

All non-squamous are tested and squamous may be tested in particular rare clinical scenarios eg never smokers

2. Different methods for the determination of ALK status were specified in the trials of ceritinib (Ventana immunohistochemistry test) and crizotinib (Vysis ALK Break Apart FISH Probe Kit [Abbott Molecular]).
    a. Which of these 2 tests for ALK status is used routinely or most commonly in the NHS? Or are other tests more common? Previously FISH was most commonly used but practice has changed and most centres now use IHC. IHC is cheaper and less pathologist intensive than FISH.
    b. Do the different testing methods differ in diagnostic accuracy? Results are fairly concordant We understand that the majority of people with ALK-positive advanced NSCLC in England receive crizotinib first-line. Are there any circumstances in which people would receive first-line pemetrexed-based therapy instead of crizotinib (or ceritinib)? There may still be a small number of patients where chemo is started as 1st line therapy due to insufficient tissue for testing and concern that repeat biopsy may introduce delays, but most patients will receive 1st line TKI (or a suitable clinical trial)

3. The Summary of Product Characteristics for ceritinib advises that treatment should continue "*as long as clinical benefit is observed*". That is, treatment could continue beyond disease progression (as per the clinical trial protocol).
    a. How is clinical benefit defined in clinical practice? Patients often have an excellent response to ALK TKI therapy with substantial tumour shrinkage and little residual disease by recist criteria. In this setting, very minor tumour growth may be classed as PD by recist (eg a tumour which started off at 130mm could reduce easily to 10mm and an increase of 20% ie. Up to 12mm would then constitute PD) but this may not be clinically meaningful. Another example is that a new lesion could develop when the rest of the disease remains in response and so the new lesion may be treated with a local ablative therapy and the TKI, which is controlling the rest of the disease, is continued. Patients need to have significant radiological progression or clinical symptoms of progression to change therapy. There is no strict definition of this.
    b. When would it be clinically appropriate to stop treatment with ceritinib? How would the decision to stop treatment be made? See answer above - it depends on the clinical scenario how long treatment continues beyond strict recist criteria PD. If there has been a single area of disease which is treated with ablative therapy, it may be 6-12 months before further progression occurs necessitating a treatment change. If it is more general progression then may only be a couple of cycles. The other factor that influences this decision is available further ALK TKI

therapy: if there is access to another effective treatment through a clinical trial or an expanded access programme, the patient may change sooner (there is commonly a reluctance from these patients to start chemotherapy).

4. The Summary of Product Characteristics for ceritinib does not limit its use to non-squamous ALK-positive NSCLC, although it states that "there is limited information for ceritinib in ALK-positive tumours with non-adenocarcinoma histology" (96.5% of patients in the pivotal trial had adenocarcinoma). Do you expect ceritinib to be used in people with ALK-positive non-adenocarcinoma histology? Only very rarely – if we have a never smoking squamous patient we would test for ALK. There may be tumour heterogeneity, or mixed histology with the biopsy only representing one small area of disease, so a squamous biopsy may not represent the histology of the whole tumour, but we know that even when there is histological heterogeneity, these molecular aberrations are driver mutations and present throughout the tumour and so are detectable. The other possibility is that there may be misreporting of the histology and on expert pathology review a squamous cancer may be revised to non-squamous. These are all very occasional scenarios.

5. Could 2nd line crizotinib be used after failure of 1st line ceritinib? There are case reports of response to crizotinib after ceritinib due to development of certain resistance mutations, but there are other more effective 3rd generation ALK TKIs in development which are more effective in this arena (Lorlatinib, Brigatinib, Alectinib)

Thank you again for agreeing to be an expert for this appraisal, and we look forward to hearing from you in due course.

Kind regards,

Kate Moore

Technology Appraisals Project Manager - Committee D

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Evidence Review Group's Report
Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer

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None.

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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.

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Contributions of authors

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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

Copyright statement

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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

BIRC: Blinded independent review committee

BSA: Body Surface Area

BSC: Best Supportive Care

CDF : Cancer Drug Fund

CRD : Centre for Research and Dissemination

CS: Company's Submission

CSR: Clinical Study Report

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

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

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

NSCLC: Non-Small-Cell Lung Cancer

ORR: Objective Response rate

OS: Overall Survival

PAS: Patient Access Scheme

PD: Progressed Disease

PF: Progression Free

PFC: Points for clarification

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

SOD: Sum of diameters

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

The relevant health problem in the present appraisal is anaplastic lymphoma kinase (ALK)-positive (+) advanced non-small-cell lung cancer (NSCLC).

1.1 Critique of the decision problem in the company's submission

The population specified in the final NICE scope was, 'people with untreated, anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer'. This is the population specified in the submission's decision problem and the population included in the one relevant Phase III, randomised controlled trial (RCT) of ceritinib (ASCEND-4). This is also the population included in the RCT of crizotinib, used for the indirect comparison with ceritinib.

The intervention in the company submission (CS), and in the final NICE scope, is ceritinib (Zykadia®). Marketing authorisation for ceritinib as a first-line treatment for adult patients with ALK+ advanced NSCLC was received on 26 June 2017. In addition, ceritinib had already received marketing authorisation, on 6 May 2015, as a second-line treatment for adult patients with ALK+ advanced NSCLC previously treated with crizotinib. The licensed recommended and maximum dose of ceritinib is 750 mg, taken orally, once a day.

The comparators specified in the final NICE scope were crizotinib and pemetrexed, in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only), with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only). In the CS, only crizotinib is included as a comparator, which the ERG agrees with as crizotinib is the current standard of care and all eligible patients, who are well enough to tolerate treatment, are treated with crizotinib. Crizotinib is a first-generation ALK inhibitor and is administered orally at a dose of 250 mg twice daily.

The outcomes listed in the NICE final scope were: overall survival; progression-free survival; response rate; adverse effects of treatment; and health-related quality of life. These are all included in the CS. In addition, duration of response (DOR), disease control rate (DCR), and time to response (TTR) are included in the CS. Overall survival, progression-free survival, adverse effects of treatment and health-related quality of life were used to inform the economic analysis. As the submission makes a case for specific beneficial effects, in terms of brain metastases, additional intracranial outcomes are reported, but these are not included in the decision model.

The submission includes a Patient Access Scheme comprising a simple discount of [redacted]. Consideration of a confidential PAS for crizotinib is included in a confidential appendix.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review of relevant trials. Evidence for the clinical effectiveness of ceritinib was from ASCEND-4, a Phase III company-sponsored trial. ASCEND-4 was an international, multicentre, open-label RCT comparing ceritinib with pemetrexed/cisplatin plus pemetrexed maintenance therapy. The study included patients with advanced or metastatic non-squamous ALK+ NSCLC, untreated with systemic therapy (with the exception of adjuvant or neoadjuvant therapy, if relapse had occurred at least 12 months after the end of therapy). If present, brain metastases were required to be asymptomatic or neurologically stable (including not having required increasing doses of steroids, within the two weeks prior to screening, to manage central nervous system symptoms).

Patients were randomised to receive ceritinib 750 mg, administered orally, once daily (and continuously) in a fasted state, or chemotherapy (CT). CT was pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or (based on the investigator's choice) carboplatin (AUC 5–6), administered every 21 days. Patients who completed four cycles of CT (induction), without progressive disease, subsequently received pemetrexed as single-agent maintenance every 21 days. Patients in the CT group, in the treatment and post-treatment follow-up phases, were allowed to cross over to ceritinib after centrally (blinded independent review committee confirmed – BIRC), RECIST-defined progressive disease.

The primary outcome was median progression-free survival (PFS), defined as the time from the date of randomisation to the date of the first radiologically documented disease progression by central review, or death due to any cause. RECIST 1.1 criteria were used to assess response.

The key secondary objective was overall survival (OS), defined as the time from date of randomisation to date of death due to any cause.

The results found that ceritinib prolonged PFS compared with CT in all patients: median PFS was 16.6 (95% CI 12.6–27.2) months on ceritinib compared with 8.1 (95% CI 5.8–11.1) on pemetrexed/cisplatin (CT); HR 0·55 (95% CI 0.42–0.73). The treatment benefit in patients with brain metastases at baseline was numerically smaller that in those without (HR 0.80 compared with 0.45). At the time of the analysis (24 June 2016), the OS data were immature; Median OS was 'not reached' in the ceritinib group and was estimated as 26.2 months in the CT group (HR, 0.73; p=0.056). A sensitivity analysis that adjusted for crossover of CT patients to ceritinib after disease progression had little impact on the result (HR 0.73; 95% CI, 0.49–1.10), probably due to the limited follow-up data.

The results, both from central and local assessment, favoured ceritinib in terms of tumour response, time to first response and duration of response. The results for intracranial tumour responses in patients with measurable brain metastases at baseline indicated that the intracranial tumour responses to ceritinib and to CT were similar to the whole-body responses. Intracranial outcomes were not assessed in patients without BM at baseline, therefore, the impact of ceritinib in preventing the development of new BM has not been assessed in the CS.

Time to definitive symptom deterioration was assessed using both the LCSS and QLQ-LC13 questionnaires, and the results for both tools demonstrated a statistically significant difference in favour of ceritinib.

In ASCEND-4 the median duration of ceritinib exposure was 66.4 weeks (IQR 30.0 to 83.7). The median relative dose intensity was 78.4% (IQR 63.2 to 97.5), with a mean dose of 626.0 mg (SD 124.8). Adverse events were common on ceritinib in the ASCEND-4 trial though most could be managed with dose adjustment. Dose adjustment was common: 68% of ceritinib patients required at least one dose reduction and 78% required at least one dose interruption. This level of dose adjustment is higher than that seen with for crizotinib in the same indication (the ALEX trial see below): dose reduction 25%; 19% dose interruption; and dose intensity was 92.4%.

Comparison of ceritinib with crizotinib

In the CS the evidence for crizotinib was derived from the PROFILE 1014 trial. PROFILE 1014 was an open-label RCT of crizotinib, compared with pemetrexed/cisplatin chemotherapy, in previously untreated advanced or metastatic ALK+ NSCLC. The design and population of PROFILE 1014 was similar to that of ASCEND-4, though there were some differences between the trials. The most important difference was the difference in the comparator: maintenance pemetrexed was included in the chemotherapy treatment protocol for ASCEND-4 but not in PROFILE 1014. Maintenance pemetrexed has been shown to improve survival among patients with advanced NSCLC who have not progressed during pemetrexed-cisplatin induction therapy.

The ERG identified an additional relevant trial of crizotinib: the ALEX trial, which compared crizotinib with alectinib (a third ALK-inhibitor) as first-line treatment in ALK+ advanced NSCLC. This trial provides published, directly relevant data on crizotinib. The characteristics of this trial and those of the ASCEND-4 and PROFILE 1010 are very similar. The ERG concluded that three trials, ASCEND-4, PROFILE-4 and ALEX, are directly relevant for an indirect comparison of ceritinib with crizotinib in the present assessment. However, as neither of the crizotinib trials use the same comparator as the ASCEND-4, these three trials cannot be combined in an indirect analysis through a common comparator.

The CS therefore presented a Matching-Adusted Indirect Comparison (MAIC) of ceritinib and crizotinib using only the ALK inhibitor arm of ASCEND-4 and PROFILE 1040 (MAIC 1). After a request from the ERG, the company then presented a second MAIC using only the ALK inhibitor arm of ASCEND-4 and ALEX (MAIC 2). These comparisons suggest that ceritinib may be more effective in prolonging PFS than crizotinib: without matching, the indirect comparison using the different sources of crizotinib generates a HR of [redacted]. With matching the first MAIC generates a (unreasonably) high median PFS on ceritinib and an improved HR of [redacted]. The second MAIC analysis generates similar values for median PFS and a slightly increased HR of [redacted]. The two matched HRs for OS were similar ([redacted] and [redacted]) and lower than the unmatched estimate of [redacted].

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

ASCEND-4 was a good quality trial but for the assessment of OS a major limitation of the trial design was that patients were allowed to remain on therapy despite disease progression and to switch from CT to ceritinib. This resulted in confounding of the OS outcome.

Follow-up was also too short for definitive assessment of OS.

Compared to a real world cohort (UK and Europe), the patients in all the relevant trials are slightly younger, have a higher proportion of females and a lower proportion of former of current smokers and, as might be expected in a trail, a higher proportion of trial patients are ECOG status 0 or 1. The clinical adviser to the ERG commented that, except that a higher proportion of men might be expected in clinical practice, the trial population can be considered generalisable to NHS practice.

Intracranial outcomes were not assessed in patients without BM at baseline, therefore the impact of ceritinib in preventing the development of new BMs has not been assessed in the CS.

As no relevant direct head-to-head trials of ceritinib and crizotinib have been conducted, an indirect comparison was appropriate. Unfortunately, because the comparator arms in the available trials differed too much to be used as a common comparator it was not possible to perform an 'anchor-based' analysis of first-line ceritinib and crizotinib. The ERG, therefore, agrees that an indirect comparison using only the ALK inhibitor arm of the identified trials is the only option available. This does not mean that the method is not subject to significant limitations, and that the results of such an analysis could be anything other than highly uncertain. In addition, the ERG believes that the ALEX trial should also have been included in the analysis. The ERG notes the following specific limitations of the MAIC analysis.

- The MAIC method was developed as an improvement on standard indirect comparison methods, which use aggregate data only; it was not developed as a method to be used without a common comparator arm.
- The comparisons with ceritinib are still observational and subject to a high risk of bias: despite the matching, the analysis can still be subject to the effects of residual confounding due to unobserved differences between the trials.
- In the present context the method is being applied in the absence of a common comparator so there is nothing to use as a measure of the success of the matching to reduce confounding.
- The matching process reduces the amount of data (the sample size of the ceritinib arm) so precision is reduced.
- The ERG also noted that in MAIC analysis presented in the CS the whole ASCEND-4 population was matched to the whole PROFILE 1014 population. The ERG believes this is inappropriate given that only the ceritinib and crizotinib arms were being compared in the analysis. Furthermore in the MAIC using the ALEX data, only the ceritinib and crizotinib arms were matched.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic submission included a systematic review of published evidence on the cost-effectiveness and health-related quality of life associated with ceritinib in the first-line treatment on NSCLC patients. No review of resource use and costs was undertaken. The review identified one study relevant to the current submission, which was a previously undertaken technology appraisal for crizotinib, in a first-line indication (TA 406).

The cost-effectiveness of ceritinib was informed by a *de novo* economic evaluation conducted by the company. The company's model used a partition survival model approach or "area under the curve" analysis. The model structure comprised of three mutually exclusive health states: (i) pre-progression, (ii) progressed disease, and (iii) death, which is an absorbing state. The proportion of patients in each state, along with the efficacy data, treatment and comparator dosage and duration of first-line therapy was determined by the ASCEND-4 trial for ceritinib and the PROFILE 1014 trial for crizotinib. The comparison between ASCEND-4 ceritinib patients and PROFILE 1014 crizotinib patients was based on the results of the MAIC analysis. In response to clarification questions, a number of adjustments and additional analyses were undertaken within the MAIC analysis, to assess the uncertainty within that analysis. The remaining inputs were informed by studies identified in previous economic evaluations.

The company's base case model found ceritinib to be more costly (cost difference of £14,985) and more effective (0.54 QALY gain) compared with crizotinib. The deterministic ICER (without PAS) was £27,936 per QALY. When the PAS for ceritinib is included, ceritinib dominates crizotinib, that is, it is less costly and more effective. The mean probabilistic ICER (without PAS) was £29,239 per QALY. The predicted probability that ceritinib was cost-effective compared with crizotinib, using a threshold of £20,000, £30,000 and £50,000 per QALY was 26.2%, 53.6% and 71% respectively. It is important to note that neither of these results include the PAS which is in place for crizotinib. Results with the PAS for crizotinib are presented in a supplementary confidential appendix to this report.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG presented a number of concerns in its critique of the company's model, which included: the uncertainty incorporated into the model due to the MAIC analysis; the selection of second-line therapies; the choice of survival curve for OS; the estimation of time on first-line treatment; the utility values in the post-progression health state; and, treatment administration costs.

OS and PFS based on MAIC analysis

The results of the MAIC analysis to compare the ceritinib population of ASCEND-4 with the crizotinib population of PROFILE 1014 are highly uncertain, and potentially subject to confounding bias. This uncertainty has significant consequences in terms of accurately determining the cost-effectiveness of ceritinib, as the model is very sensitive to the magnitude of the OS benefits. The ERG considers this uncertainty as a substantial weakness in the company's submission and it means that the estimated ICER is subject to considerable uncertainty.

Second-line therapies

The proportion of people receiving second-line therapy in the ASCEND-4 and PROFILE 1014 trials was 35% and 43% respectively. This contrasts with the model, where 60% of patients were assumed to receive subsequent active therapy. This inconstancy is problematic because the clinical data used to populate the economic model was based on the ASCEND-4 and PROFILE 1014 and therefore the costs used in the model are inconstant with the clinical data used in the model.

Further to the above, the distribution of therapies assumed in the model is not considered reflective of general practice. The company provided an alternative scenario using estimated distributions based on clinical advice, however this scenario does not account for how subsequent therapy may have impacted on post-progression survival. These differences are potentially very significant as demonstrated in (TA395[1]) that evaluated ceritinib as a second-line treatment for NSCLC.

Survival curve for OS

The ERG is concerned about the parametric distribution selected to extrapolate overall survival. The company selected the exponential curve which produces the most optimistic long-term estimates of survival compared with the other distributions within the model, with [redacted] of patients alive at five years. These estimates are inconsistent with clinical experience of ALK inhibitors and real world data reporting on the survival of patient who had received crizotinib, where a five-year survival rate might be expected to be around 20%.

Time on treatment

The ERG have a number of concerns regarding how treatment duration was modelled by the company. The approach used in the base-case analysis, appears to underestimate the actual time on treatment for ceritinib and is inconsistent with the approach used to estimate PFS and OS.

Treatment administration costs

The treatment administration costs are likely to be underestimated, particularly in the light of the low relative dose intensity seen with ceritinib. The costs included account for a pharmacist's time only and ignore additional clinician or nurse time and administration costs.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company conducted a systematic review of relevant trials. Evidence for the clinical effectiveness of ceritinib was from a good quality RCT comparing ceritinib with pemetrexed/cisplatin plus pemetrexed maintenance therapy.

Cost-effectiveness evidence

The ERG considers the company's submission to broadly meet the requirements of the NICE reference case. The choice of model structure is appropriate and is able to capture the disease progression and treatment pathway of NSCLC patients. The model incorporated a range of scenario analyses, particularly relating to time on treatment, and second-line therapy distributions that allowed the impact of alternative assumptions to be explored.

1.7 Weaknesses and areas of uncertainty

Clinical evidence

The follow-up duration in ASCEND-4 at the latest data cut is too short for a reliable assessment of OS.

Whilst the ERG acknowledges that an indirect comparison of individual trial arms was the only option available to compare ceritinib and crizotinib, it is unclear whether the results derived from the MAIC analyses are any more reliable than that from the unadjusted data.

The MAIC generated results for ceritinib compared with crizotinib for OS are even more uncertain, being the result of an observational comparison of immature, highly uncertain data.

Cost-effectiveness evidence

The main areas of uncertainty in the cost-effectiveness analysis relate to the clinical evidence available to populate the model: the treatment comparison based on the MAIC analysis; the immature OS data and the overly optimistic extrapolation of the OS. There is also uncertainty regarding the distribution of second-line therapies in both the ceritinib and crizotinib arm; the methods used to estimate of duration of first-line treatment; utility values in the post-progression health state; and, the duration of post-progression treatment.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG corrections of calculation errors suggest that the ICER for ceritinib compared with crizotinib is £26,354 per QALY gained (with neither PAS applied). With ceritinib PAS applied, ceritinib dominated crizotinib. The ERG's additional exploratory analyses, using a range of alternative assumptions, indicate that the company's base-case is likely to be overly optimistic and overestimate the benefits of ceritinib.

The ERG conducted a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The most important of these scenarios relate to changes made by the ERG to the selection of survival curve to model overall survival, and the method used to estimate time on treatment. The ERG also presents an alternative base-case based on a combination of a number of these scenario analyses.

The ERG explored the following amendments to the company's revised base-case:

1. Corrections for calculation errors;
2. Adjustment of ceritinib clinical data (OS, PFS and treatment duration) to the PROFILE 1014 population;
3. Estimating time on treatment for ceritinib using patient-level data and estimating the relative time on treatment for crizotinib using a hazard ratio;
4. Alternative survival curves to model OS;
5. Alternative trial data (ALEX study) to model effectiveness of crizotinib;

6. Assuming the proportion of patients receiving second-line therapy is in line with the ASCEND-4 and PROFILE 1014 trials;
7. Quality of life: explored alternative utilities for post-progressed patients (reflecting the expected quality of life of patients receiving second-line treatment as per the ASCEND-4 and PROFILE 1014 trials);
8. Quality of life: explored alternative utility for post-progressed patients (reflecting the expected quality of life of patients receiving second-line treatment as per a "real world" scenario);
9. Added additional administration cost for ceritinib and crizotinib to reflect need to monitor tolerance to dose;
10. Added drug wastage for ceritinib and crizotinib.

The results of these scenario analyses including the ERG's preferred range of scenarios are summarised in Table 1.

Table 1 Summary of the relevant amendments to the company's revised base-case and impact of those amendments on the ICER (without PAS)

#	Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
-	***CS base-case[$] (corrected)***	*Ceritinib*	115,116	3.69	16,133	0.67	26,354	**n/a**
		Crizotinib	97,492	3.02	-	-	-	-
1	Proportional hazard of treatment duration	*Ceritinib*	137,017	3.69	23,234	0.67	34,743	+8,389
		Crizotinib	113,783	3.02	-	-	-	-
2	Clinical data matched to the PROFILE 1014 population	*Ceritinib*	117,531	3.94	19,169	0.70	27,202	+848
		Crizotinib	98,362	3.24	-	-	-	-
3	Weibull curve to model OS	*Ceritinib*	114,283	3.25	18,553	0.56	33,034	+6,680
		Crizotinib	95,730	2.69	-	-	-	-
4	Gompertz curve to model OS	*Ceritinib*	111,454	2.66	17,775	0.39	45,257	+18,903
		Crizotinib	93,679	2.27	-	-	-	-
5	Data from the ALEX trial to model crizotinib (ceritinib unadjusted data from the ASCEND-4 trial)	*Ceritinib*	115,116	3.69	18,841	0.62	30,212	+3,858
		Crizotinib	96,275	3.06	-	-	-	-
6	Data from the ALEX to model crizotinib (ceritinib data from ASCEND-4 adjusted to the ALEX trial population)	*Ceritinib*	115,643	3.76	19,044	0.63	30,189	+3,835
		Crizotinib	96,599	3.13	-	-	-	-
7	Proportion of patients on second-line treatment from ASCEND-4 and PROFILE 1014	*Ceritinib*	111,744	3.69	16,692	0.67	24,961	-1,393
		Crizotinib	95,052	3.02	-	-	-	-
8	Alternative post-progression utilities (trial scenario)	*Ceritinib*	137,017	3.03	23,234	0.53	43,894	+17,540
		Crizotinib	113,783	2.50	-	-	-	-
9	Alternative post-progression utilities (real world scenario)	*Ceritinib*	137,017	3.03	23,234	0.48	48,178	+21,824
		Crizotinib	113,783	2.55	-	-	-	-
10	Drug wastage for ceritinib and crizotinib	*Ceritinib*	120,756	3.69	16,949	0.67	25,345	-1,009

#	Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
		Crizotinib	103,807	3.02	-	-	-	-
11	Additional administration cost	*Ceritinib*	123,263	3.69	19,845	0.67	29,676	+3,322
		Crizotinib	103,418	3.02	-	-	-	-
12	Drug wastage and administration cost (#9 + #10)	*Ceritinib*	129,084	3.69	19,171	0.67	28,667	+2,313
		Crizotinib	109,914	3.02	-	-	-	-
13	**ERG preferred scenario (#1 + #2 + #4 + #7 + #8 + #12)**	***Ceritinib***	**156,083**	**2.40**	**25,596**	**0.37**	**69,255**	+42,901
		Crizotinib	**130,487**	**2.03**	**-**	**-**	**-**	**-**

$, all ERG corrections and adjustments implemented to the company's base-case model; CS, company submission; PAS, patient access scheme; ICER, incremental cost-effectiveness ratio; Inc, incremental; n/a, not applicable; QALY, quality adjusted life year; OS, overall survival; ERG, evidence review group

2 Background

2.1 Critique of company's description of underlying health problem.

The relevant health problem in the present appraisal is anaplastic lymphoma kinase (ALK)-positive (+) advanced non-small-cell lung cancer (NSCLC).

The ERG believes that the company's description of the underlying health problem is appropriate and is relevant to the decision problem under consideration. In summary, the company submission (CS) correctly states that most (80-90% of) lung cancers are NSCLC and that, of these, ALK+ represents around 2-7% of all NSCLC[2, 3] and are almost exclusively non-squamous.[2] ALK+ NSCLC can be considered a unique lung cancer subpopulation, as ALK positivity and other genetic mutations (e.g., mutations in the endothelial growth factor receptor [EGFR] tyrosine kinase [TK]) tend to be mutually exclusive, except in a few rare cases.[4-8]

The CS included an estimate of the number of patients diagnosed annually in England and Wales with ALK+ advanced NSCLC (Table 2). This estimate reflects that given in the technology appraisal of crizotinib in ALK+ advanced NSCLC.[9]

Table 2 Estimate of the number of patients in England and Wales diagnosed with ALK+ advanced NSCLC (CS Table 3)

	Proportion, %	Number of patients
Annual number of lung cancer cases in England and Wales[10]	-	38,269
Patients presenting with NSCLC[10]	88	33,677
Patients diagnosed at stage III/IV[11]	74	24.921
Patients with non-squamous histology[12, 13]	55	13706
Patients with ALK+ advanced NSCLC[14]	3.4	466

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.[14] These findings are supported by the results reported in Bang 2011,[15] who summarises the findings of 14 different studies, focussing on a total number of 2,864 patients. The results of this study found an average percentage across all of the studies of 3.4%, as well, with estimates varying from 1.6% to 11.7%. The ERG identified some further studies of the prevalence of ALK fusion, which reported figures ranging from 3.2% to 6.2%.[16-22]

The ERG notes that based on a meta-analysis of 27 studies (6,950 patients with NSCLC), it was calculated that 6.8% of NSCLC patients are ALK+.[8] Using this figure, the number of cases of ALK+

NSCLC would be 2,290, giving an estimate of 1,695 patients with advanced disease (74% of all ALK+ NSCLC).

2.2 Critique of company's overview of current service provision

That crizotinib, a first generation ALK+ inhibitor, is the current standard of care for previously untreated ALK+ advanced NSCLC, is correctly stated in the CS, with chemotherapy (pemetrexed plus carboplatin or cisplatin) having been superseded. This was supported by an advisory board of nine UK oncologists, who were asked to comment on their treatment strategies in the ALK+ population, assuming that ceritinib received a first-line licence (since the advisory board pre-dated this licence being granted): no clinician suggested that they would use chemotherapy in the first-line setting. The clinical advisor to the ERG agrees with the medical expert's opinion in the CS that 90% of eligible patients in the UK will be treated with crizotinib; only those who have specific contraindications, or are too ill for treatment, will not receive crizotinib.

As crizotinib is the standard of care for ALK+ patients, testing for this mutation is now standard practice in the NHS, for NSCLC patients. This was confirmed by the clinical advisor to the ERG.

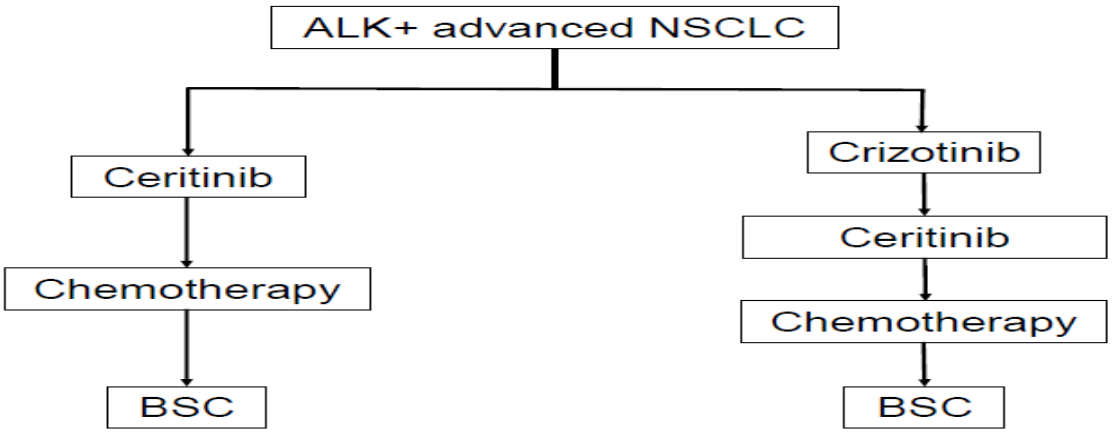
The ERG notes that the characterisation of crizotinib, as providing poor control of intracranial disease, may be overstated. The data from the Phase III trial of crizotinib (PROFILE 1014), that included patients with treated and neurologically stable brain metastases, found that intracranial lesions progressed, or new intracranial lesions developed, in 25 patients in the crizotinib group and in 26 patients in the chemotherapy group (15% each).[23] However, there were statistically significant improvements in the intracranial-disease control rate, at 12 and 24 weeks, in patients with brain metastases, and there were non-statistically significant improvements in intracranial time to progression, in patients with and without brain metastases at baseline, compared with treatment with chemotherapy.[24] The clinical advisor to the ERG suggests that, as brain metastases are a common development with NSCLC, the additional survival provided by crizotinib allows time for the appearance of brain metastases, which would not have been seen with chemotherapy.

Ceritinib and alectinib are second-generation ALK inhibitors. Alectinib is licensed by the EMA for ALK+ advanced NSCLC, previously treated with crizotinib, but it has not been recommended by NICE (Guidance not issued). Ceritinib is the subject of this appraisal.

The anticipated position of ceritinib in the treatment of ALK+ advanced NSCLC is given in Figure 1 (Figure 3 of the CS). This makes clear that, whilst currently first-line crizotinib can be followed by second-line ceritinib, if ceritinib is recommended to be used first line, crizotinib cannot be used second line. As stated in the CS, this is because patients who have developed resistance to second-

generation ALK inhibitors have a high risk of resistance to the first-generation ALK inhibitor, crizotinib. This was confirmed by the clinical advisor to the ERG.

Figure 1 Place of ceritinib in the treatment of ALK+ NSCLC (Figure 3 of the CS)



3 Critique of company's definition of decision problem

3.1 Population

The population specified in the final NICE scope was, 'people with untreated, anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer'. This is the population specified in the submission's decision problem and the population included in the one relevant Phase III, randomised controlled trial (RCT) of ceritinib (ASCEND 4). This is also the population included in the RCT of crizotinib, used for the indirect comparison with ceritinib (see Section 4.3).

3.2 Intervention

The intervention in the CS, and in the final NICE scope, is ceritinib (Zykadia®).

As stated in the CS, ceritinib is a highly selective, potent, second-generation TK inhibitor of ALK, a protein involved in the regulation of the RAS and JAK/STAT signalling pathways. Ceritinib is a second-generation ALK inhibitor that has greater affinity and specificity for ALK than the first-generation ALK inhibitor, crizotinib. Ceritinib has been shown to overcome resistance to crizotinib in preclinical and clinical (phase 1) studies.[25-27]

Marketing authorisation for ceritinib as a first-line treatment for adult patients with ALK+ advanced NSCLC was received on 26 June 2017. In addition, ceritinib had already received marketing authorisation, on 6 May 2015, as a second-line treatment for adult patients with ALK+ advanced NSCLC previously treated with crizotinib.

The Summary of product Characteristics (SmPC)[25] for ceritinib states that,

"An accurate and validated ALK assay is necessary for the selection of ALK-positive NSCLC patients (see section 5.1).

ALK-positive NSCLC status should be established prior to initiation of Zykadia therapy. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised."

The licensed recommended and maximum dose of ceritinib is 750 mg, taken orally, once a day.

3.3 Comparators

The comparators specified in the final NICE scope were crizotinib and pemetrexed, in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only), with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only). In the CS, only crizotinib is included as a comparator. The ERG agrees with this: as

stated in Section 2.2, crizotinib is the current standard of care and all eligible patients, who are well enough to tolerate treatment, are treated with crizotinib.

Crizotinib is a first-generation ALK inhibitor and is administered orally at a dose of 250 mg twice daily. The crizotinib data used in the submission are from the Phase III RCT, PROFILE 1014. The ERG identified additional RCT data for first-line crizotinib in ALK+ advanced NSCLC. This was a trial comparing alectinib with crizotinib (the ALEX trial).[28]

3.4 Outcomes

The outcomes listed in the NICE final scope were:

- overall survival
- progression-free survival
- response rate
- adverse effects of treatment
- health-related quality of life.

These are all included in the CS. In addition, duration of response (DOR), disease control rate (DCR), and time to response (TTR) are included in the CS. As the submission makes a case for specific beneficial effects, in terms of brain metastases, additional intracranial outcomes are reported:

- overall intracranial response rate (OIRR)
- intracranial disease control rate (IDCR)
- intracranial clinical benefit rate (ICBR)
- duration of intracranial response (DOIR)

3.5 Other relevant factors

The submission includes a Patient Access Scheme comprising a simple discount of [redacted].

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)

A systematic review to identify relevant trials of effectiveness was conducted and reported in Appendix D 1.1 and D 1.2 of the CS.

4.1.1 Searches

Reporting

The databases used for the effectiveness review are reported as being MEDLINE, MEDLINE in Process (via OVIDSP), EMBASE (via OVIDSP) and the Cochrane Library (via OVIDSP). The Cochrane databases used included: Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Systematic Reviews Database, Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment (HTA) Database. This is reported in the CS Section D.1.1.2 (Data sources).

The search strategies used in each of the three databases are fully reproduced in the CS Section D.1.1.3 and the date that they were conducted is given. The numbers of records retrieved matches the number given in the PRISMA diagram.

The conference websites used to identify potentially relevant posters and abstracts are not listed here, but are given on page 17 where the PRISMA flow diagram for the effectiveness review is provided.

Although the searches were designed to identify RCTs, the methods did not report searches of any freely available trials registers, such as ClinicalTrials.gov or the WHO ICTRP. However, in the results of the review (Section D 1.1.7) the CS reports that the search of ClinicalTrials.gov identified 7 ongoing clinical trials – ASCEND 4 and six of crizotinib. These crizotinib trials are not listed. The ERG believes that one of these trials was the relevant ALEX trial of crizotinib versus alectinib as first-line treatment for ALK+ advanced NSCLC,[28] which the ERG has identified (see Use of search filters, below).

Strategy

The strategy, used in MEDLINE, Embase and the Cochrane Library, consists of three sections combined with AND search operator, i.e. 1) non-small-cell lung cancer 2) advanced stage and 3) anaplastic lymphoma kinase. In the MEDLINE and Embase databases limits were then applied in

terms of RCT publication type, human only studies, English language, and date. For the Cochrane Library, the limits correctly consisted of language and date only.

Specific drug names were not used in the search strategies and consequently studies that referred to named drug comparators will not have been missed by using this approach.

Sections 2 and 3 of the search strategy rely solely on the use of free-text searching of the title and abstract fields, and do not use any subject headings (MeSH or EMTREE), although terms are available, e.g., Receptor Protein-Tyrosine Kinases (MeSH) that could have been included in section 3, alongside line 8; similarly Neoplasm Metastasis (MeSH) could have been included in section 2, alongside line 6.

It is not known whether this limitation could have resulted in any additional studies not being identified.

Line 6 of the search strategy attempts to capture the concept of advanced cancer by using a number of synonyms described using free-text terms. Some potentially relevant search terms were not included, however, e.g., stage 3, stage 4, T3 or T4.

None of the free-text search statements in sections 1,2 or 3 make use of the adjacency operator, which has the potential to improve the relevance of the records identified and to increase the overall precision of the search strategy. There are also some potentially relevant phrases that would not be identified by the current line 8, e.g., "anaplastic lymphoma receptor tyrosine kinase". This could be corrected by either using the relevant MeSH terms e.g. *Receptor Protein-Tyrosine Kinases* or by making use of the adjacency operator, e.g., *ALK adj4 rearranged.* Again it is not known whether this could have resulted in any additional studies not being identified.

Use of search filters

The RCT filter used in the MEDLINE search relies heavily on MeSH terms – it would be preferable to use a RCT filter (such as the Cochrane Highly Sensitive Filter) that includes a number of free-text terms to minimise the possibility of not identifying records that are in the MEDLINE In Process section of MEDLINE and have not yet been indexed.

Using the current strategy could result in records from the In Process section of MEDLINE (and present in the search results at line 9) being inadvertently removed at line 28, when the RCT filter is combined with the topic terms.

This can be demonstrated when the search is re-run and the records in the results set at line 9 are reviewed. At this point the results include the three sample records as listed below. When the current search filter is used, these records are all removed from the search results by line 28.

1. Cho BC, Kim DW, Bearz A, Laurie SA, McKeage M, Borra G, Park K, Kim SW, Ghosn M, Ardizzoni A, Maiello E, Greystoke A, Yu R, Osborne K, Gu W, Scott JW, Passos VQ, Lau YY, Wrona A. ASCEND-8: A Randomized Phase 1 Study of Ceritinib 450 mg or 600 mg Taken With a Low-Fat Meal Versus 750 mg in Fasted State in Patients With Anaplastic Lymphoma Kinase (ALK)-Rearranged Metastatic Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol [Internet]. 2017 [cited 2017 Jul 17];In: Ovid MEDLINE(R) Epub Ahead of Print [Internet].
2. Nishio M, Kim DW, Wu YL, Nakagawa K, Solomon BJ, Shaw AT, Hashigaki S, Ohki E, Usari T, Paolini J, Polli A, Wilner KD, Mok T. Crizotinib Versus Chemotherapy in Asian Patients with Advanced ALK-positive Non-small Cell Lung Cancer. Cancer Res. Treat. [Internet]. 2017 [cited 2017 Jul 06];In: Ovid MEDLINE(R) Epub Ahead of Print [Internet].
3. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T, ALEX Trial Investigators. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med [Internet]. 2017 [cited 2017 Jun 06];In: Ovid MEDLINE(R) Epub Ahead of Print [Internet].[28]

Note: these records would not have been identified when the search was originally run, in May 2017, as they were all added to MEDLINE during July 2017. Similarly, other records could have been missed by the May 2017 search.

The ERG notes that, of these references identified, the ALEX trial ([28]) is of direct relevance to the present assessment, being a trial of crizotinib in the exact population of interest. This is discussed further in Section 4.2.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria, used to select studies for inclusion in the systematic review of effectiveness of first-line treatments for advanced ALK+ NSCLC, are detailed in Table 4 of Appendix D.1.1 of the CS. The ERG considers these criteria to be appropriate. The criteria did not specify any interventions or comparators, but given that the population was specifically ALK+, only studies of ALK inhibitors would be selected for the review. Only English-language studies were included, however, given the current interest in ALK+ inhibitors, the relevant trials are published in major English-language journals, and therefore only secondary publications of these trials would be missed.

4.1.3 Critique of data extraction

The methods of data extraction are reported in the CS Section D1.1.5 and were appropriate.

4.1.4 Quality assessment

The quality assessment of the studies identified for inclusion in the systematic review of effectiveness is reported in the Appendix Section D1.1.9. The assessment considered the following factors relating to quality and the risk of bias:

- Was randomisation carried out appropriately?
- Was the concealment of treatment allocation adequate?
- Were groups similar at the outset of the study in terms of prognostic factors?
- Were care providers, participants, and outcome assessors blind to treatment allocation?
- Were there any unexpected imbalances in dropouts between groups?
- Did the authors measure more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis?

This assessment appears to have been appropriate and well conducted. However, it is unclear to the ERG why some factors were rated unclear for the ASCEND 4 trial: as this trial was the company's own study any unclear details could surely have been clarified? Ratings of unclear are usually reserved for cases where reviewers are restricted to published sources with limited reporting. Details and further commentary on the results of this assessment are given in Section 4.2.2.

4.1.5 Evidence synthesis

The evidence synthesis presented in the CS was a Matching-Adjusted Indirect Comparison (MAIC). Details and further commentary on this analysis and the results are given in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Identified studies - ASCEND-4

Design of ASCEND-4

One relevant RCT of ceritinib, as the first-line treatment in ALK+ advanced NSCLC, was identified; this was ASCEND-4, a Phase III company-sponsored trial. ASCEND-4 was an international, multicentre, open-label RCT comparing ceritinib with pemetrexed/cisplatin plus pemetrexed maintenance therapy. The methods of this trial are presented in Table 5 of the CS.

In brief, the trial was an international, multicentre, open-label RCT. The study included patients with advanced or metastatic non-squamous ALK+ NSCLC, untreated with systemic therapy (with the exception of adjuvant or neoadjuvant therapy, if relapse had occurred at least 12 months after the end

of therapy). If present, brain metastases were required to be asymptomatic or neurologically stable (including not having required increasing doses of steroids, within the two weeks prior to screening, to manage central nervous system symptoms).

Patients were randomised to receive ceritinib 750 mg, administered orally, once daily (and continuously) in a fasted state, or chemotherapy (CT). CT was pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or (based on the investigator's choice) carboplatin (AUC 5–6), administered every 21 days. Patients who completed four cycles of CT (induction), without progressive disease, subsequently received pemetrexed as single-agent maintenance every 21 days. Patients in the CT group, in the treatment and post-treatment follow-up phases, were allowed to cross over to ceritinib after centrally confirmed, RECIST-defined (BIRC) progressive disease.

The primary outcome was median progression-free survival (PFS), defined as the time from the date of randomisation to the date of the first radiologically documented disease progression by central review, or death due to any cause. Tumour assessments for response/progression determination were performed by computed tomography scan or magnetic resonance imaging (MRI) of the chest and abdomen, at baseline and then every 6 weeks (2 cycles), after day 1 cycle 1 to month 33, and then every 9 weeks (3 cycles), thereafter. A final scan was required at the end of treatment. RECIST 1.1 criteria were used to assess response, and responses were confirmed within 4 weeks of the initial observation of a response.

The key secondary objective was overall survival (OS), defined as the time from date of randomisation to date of death due to any cause.

Other secondary endpoints were:

- progression-free survival (PFS) (local assessment)
- objective overall response rate (ORR)
- duration of response (DOR)
- disease control rate (DCR)
- time to response (TTR)
- overall intracranial response rate (OIRR)
- intracranial disease control rate (IDCR)
- duration of intracranial response (DOIR)
- Patient reported outcomes (PROs): EORTC QLQ-C30, QLQ-LC13, LCSS, EQ-5D
- Safety

Pre-planned subgroups were:

- Geographic area (South America, Europe, Asia Pacific);
- Age
- Gender
- Brain metastasis at screening: absence or presence
- WHO status: 0 or ≥1
- Race: Asian, Caucasian
- Previous adjuvant chemotherapy
- Disease burden per central assessment: baseline sum of diameters (SOD) for target lesions <median SOD for target lesions; baseline SOD for target lesions ≥median SOD for target lesions
- Smoking history.

The trial was appropriately designed although the open-label treatment administration made it susceptible to bias. This was ameliorated by the primary (PFS) outcome being assessed centrally and the key secondary outcome, of OS, being an objective outcome.

Patient disposition and baseline characteristics in ASCEND-4

The patient disposition is presented in Figure 5 of the CS. Of 425 patients screened, 189 were randomised to ceritinib and 187 to CT. All patients randomised to ceritinib received treatment, compared with only 175/189 randomised to CT. Of the ceritinib patients, 94 discontinued therapy, compared with 145 CT patients.

The baseline characteristics of the trial patients are summarised in Table 3. The median age of patients was 54 years, and approximately three-quarters of patients (78.5%) were aged <65 years. The patient characteristics were well balanced across the trial arms. The clinical adviser to the ERG commented that, except that a higher proportion of men might be expected in clinical practice, the trial population can be considered generalisable to NHS practice.

Table 3 Characteristics of patients in ASCEND-4 (adapted from CS Table 6)

Baseline characteristics	**Ceritinib (n=189)**	**Chemotherapy (n=187)**
Age, median years (range)	55 (22–81)	54 (22–80)
Female, n (%)	102 (54)	114 (61)
Race, n (%) Asian	76 (40)	82 (44)

Baseline characteristics	**Ceritinib (n=189)**	**Chemotherapy (n=187)**
Caucasian	104 (55)	98 (52)
Other	9 (5)	7 (4)
WHO performance status, n (%)		
0	69 (37)	70 (37)
1	107 (57)	105 (56)
2	13 (7)	11 (6)
Missing	0 (0)	1 (1)
Smoking history, n (%)		
Current smoker	15 (8)	15 (8)
Ex-smoker	66 (35)	50 (27)
Never smoked	108 (57)	122 (65)
Histology or cytology, n (%)		
Adenocarcinoma	180 (95)	183 (98)
Locally advanced (stage IIIb) n (%)	9 (5)	5 (3)
Metastatic (stage IV) n (%)	180 (95)	182 (97)
Metastatic site of cancer, n (%)		
Bone	77 (41)	80 (43)
Brain	59 (31)	62 (33)
Liver	34 (18)	39 (21)
Previous antineoplastic therapy, n (%)		
Surgery		
Yes	44 (23)	43 (23)
Radiotherapy		
Yes	37 (20)	40 (21)
Previous radiotherapy to the brain		
Yes	24 (13)	26 (14)
Time from radiotherapy to the brain to randomisation ≤3 months, n/N[a] (%)	22/24 (92)	23/26 (89)
Medication: chemotherapy setting		
Adjuvant	10 (5)	7 (4)
Neoadjuvant	0	2 (1)
Receipt of one previous regimen of neoadjuvant or adjuvant chemotherapy	10 (5)	9 (5)

To further assess the generalisability of the ASCEND-4 trial population to clinical practice, the ERG compared the patient characteristics in the ceritinib arm with those from a recently presented retrospective chart review of patients treated with first-line crizotinib, in the UK and Europe (see Table 4).29 The comparison indicated that the trial patients were slightly younger, had a higher

proportion of females and a lower proportion of former of current smokers and, as might be expected, a higher proportion of trial patients were ECOG status 0 or 1.

Table 4 Baseline characteristics of participants in ASCEND-4, compared with a real-world cohort from Davis et al. 2017 (1st-line ceritinib)

	ASCEND-4	Davis 2017[29]
Country	International	UK/EUR
Age –mean (SD) years	54.5 (12.8)	[redacted]
Age – median (range) years	55 (22-81)	
Male	46%	[redacted]
Ethnicity White/Caucasian		[redacted]
Asian		
Smoking status - Former or present	43%	[redacted]
Histology - Adenocarcinoma	95%	[redacted]
ECOG performance status – 0 or 1	93%	[redacted]

4.2.2 Summary of the quality of the included trial

A quality assessment of ASCEND-4 was included in the CS (Section D 1.1.9). This was checked by the ERG and implications for risk of bias were considered (Table 5).

Table 5 Quality assessment of the ASCEND-4 trial (adapted from the CS, Appendix D Table 7)

Study name	CS	ERG	ERG Risk of bias
Was randomisation carried out appropriately?	Yes	Yes	Low
Was the concealment of treatment allocation adequate?	Unclear	Yes	Low
Were groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Low
Were care providers, participants, and outcome assessors blind to treatment allocation?	No	Care providers, participants and investigators were not blinded. However progressed disease (PD) was determined centrally by blinded assessors.	Low for primary outcome and other outcomes which was conducted centrally and OS. High for subjective outcomes.
Were there any unexpected imbalances in dropouts between groups?	Unclear	Yes - 12 patients randomised to CT did not receive therapy. Also a further 16 dropped out due to patient's decision compared with 7 on ceritinib	High
Did the authors measure more outcomes than they reported?	Yes	Yes	NA
Did the analysis include an intention-to-treat analysis?	Yes	Yes	Low

The ERG agrees with the assessments in the CS, except for the 'unclear' ratings given to 'was concealment of treatment allocation adequate?' and 'were there any unexpected imbalances in dropouts between groups'. In the Clinical Study Report (CSR) of ASCEND-4 it states that, patients were randomised to ceritinib or chemotherapy via the Interactive Response Technology (IRT). Therefore, there is no reason to suspect that the investigator's knowledge of treatment influenced allocation. It is possible that, on learning of the treatment to be given to an individual patient, the clinician or patient may have been influenced by that knowledge, in terms of deciding whether or not to continue in the trial, or their perception of how effective the treatment was. However, this is not an issue of allocation concealment. It may well explain at least some of the 12 patients randomised to CT who did not receive treatment (187 were randomised, 175 received chemotherapy): 7 due to patient or guardian decision; 2 due to physician decision.

In terms of risk of bias, the open-label nature of the trial puts all subjective outcomes at a high risk of bias. However, the primary outcome was centrally (BIRC) assessed progression-free survival and, therefore, should not have been subject to this bias. Similarly, other outcomes derived from the centrally determined identification of progressed disease (PD) will also have avoided bias. OS, as an objective outcome, is not at risk of bias. Of the intracranial outcomes, OIRR and DOIR were both assessed by a blinded central neurologist. For the whole-body tumour response, there was some imbalance in the proportion of unknown results, which was higher in the CT group than in the ceritinib group; this was mostly due to not having a valid post-baseline assessment. This imbalance could be due, in part, to the open-label nature of the trial.

The open-label design of the trial had the potential to bias withdrawal rates. The detailed information provided by the company, in their clarification response, demonstrated that withdrawal due to reasons other than disease progression, death or adverse events was slightly higher in the CT group: 25 versus 19, with the biggest difference in withdrawal due to patient or guardian decision, 16 on CT, compared with 7 on ceritinib.

For the assessment of OS, a major limitation of the trial design was that patients were allowed to remain on therapy despite disease progression. Specifically, patients who had RECIST-defined progressive disease, per local assessment and confirmed by the BIRC, but who, in the opinion of the Investigator, had evidence of continued clinical benefit from study treatment on either the ceritinib arm or the chemotherapy arm, continued to receive study treatment in the treatment phase. In addition, following disease progression, patients in the chemotherapy arm were allowed to cross over to receive ceritinib therapy. This resulted in confounding of the OS outcome, which is discussed further in Section 4.2.3.

4.2.3 Summary of the results of the ASCEND-4 trial

Data cut

In their clarification response, the company confirmed that the data cut presented in the CS was the latest one and that there were no further planned analyses for PFS (since the final PFS analysis has already been presented in the ASCEND-4 primary paper, as per the study protocol). The company stated that updated efficacy assessments for OS will be completed as per the protocol; the third interim analysis for OS is planned for when approximately 215 deaths have been observed, and a final analysis will be conducted when approximately 253 deaths have been observed. Latest estimates indicate that these are likely to become available in [redacted], respectively.

Treatment exposure

In ASCEND-4 the median duration of ceritinib exposure was 66.4 weeks (IQR 30.0 to 83.7) and the median relative dose intensity was 78.4% (IQR 63.2 to 97.5), with a mean dose of 626.0 mg (SD 124.8). Of the 73 patients who developed (BIRC) progressive disease on ceritinib, 61 (84%) continued on ceritinib and 36 (49%) continued ceritinib for at least two cycles post-progression, with a median additional exposure of 9.6 weeks (IQR 2.9 to 23.7).[30] The CS and CSR provide information on other post-progression treatment: of the 94 patients who discontinued ceritinib, 33 patients (note the CS says 34) received subsequent systemic therapies as their first next treatment. These treatments included platinum-based doublet chemotherapy (24 patients: 16 patients in combination with pemetrexed, six patients in combination with paclitaxel, and two patients in combination with gemcitabine), single-agent chemotherapy (two patients), ALK inhibitor therapy (six patients: three patients received crizotinib, two patients received lorlatinib, and one patient received a ceritinib marketed drug), and Chinese patent medicine (one patient).

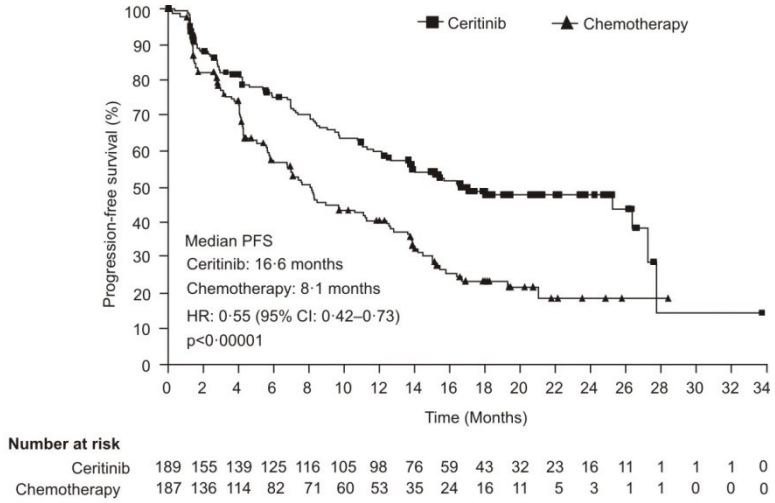
Of the 145 CT patients who discontinued CT therapy, 105 patients (72%) received an ALK inhibitor after CT discontinuation: 80 patients crossed over to receive ceritinib (and a further patient received ceritinib as their next therapy), 23 patients received crizotinib, and one received alectinib. Conversely, in the ceritinib group, 34 (18%) of 189 patients had received subsequent anti-cancer therapy: 24 received platinum-based doublet CT, and six received an ALK inhibitor (ceritinib, n=1; crizotinib, n=3; or lorlatinib, n=2).

Progression-free survival (central assessment)

Table 6 Summary of PFS (central assessment) in ASCEND-4 (Adapted from CS Table 11)

	All patients (ITT)	
	Ceritinib	Chemotherapy
PFS events, n/N (%)	89/189 (47.1)	113/187 (60.4)
Median PFS months (95% CI)	16.6 (12.6–27.2)	8.1 (5.8–11.1)
HR (95% CI)	0·55 (0.42–0.73); p<0.00001	

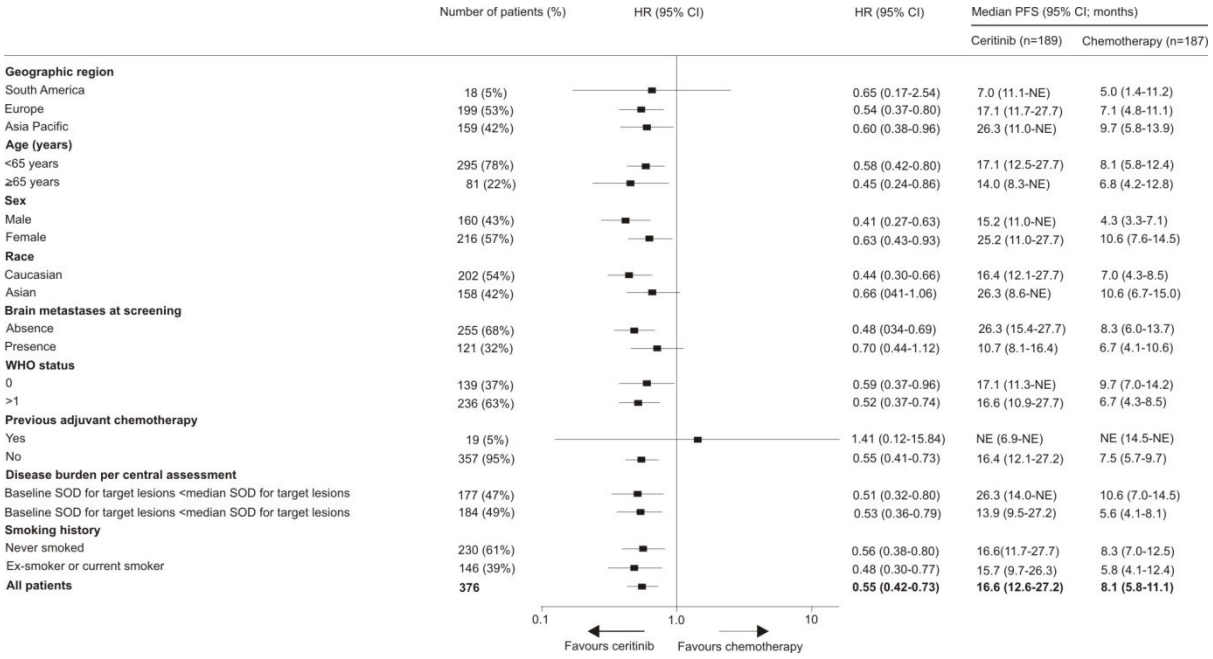
Figure 2 Kaplan–Meier plots of PFS in ASCEND-4 (central assessment)



The results (Table 6) show that ceritinib prolonged PFS, compared with CT, in all patients (HR 0·55, 0.42 to 0.73). The CS states that the results, based on local assessment, corroborated those, based on central assessment, with concordance rates of 88% and 87% for ceritinib and CT, respectively.

The CS reports a Cox regression model analysis to evaluate the effects of baseline patient characteristics on PFS results. The results are given in Figure 3 (CS Figure 12). The results indicate that the effects of ceritinib were consistent across all subgroups considered, except for the subgroups with previous adjuvant chemotherapy, where the sample size was very small. The treatment benefit, in patients with brain metastases at baseline, was numerically smaller that in those without (HR 0.80, compared with 0.45). Median PFS was greatest in patients without brain metastases treated with ceritinib (26.3 months).

Figure 3 PFS in different subgroups in ASCEND-4 (CS Figure 12)



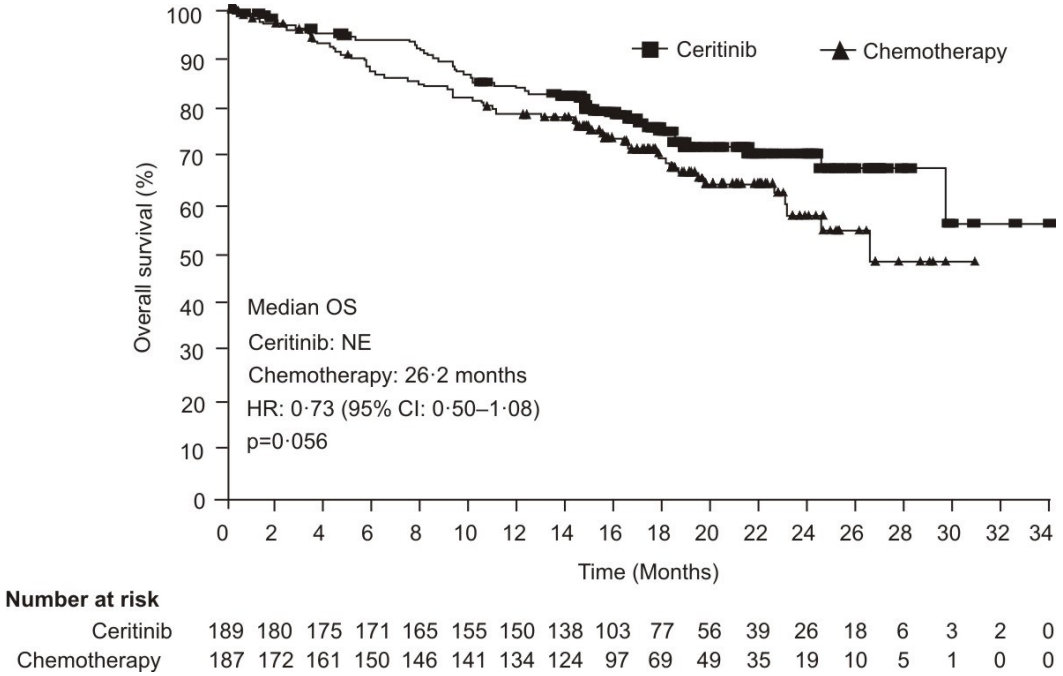
Overall survival

At the time of the analysis, the OS data were immature; only 107 events (42% of the required OS events) had occurred. The study did not cross the efficacy-stopping boundary for OS (–3.2546 [Z-scale], corresponding to p=0.0006 on the p-value scale), and is, therefore, ongoing.

Table 7 OS– events and percent survival at data cut-off in ASCEND-4 (CS Table 13)

	Ceritinib	**Chemotherapy**
n/N (%)	48/189 (25.4)	59/187 (31.6)
Median OS	NE (29.3–NE)	26.2 (22.8–NE)
HR (95% CI), p-value	0.73 (0.50–1.08) p=0.056	
Percent event-free probability estimate		
At 12 months, % (95% CI)	83.6 (77.4–88.2)	78.7 (71.9–84.1)
At 24 months, % (95% CI)	70.6 (62.2–77.5)	58.2 (47.6–67.5)

Figure 4 Kaplan–Meier plot of OS in ASCEND-4 (CS Figure 7)



At the data cut-off (24 June, 2016), 48 (25.4%) patients randomised to the ceritinib group had died (estimated 24-month OS rate of 70.6%) compared with 59 (31.6%) randomised to CT (24-month OS of 58.2% for CT). Median OS was 'not reached' in the ceritinib group, and was estimated as 26.2 months in the CT group (HR, 0.73; p=0.056).

However, this as-randomised analysis does not account for any crossover of CT patients to ceritinib following disease progression. At the time of the data cut, 105 (72%) of 145 patients randomised to CT had received an ALK inhibitor after discontinuation of CT. This included 80 patients who crossed over to receive ceritinib; and 23 who received crizotinib. In the ceritinib group, 34 (18%) of 189 patients had received subsequent anti-cancer therapy: 24 received platinum-based doublet CT, and six received an ALK inhibitor (ceritinib, n=1; crizotinib, n=3; or lorlatinib, n=2). A sensitivity analysis, using rank-preserving structural failure time (RPSFT) methods, was performed to correct for the confounding introduced by patients crossing over from CT to ceritinib. The resulting HR estimate was similar to that from the primary OS analysis, suggesting that crossover from CT to ceritinib, on disease progression, did not affect the difference in OS between the treatment groups for this data-cut (HR 0.73, 95% CI 0.49 to 1.10). The duration of follow-up is currently insufficient to conclude whether there is a difference in OS according to the RPSFT analysis. In their clarification response, the company confirmed that the RPSFT method of adjustment for crossover was the one specified in the trial protocol and other methods were not explored.

The ERG notes that this adjustment for crossover to ceritinib does not adjust for the post-ceritinib treatments received in those randomised to ceritinib, nor does it account for patients who remained on ceritinib post (centrally determined) disease progression, as permitted by the protocol.

Tumour response

Whole-body tumour response rates are reported in the CS (CS Section B 2.6.4) and reproduced here (Table 8). The results, both from central and local assessment, favour ceritinib in terms of tumour response, time to first response and duration of response. There is some imbalance in the proportion of unknown results, which were higher in the CT group than the ceritinib group; these were mostly due to not having a valid post-baseline assessment. This imbalance could be due, in part, to the open-label nature of the trial.

Table 8 Summary of whole-body tumour response rates in ASCEND-4 (CS Table 14)

Response	Central assessment		Local assessment	
	Ceritinib (n=189)	Chemotherapy (n=187)	Ceritinib (n=189)	Chemotherapy (n=187)
ORR, n (%) (95% CI)	137 (72.5) (65.5–78.7)	50 (26.7) (20.5–33.7)	139 (73.5) (66.7–79.7)	60 (32.1) (25.5–39.3)
CR, n (%)	1 (0.5)	0	5 (2.6)	0
PR, n (%)	136 (72.0)	50 (26.7)	134 (70.9)	60 (32.1)
SD, n (%)	23 (12.2)[a]	88 (47.1)[b]	30 (15.9)	82 (43.9)
PD, n (%)	19 (10.1)	26 (13.9)	11 (5.8)	21 (11.2)
Unknown, n (%)	10 (5.3)	23 (12.3)	9 (4.8)	24 (12.8)
Median time to first response (in responders), weeks (range)	6.14 (5.1–61.7)	13.36 (5.1–90.1)	6.29 (5.1–71.9)	12.64 (4.7–84.0)
Median DOR (in responders), months (95% CI)	23.9 (16.6–NE)	11.1 (7.8–16.4)	23.3 (17.6–NE)	8.0 (5.8–13.4)
Estimated 21-month event-free rate, % (95% CI)	59.0 (49.3–67.4)	NE	53.9 (42.9, 63.6)	13.8 (1.6–39.1)

Soria et al Supplementary appendix[31] [a]Three NCRNPD cases are based on patients with non-measurable disease. [b]Nine NCRNPD cases are based on patients with non-measurable disease, CI, confidence interval; CR, complete response; DOR, duration of response; NCRNPD, non-CR/non-PD; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

Intracranial outcomes

The results for intracranial tumour responses in patients with measurable brain metastases (BM) at baseline are presented in the CS (Table 16); these results indicate that the intracranial tumour responses to ceritinib and to CT are similar to the whole body response (OIRR with ceritinib 72.7% (95% CI 49.8% to 89.3%), and with CT 27.3% (95% CI 10.7% to 50.2%).

Intracranial outcomes were assessed in only those patients with BM at baseline, therefore the impact of ceritinib in preventing the development of new BMs has not been assessed in the CS.

Symptom severity and HRQoL

The CS reports that symptom severity and HRQoL were assessed on treatment using the QLQ-C30, QLQ-LC13, LCSS and EQ-5D instruments. Compliance was good, with ≥80% of patients completing the questionnaires at most time points. Further data confirming this were provided in the company's clarification response.

The primary patient-reported outcome (PRO) of interest was the time to definitive symptom deterioration for the composite endpoint of lung cancer specific symptoms (pain, cough and dyspnoea). The clinical advisor to the ERG advised that this was a clinically relevant outcome. Time to definitive symptom deterioration was assessed using both the LCSS and QLQ-LC13 questionnaires, and the results for both tools demonstrated a statistically significant difference in favour of ceritinib (CS Figures 9 and 10). Using the LCSS, the median time to definitive symptom deterioration was not reached in the ceritinib group, compared with 18.4 months in the CT group ($p<0.005$). Using the QLQ-LC13 assessment, the median time to definitive symptom deterioration was 23.6 months in the ceritinib group, compared with 12.6 months in the CT group ($p<0.001$).

Data collected using the LCSS and QLQ-LC13 were also used to compare improvements in symptom severity during the time on therapy in the two treatment groups; these are reported in CS, Figure 10. Ceritinib was associated with improvements in all LCSS symptom scores, compared with CT, with the difference being statistically significant for four out of six of the individual scores. Total LCSS, total symptom distress, normal activity status, overall HRQoL, and average symptom burden index, all improved significantly, compared with CT. Similarly, all QLQ-LC13 symptom scores were indicative of a greater improvement with ceritinib, compared with CT, and the difference was statistically significant for eight of the 10 symptoms.

The CS also presents results for EORTC QLQ-C30 (CS, Figure 11). Comparison of scores found a statistically significant treatment difference in favour of ceritinib for four of the six functional domains and six of the nine symptom scales. However, two of the symptom scores – nausea and vomiting, and diarrhoea – were significantly higher (indicating more severe symptoms) in the ceritinib group.

EQ-5D scores, assessed using the EuroQol index and the VAS, are presented in Table 6 (CS, Table 17).

Table 9 EQ-5D scores during treatment with ceritinib or chemotherapy in ASCEND-4 (CS, Table 17)

Time window (overall)	Ceritinib (N=189)	Chemotherapy (N=187)	Treatment difference (Ceritinib vs chemotherapy)	p-value
EQ-5D Index				
N	180	159	-	<0.001
LS Mean	0.8132	0.7708	0.04	
95% CI	(0.78408-0.84231)	(0.73905-0.80264)	(0.02, 0.07)	
EQ-VAS				
N	180	156	-	0.053
LS Mean	77.0	74.7	2.3	
95% CI	(74.18-79.73)	(71.64-77.71)	(-0.03, 4.59)	

4.3 Critique of trials identified and included in the indirect comparison and/or multiple-treatment comparison

The only comparator considered in the CS was crizotinib. The systematic review of effectiveness identified two trials of crizotinib; these are listed in Table 10.

Table 10 List of included studies of relevant comparator (crizotinib) from the systematic review of effectiveness (adapted from CS, Appendix D Table 4)

Study name	Title of main publication
NCT01639001[32, 33]	Phase 3 study of first-line crizotinib vs pemetrexed-cisplatin/carboplatin (PCC) in East Asian patients (pts) with ALK+ advanced non-squamous non-small cell lung cancer (NSCLC)
PROFILE 1014[23, 24]	First-line crizotinib versus chemotherapy in ALK-positive lung cancer
	Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: Results from PROFILE 1014

The design of PROFILE 1014 is described in the CS, Appendix D 2.1.1, where a detailed comparison with ASCEND-4 is also presented. PROFILE 1014 was an open-label RCT of crizotinib, compared with pemetrexed/cisplatin chemotherapy, in previously untreated advanced or metastatic ALK+ NSCLC. The design and population of PROFILE 1014 was similar to that of ASCEND-4, though there were some differences between the trials.

Firstly, the method used to confirm ALK status differed. In ASCEND-4, ALK status was determined centrally using the VENTANA anti-ALK (D5F3) immunohistochemistry (IHC) assay, while in PROFILE 1014, ALK status was evaluated centrally using the Vysis ALK Break Apart FISH Probe

Kit (Abbott Molecular). In their clarification response, the company stated that at least 12 studies had compared D5F3 IHC with FISH and that the correlation between the results with these two tests is excellent, and inter-observer concordance using D5F3 IHC in a series of lung adenocarcinoma with known ALK genotype (with a panel of international pathologists) was high. Therefore, there is no reason to suspect that the use of different ALK testing methods, in ASCEND-4 and PROFILE 1014,should have any significant implications regarding the patient populations involved in these two studies, or the results reported for these studies. The company reported that, based on their clinician study, most centres in the UK use IHC for first-line ALK testing, with FISH sometimes being used to confirm the results.

Secondly, the treatment protocols for the CT arms in ASCEND-4 and PROFILE 1014 differed. Four cycles of CT were administered in ASCEND-4, whereas up to six cycles were permitted in PROFILE 1014. In addition, while maintenance pemetrexed was included in the chemotherapy treatment protocol for ASCEND-4 (for eligible patients who did not progress during the initial cycles), patients randomised to chemotherapy in PROFILE 1014 did not have on-protocol access to maintenance pemetrexed or other chemotherapies. Maintenance pemetrexed has been shown to improve survival among patients with advanced NSCLC who have not progressed during pemetrexed-cisplatin induction therapy.[34] Thus the chemotherapy group, in the ASCEND-4 trial, would be expected to have a better outcome than the corresponding group in PROFILE 1014. This means that comparing the treatment difference between chemotherapy and the ALK inhibitor in the two studies would underestimate the benefit of ceritinib.

A further difference between ACSEND-4 and PROFILE 1040 was the inclusion criteria relating to patients with BM. In PROFILE 1014, only patients with treated BM were enrolled and all had received radiotherapy, had stable disease for at least two weeks before entering the trial and were no longer receiving corticosteroid therapy. In contrast, in ASCEND-4 only 39% of patients with BM received radiotherapy prior to study entry. The CS states that this difference in inclusion criteria is likely to favour crizotinib, as the benefits of radiotherapy may have contributed to the intracranial responses observed in PROFILE 1014.

Despite these differences, the ERG agrees that PROFILE 1040 is a directly relevant trial in any comparison with ceritinib.

The trial in East Asian patients was not considered for inclusion in the indirect comparison with ceritinib; the CS states that this was because the trial population was not generalisable to the NHS. The ERG agrees with this, and also acknowledges that, as the trial has been published only as an abstract, using the data would not have been possible. In their clarification response, the company did

supply further details of this trial (see response to question A6). Based on this information, the ERG notes that, other than the specifically Asian population (92% Han Chinese), this trial was very similar to the PROFILE 1040 trial. Compared with chemotherapy, crizotinib significantly prolonged PFS (HR 0.40, 95% CI 0.29 to 0.57; 1-sided p<0.0001). The median PFS was 11.1 months (95% CI 8.3 to 12.6 months) for crizotinib and 6.8 months (95% CI 5.7 to 7.0 months) for chemotherapy.[32] The OS data were immature, with only 35% of the required OS events. There was a numerical (not statistically significant) improvement in OS with crizotinib (HR 0.90, 95% CI 0.56 to 1.45; 1-sided p=0.33).

In addition six ongoing trials of crizotinib were identified from ClinicalTrials.gov. The CS does not state why these ongoing trials were not considered further. The ERG assumes that it was because only very limited information is available from ClinicalTrials.gov: even if the trials were completed, limited, if any data, would be available.

As detailed in Section 4.1.1, the ERG identified the relevant ALEX trial of crizotinib versus alectinib as first-line treatment in ALK+ advanced NSCLC.[28] This trial provides published, directly relevant data on crizotinib. The ERG compared the characteristics of this trial (based on the available published paper[28] with those of the ASCEND-4 and PROFILE 1014 trials (as compared in the CS, Section D2.2.1 Table 8) and found the trials to be very similar. The main difference between ALEX and the other two trials was that the primary outcome was investigator-determined, rather than centrally determined, PFS. However, independent review committee PFS was a secondary outcome. Also, in the ALEX trial, treatment with crizotinib continued until disease progression, and it was not clear if, as in the other trial, some patients continued to receive treatment post-progression. This is in contrast to the ASCEND-4 and PROFILE 1014 trials, in which treatment with ceritinib and crizotinib, respectively, continued post-disease progression in a significant proportion of patients. This difference is only relevant to the comparison of OS results. There were some differences in the eligibility criteria relating to BM: patients with asymptomatic brain or leptomeningeal metastases were eligible; previous CNS radiotherapy was allowed if completed at least 14 days prior to enrolment. In summary, the ERG concludes that three trials, ASCEND-4, PROFILE-4 and ALEX, are directly relevant for an indirect comparison of ceritinib with crizotinib in the present assessment.

4.4 Critique of the indirect comparison and/or multiple-treatment comparison

4.4.1 Method of the indirect comparison

As no relevant direct head-to-head trials of ceritinib and crizotinib have been conducted, an indirect comparison should be considered. Indirect comparisons usually draw on trials where the treatments of interest have been compared (separately) with a common comparator, such as placebo.

The CS states that although the ASCEND-4 and PROFILE 1014 trials enrolled similar patient populations and included CT as a comparator, the CT arms differed too much to be used as a common comparator (see section 4.3 above).

Therefore, the company considered that it was not possible to perform an 'anchor-based' analysis of first-line ceritinib and crizotinib. An alternative option would be a doubly indirect comparison in which a 'bridge' between ceritinib and crizotinib is constructed using a third randomised trial that includes a head-to-head comparison of the chemotherapy regimens used in ASCEND-4 and PROFILE 1014. However, such doubly indirect comparisons have important limitations, even when suitable bridging trials are available,[35] and no suitable trial was identified for the present analysis, based on a further systematic literature review (not described here). Thus, the company decided that a MAIC would be the best approach to compare the efficacy for ceritinib and crizotinib.

The ERG agrees that there are significant limitations of a yet more indirect comparison using a direct comparison of pemetrexed, with pemetrexed plus maintenance, as a link between the ceritinib and crizotinib trials. It, furthermore, acknowledges that the PARAMOUNT trial,[34] which is a direct comparison of pemetrexed, with pemetrexed plus maintenance, was conducted in patients with NSCLC but not specifically ALK+, and so could not be used as a link in a network of trials.

The ERG, therefore, agrees that an indirect comparison using only the ALK inhibitor arm of the identified trials is the only option available. This does not mean that the method is not subject to significant limitations, and that the results of such an analysis could be anything other than highly uncertain. In addition, as stated above the ERG believes that the ALEX trial should also have been included in the analysis.

The ERG presents a brief overview of the MAIC method below and discusses the specific methods used in the CS and the reliability of the results.

Overview of the MAIC method

The MAIC method was developed as an improvement on standard indirect comparison methods, which use aggregate data only; it was not developed as a method to be used without a common

comparator arm.[36] Although aggregate data are routinely available from trial publications, they are subject to potential bias due to differences between trial populations. However, where individual patient data are available, there is the potential for 'matching' between the trials and hence reducing the between-trial differences. A typical situation can be where a company holds individual patient data (IPD) on one drug and it wants to conduct an indirect comparison using published, aggregate data for a comparator drug. The MAIC approach proposes matching the IPD data to the aggregate data; this is accomplished by re-weighting patients in the IPD data set by their odds of having been enrolled in the aggregate data trial.

There are significant limitations to this type of analysis. Despite the matching, the analysis can still be subject to the effects of residual confounding, due to unobserved differences between the trials. The availability of a common randomised placebo (or same active control) arm allows some assessment of this confounding. When matching adjustment reduces the differences in the control arms' outcomes between the trials, then it suggests that the matching adjustment is reducing the potential for bias. But even then the indirect comparison is still an observational, not randomised comparison.

This summary of the MAIC methodology highlights the serious limitations of the MAIC presented in the CS. Importantly, in the present context, the method is being applied in the absence of a common comparator. This means that there is nothing to use as a measure of the success of the matching to reduce confounding. There is a possibility that the adjustment on a small number of observed factors may actually increase the confounding due to unknown ones. As the matching process reduces the amount of data (the sample size of the ceritinib arm), precision is reduced.

Additional crizotinib data

As stated earlier, the ERG identified a third trial of crizotinib, conducted in the same ALK+ NSCLC population as the ASCEND-4 and PROFILE 1014 trials: the ALEX trial.[28] In response to a request from the ERG, the company conducted a second MAIC analysis including the crizotinib data from ALEX.

Conduct of the MAIC analysis

The CS reports that in the MAIC, the patient population in ASCEND-4 was re-weighted to match the average baseline characteristics of the patient population in PROFILE 1014. These weights were based on a propensity score model. After matching, efficacy outcomes were compared across balanced trial populations using an unstratified weighted log-rank test (for PFS and OS).

Based on the feasibility assessment, the key baseline characteristics that were reported in both trials were matched among the pooled population treated with ceritinib or platinum-based CT and

pemetrexed maintenance therapy in ASCEND-4, and the pooled population treated with crizotinib or platinum-based chemotherapy, without maintenance therapy, in PROFILE 1014. The characteristics included for the baseline adjustment represented those thought to have potential associations with any of the studied outcomes. These were:

- Age < 65 years
- % Female
- Race -% White
- Race - % Asian
- Current smoker %
- Former smoker %
- Adenocarcinoma %
- Eastern Cooperative Oncology Group (ECOG) performance status, 0-1 %
- Metastatic disease %
- Baseline brain metastases % (at randomisation for ASCEND-4)

After applying the weights to patients enrolled in ASCEND-4, all these selected baseline characteristics exactly matched those of PROFILE 1014, and the effective sample size for ASCEND-4 was reduced to 340 (as compared to the actual sample size of 376). The CS states that the extent of weighting required to achieve this balance was mild, and there was no evidence of extreme weights, consistent with good overlap between the populations.

For the second MAIC the weighting was slightly different, due to the different source of crizotinib data. The age characteristic was < 54 years; this was because, from the published source, the only data were that, in the crizotinib arm, the median age was 54 years (i.e. 50% were under 54). The characteristic 'Race-White %' could not be matched because, in the ALEX trial, race was reported only as Asian or non-Asian.

ERG Comments

The ERG has the following concerns about the MAIC analysis:

A comparison of study design and the features of ASCEND-4 and Profile 1040 (CS, Section D 2.2.1.Table 8), and the crizotinib arm of ALEX (Table 11), reveals that the key baseline characteristics are very similar across all three trials. This brings into question the need to 'match' at all. Essentially what this analysis is doing is drawing an implicit comparison between arms of unrelated trials. A limited amount of matching does not overcome the inherent unacceptability of generating precise quantitative estimates based on small observational comparisons.

The ERG also questions the method used for conducting the matching in the first MAIC. The cohorts to be compared in the MAIC were the ceritinib arm of the ASCEND-4 trial and the crizotinib arm of the PROFILE 1040 trial. The ERG suggests that matching should, therefore, have been between the characteristics of these cohorts. However, in the first MAIC the whole ASCEND-4 population was matched to the whole crizotinib population. The ERG has expanded the CS Table 19 to include the characteristics selected for matching for the ceritinib and crizotinib arms, from ASCEND-4, PROFILE 1040 (and ALEX), to explore the differences between the whole population and single-arm characteristics (Table 11).

Table 11 Baseline characteristics selected for matching for the ceritinib and crizotinib arms from ASCEND-4, PROFILE 1040 and ALEX

	ASCEND-4 Whole (N =376)	ASCEND-4 ceritinib	PROFILE 1014 Whole (N=343)	PROFILE 1014 crizotinib N=172	ALEX Whole N=303	ALEX crizotinib N=151
Age < 65 years, %	78.5 (78)	75.7	84.0	86.6	77	??
Female, %	57.4	54	61.8	60	56	58
Race – White, %	53.7	55	51.3	53	NR	NR
Race – Asian, %	42.0	40	45.8	45	45.5	46
Current smoker, %	8.0	8	4.4	6	5.6	3
Former smoker, %	30.9	35	32.1	33	31.7	32
Adenocarcinoma, %	96.5	95	93.9	94		94
ECOG performance score 0 or 1, %	93.6*	93.1*	94.8	94	93.4	93
Metastatic disease, %	96.3	95	98.0	98	40.2	96
Brain metastases, %	32	31	26.8**	26**	40.3	38

*ECOG status is WHO status in ASCEND-4 trial. **Only treated BM permitted in PROFILE1014

The data in Table 11 show that the differences between the whole ASCEND-4 and PROFILE 1014 populations are not exactly reflected in the differences between the single ceritinib and crizotinib arms. Given that only mild adjustment was required to match the ASCEND-4 to the PROFILE 1014 population and yet it resulted in a large increase in the median PFS for ceritinib and a lowering of the HR, the question arises, what would the results be if the specific cohorts had been matched? Furthermore, it should be noted that in the second MAIC analysis (using the ALEX crizotinib data) the matching was only from the ceritinib arm of ASCEND to the crizotinib arm of ALEX; the methods for the two MAICs were inconsistent. The HR generated by the MAIC analysis is an

important parameter in the cost-effectiveness model directly informing the quality-adjusted life-years (QALYs) to be gained on treatment.

An additional question regarding the matching relates to the generalisability of the trial arms to reflect clinical practice. Whilst all the trials can be considered reasonably generalisable to clinical practice, Table 12 below compares them to a recently presented retrospective cohort of real-world patients from UK and Europe.[29]

Table 12 Baseline characteristics of participants in ASCEND-4, PROFILE 1014 compared with a real-world cohort from Davis et al. 2017[29]

	1st-line ceritinib	1st-line crizotinib	1st-line crizotinib	1st-line crizotinib
	ASCEND-4	PROFILE 1040	ALEX	Davis 2017[29]
Country	International	International	International	UK/EUR
Age – years Mean (SD)	54.5 (12.8)		53.8 (13.5)	[redacted]
Age – median (range) years	55 (22-81)	52 (22-76)	54 (18-91)	
Male %	46%	40%	42%	[redacted]
Ethnicity White/Caucasian				[redacted]
Asian				
Smoking status % Former or present	43%	40%	42%	[redacted]
Histology - Adenocarcinoma	95%	94%	94%	[redacted]
ECOG performance status – 0 or 1 (%)	93%	94%	94%	[redacted]

This comparison suggests that although the trials are similar, ASCEND-4 was closest to the real-world UK/European cohort in terms of age, sex, smoking status and ECOG status. Thus, matching to either PROFILE 1014 or ALEX will not have enhanced the generalisability of the results of the comparison, it may well have made them less reflective of those to be expected in clinical practice.

Across both MAICs, matching for brain metastases was problematic. The CS states that ASCEND-4 and PROFILE 1040 differed in terms of the inclusion criteria relating to patients with brain metastases. The CS states that, "among patients with brain metastases at baseline, all patients in the PROFILE 1014 trial had received radiotherapy, had stable disease for at least two weeks before entering the trial and were no longer receiving corticosteroid therapy. In contrast, in ASCEND-4 only 39% of patients with brain metastases received radiotherapy prior to study entry. This difference in

inclusion criteria is likely to favour crizotinib, as the benefits of radiotherapy may have contributed to the intracranial responses observed in PROFILE 1014."

In their clarification response they further state,

"Although the MAIC adjusted for the baseline presence of brain metastases in the PROFILE 1014 population, this cross-trial difference in the inclusion criteria for patients with brain metastases was not adjusted for in the MAIC. If patients derived some lasting benefit from this prior radiation treatment, this could have created a bias against ceritinib versus crizotinib in the MAIC of PFS and OS outcomes."

However, the ERG notes that PROFILE 1014 enrolled only treated BM and, therefore, it does not seem appropriate to match the percentage of all BM in ASCEND-4 to the percentage of treated BM, in PROFILE 1014. Similarly, the ALEX trial reported only the proportion of patients with CNS metastases, not specifically brain metastases. Again it does not seem appropriate to match the percentage of all BM in ASCEND-4 to the percentage of CNS metastases in ALEX. The direction of effect of this (mis)matching is unclear to the ERG.

4.4.2 Results of the indirect comparison (MAIC analysis)

As reported in the CS, the results of the two trials are given in Table 13.

Table 13 Efficacy outcomes for ASCEND-4 and PROFILE 1014 (CS, Appendix Table 10)

Outcome variables	ASCEND-4 (Centrally-assessed results)		PROFILE 1014 (IRR-assessed results)	
	Ceritinib	Chemotherapy	Crizotinib	Chemotherapy
Sample size, N	189	187	172	171
Progression-free survival				
Hazard ratio,[a] (95% CI)	0.55 (0.42-0.73)		0.45 (0.35-0.60)	
Number of events, n (%)	89 (47.1)	113 (60.4)	100 (58.1)	137 (80.1)
Median, month (95% CI)	16.6 (12.6-27.2)	8.1 (5.8-11.1)	10.9 (8.3-13.9)	7.0 (6.8-8.2)
Overall survival				
Hazard ratio,[b] (95% CI)	0.73 (0.50-1.08)		0.82 (0.54-1.26)	
Number of deaths, n (%)	48 (25.4)	59 (31.6)	44 (25.6)	46 (26.9)
Median, month (95% CI)	NR (29.3- NR)	26.2 (22.8- NR)	NR	NR
1-year OS rate, % (95% CI)	83.6 (77.4-88.2)	78.7 (71.9-84.1)	84 (77-89)	79 (71-84)

CI, confidence interval; NR, not reached; PR, partial response, [a] Hazard ratio for progression or death between ceritinib/crizotinib and the corresponding chemotherapy was reported. [b] Hazard ratio for death between ceritinib/crizotinib and the corresponding chemotherapy was reported.

Table 14 presents the results of the indirect comparison of ceritinib and crizotinib, and compares the before and after matching results. The results of both MAIC analyses are included.

Table 14 MAIC results, before and after matching ASCEND-4 vs PROFILE 1040 and ASCEND-4 vs ALEX (Adapted from the CS Table 20 and clarification response Methods and Results Summary Table 2)

	Before matching				After matching			
	MAIC 1 (CS)		MAIC 2 (Company's clarification response		MAIC 1 (CS)		MAIC 2 (Company's clarification response	
	Ceritinib (ASCEND-4) N=189	Crizotinib (PROFILE 1014) N=172	Ceritinib (ASCEND-4) N=189 (ESS=174)	Crizotinib (ALEX) N=151	Ceritinib (ASCEND-4) N=189 (ESS=171)	Crizotinib (PROFILE 1014) N=172	Ceritinib (ASCEND-4) N=189 (ESS=174)	Crizotinib (ALEX) N=151
PFS Median, month (95% CI)[c]	16.6 (12.6-27.2)	10.8 (8.5-13.8)	16.6 (12.7-27.2)	10.4 (7.6-14.5)	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR (CER vs. CRZ), 95% CI	[redacted]		[redacted]		[redacted]		[redacted]	
OS Median (month)	NR	NR	NR	NR	NR	NR	NR	NR
OS HR (CER vs. CRZ), 95% CI	[redacted]		[redacted]		[redacted]		[redacted]	
1-year OS rate, 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The results show that, without matching, the indirect comparison using the different sources of crizotinib generates a HR of [redacted]. With matching the first MAIC generates a (unreasonably) high median PFS on ceritinib and an improved HR of [redacted]. The second MAIC analysis generates similar values for median PFS and a slightly increased HR of [redacted]. The two matched HRs for OS were similar ([redacted] and [redacted]) and lower than the unmatched estimate of [redacted].

ERG Comment

A naïve comparison of two single-arm trials would be considered as being highly uncertain. The MAIC analyses attempt to improve the reliability of such a naïve approach. However, given that the matching resulted in the loss of some data (the sample size of the ceritinib cohort was reduced in both MAICs), that the balancing in terms of BM was questionable, and that there was no common comparator to test the efficacy of the matching, it is unclear whether the results derived from the matched adjusted analyses are any more reliable than those from the unadjusted data.

The similarity of the crizotinib data from the two trials provides some modest assurance regarding the reliability of the results. However, the comparisons with ceritinib are still observational and subject to a high risk of bias. Due to the questionable method used for matching in the first MAIC, the results of the second MAIC, utilising the ALEX crizotinib data, might be expected to be more accurate, though for other unknown reasons, they might not be. Both answers could be wrong. The OS results are even more uncertain, being the result of an observational comparison of immature highly uncertain data.

Ceritinib vs crizotinib for intracranial effects

The intracranial effects of ceritinib and crizotinib were not compared in the MAIC analyses. However, the ERG notes that an implicit comparison is made in the submission: the potential benefits of ceritinib regarding its ability to cross the blood-brain barrier and the resultant potential to prevent or treat BM are stated. In contrast, the limitations of crizotinib, in treating intracranial metastases, are highlighted. Specifically, on page 17 of the CS, it states that disease control is poor with crizotinib, with many patients developing BM during therapy with crizotinib. The ERG notes that no evidence is presented in the CS to indicate the rates of new BM during treatment with ceritinib.

Also on page 71, the CS states that PFS is significantly shorter with crizotinib in patients with BM at baseline compared with those without BM. The actual results for this subgroup analysis for crizotinib from the PROFILE 1040 trial are median PFS of 9 months (95% CI 6.8 to 15.0 months) in those with treated BM at baseline, compared with 11.1 months (95% CI 8.3 to 14.0 months) in those without. This subgroup difference is much smaller than that seen for ceritinib from the ASCEND-4 trial: 10.7 months (95% CI 8.1 to 16.4 months), compared with 26.3 (15.4 to 27.7 months), respectively. Whilst for the reasons already discussed, the results cannot be directly compared between ceritinib and crizotinib, the ERG suggests that they do not provide evidence for a specific intracranial benefit with ceritinib. Further analysis and data are required to explore this further.

4.4.3 Adverse effects of ceritinib

Information on the adverse effect profile of ceritinib is provided in Section B2.10 of the CS. The treatment exposure data are summarised in Table 15 below.

Table 15 Summary of ceritinib exposure and dose adjustments in ASCEND–4 (CS, Table 21)

	Ceritinib (n=189)	**Crizotinib (PROFILE 1040)**	**Crizotinib (ALEX)**
Median duration of treatment exposure, weeks (IQR)	66.4 (30.0-83.7)	10.9 months (range 0.4-34.3	10.7 months (range 0-27)
Median relative dose intensity, % (IQR)	78.4 (63.2-97.5)	Not published	Mean (SD) 92.4% (14.1%)
Average dose, mg (mean±SD)	626.0±124.8	-	-
Proportion of patients requiring ≥1 dose reduction, n (%)	128 (67.7)	-	-
Median time to first dose reduction, weeks	9.1	-	-
Proportion of patients requiring ≥1 dose interruption, n (%)	148 (78.3)	-	-
Median time to first dose interruption, weeks	6.1	-	-

The adverse events reported for the ceritinib arm of the ASCEND-4 trial are summarised in Table 16.

Table 16 Overall summary of adverse events in the ceritinib treatment group of ASCEND-4 (n=189) (CS, Table 22)

	All grades	**Grade 3 or 4**
AEs, n (%)	189 (100)	148 (78)
AEs suspected to be related to treatment, n (%)	184 (97)	123 (65)
SAEs, n (%)	70 (37.0)	59 (31.2)
SAEs suspected to be related to treatment, n (%)	30 (15.9)	23 (12.2)
Withdrawal due to AEs, n (%)	21 (11.1)	12 (6.3)
Withdrawal due to AEs considered related to treatment, n (%)	10 (5)	
Total deaths during treatment[a], n (%)	11 (6)	
Deaths related to study drug	None	

Adverse events were common on ceritinib. All patients experienced at least one adverse event (AE), most experienced at least one AE related to ceritinib, and 65% experienced at least one Grade 3 or 4 event. However, only 5% of patients withdrew due to AEs, demonstrating that most were manageable with dose adjustments, dose interruptions, and supportive medication. The CS states that no new safety information emerged that would substantially alter the safety profile of ceritinib, as demonstrated in earlier studies in ALK+ NSCLC.

The incidence of specific AEs is reported in Tables 23 and 24 of the CS. The most common AEs were gastrointestinal, diarrhoea (85%), nausea (69%) and vomiting (66%), followed by elevation in the serum levels of liver enzymes (alanine aminotransferase (ALT) (60%), aspartate aminotransferase (AST) (53%), gamma-glutamyltransferase (GGT) (37%), and alkaline phosphatase (29%). These AEs were the most commonly reported of those related to ceritinib treatment.

Elevated liver enzymes were the most frequently reported grade 3/4 AEs (ALT 31%, GGT 29%, AST 17% and alkaline phosphatase (7%)). Grade 3/4 diarrhoea and vomiting were both reported in 5% of ceritinib patients. Other Grade 3/4 AEs were reported in less than 5% of patients.

The CS reports that the elevation of liver enzymes is a recognised effect of ceritinib and regular monitoring of liver enzymes is recommended in the SmPC for ceritinib.[25]

QTc prolongation was observed in 19 (10%) ceritinib patients in the ASCEND-4 study and was grade 3 in four patients. QTc prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death. This AE had been observed in previous clinical studies of ceritinib, and patients receiving medications associated with a risk of QTc prolongation were excluded from the study. All grade 3 events were considered to be related to ceritinib treatment, and were managed with dose adjustment or interruption. No patients discontinued treatment for QTc prolongation, and there were no grade 4 events or cases of Torsade de pointes. A further six patients reported other bradycardia events, only two of which were considered to be related to ceritinib, and neither was grade 3/4. The SmPC for ceritinib recommends periodic monitoring of electrocardiograms and electrolytes in patients with known risk factors for QTc prolongation, and heart rate and blood pressure should be monitored regularly in all patients.[25]

Other AEs highlighted in the SmPC for ceritinib and covered in the CS are hyperglycaemia, and severe, life-threatening, or fatal interstitial lung disease or pneumonitis. The SmPC recommends that patients should be monitored for fasting plasma glucose prior to the start of treatment with ceritinib; this is not stated in the CS. The CS reports that in ASCEND-4, interstitial lung disease/pneumonitis was reported in four patients; only one case was grade 3, and there were no grade 4 cases. One grade 2 case was suspected to be related to treatment. Two patients required dose adjustment/interruption and two discontinued therapy. One patient died, but the pneumonitis was not considered to be related to treatment.

The CS claims that the AE profile for ceritinib is better than that for crizotinib. The ERG is uncertain that this is the case: is it better or just different? Using the data available on the NICE website for crizotinib, from TA406, the ERG compared the rates of AEs in ASCEND-4 and PROFILE 1014

(Table 17). There is no clear difference between the rates of AEs. It is noteworthy that dose interruption and temporary discontinuation were much more common with ceritinib; this could suggest a more troublesome AE profile, requiring more active management of ceritinib treatment than for crizotinib, or it could be reflective of a better understanding of the potential risks associated with ALK inhibitors during the ASCEND-4 trial, compared with the earlier PROFILE 1040 trial.Comparison of AEs highlighted in the drugs' respective SmPCs, reveals that hepatotoxicity, interstitial lung disease/pneumonitis, QT-interval prolongation, and bradycardia are associated with both drugs. Vision loss is very rarely associated with crizotinib but not ceritinib; Grade 3 or 4 neutropenia is common with crizotinib but rare with ceritinib. Cardiac failure, gastrointestinal perforation, and renal impairment have been associated with crizotinib, whereas gastrointestinal toxicity, hyperglycaemia and lipase/amylase elevations are associated with ceritinib.

Table 17 Comparison of rates of adverse events for ceritinib (ASCEND-4 trial) with those of crizotinib (PROFILE 1040 trial)

Adverse event, No. of patients (%)	Crizotinib (PROFILE 1040) (n=171)		Ceritinib (ASCEND-4) (n=189)	
	All causality	Treatment-related	All causality	Treatment-related
With AEs	170 (99.4)	168 (98)	189 (100)	184 (97)
With serious AEs	58 (33.9)	18 (10.5)	70 (37.0)	30 (15.9)
With Grade 3 or 4 AEs	97 (56.7)	60 (35.1)	148 (78)	23 (12.2)
Permanent discontinuation	21 (12.3)	8 (4.7)	21 (11.1)	10 (5%)
Dose reduction	11 (6.4)		68%	
Temporary discontinuation	70 (40.9)		148 (78.3)	
Total deaths during treatment, n (%)	20 (12)	None	11 (6)	None

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

4.6 Conclusions of the clinical effectiveness section

Although the NICE scope included chemotherapy as a comparator for this appraisal, since the positive NICE recommendation for crizotinib in the first-line treatment of advanced or metastatic ALK+ NSCLC, crizotinib has become the standard of care for this indication. It is, therefore, appropriate that crizotinib is the sole comparator considered in the CS.

A systematic review was conducted to identify trials of ceritinib and the comparator crizotinib. The methods used were generally appropriate, but because the search filter applied depended heavily on MeSH terms, some relevant records were missed. In particular, one directly relevant trial of crizotinib (comparing it with alectinib in the population of interest) was identified by the ERG.

The evidence for ceritinib was based on a single trial, ASCEND-4. This was a RCT of ceritinib as first-line treatment in ALK+ advanced or metastatic NSCLC. ASCEND-4 was a Phase III, international, multicentre open-label RCT comparing ceritinib with pemetrexed/cisplatin plus pemetrexed maintenance therapy. When this trial was planned this pemetrexed regimen was the latest standard of care in untreated advanced or metastatic NSCLC.

A comparison of the patient characteristics in the ceritinib arm of ASCEND-4 with those from a recently presented retrospective chart review of patients treated with first-line crizotinib in the UK and Europe, indicates that the trial patients were slightly younger, had a higher proportion of females and a lower proportion of former or current smokers, and, as might be expected in a trial, a higher proportion of trial patients were ECOG status 0 or 1. The clinical adviser to the ERG commented that, except that a higher proportion of men might be expected in clinical practice, the trial population can be considered generalisable to NHS practice.

ASCEND-4 was a good-quality trial. Although the open-label treatment administration made it susceptible to bias, this was ameliorated by the primary (PFS) outcome assessment being assessed centrally, and the key secondary outcome of OS being an objective outcome. There was some bias in patient withdrawals, which were higher in the CT arm. For the assessment of OS, a major limitation of the trial design was that patients were allowed to remain on therapy despite disease progression and to switch from CT to ceritinib. This resulted in confounding of the OS outcome. Follow-up was also too short for a definitive assessment of OS.

The results found that ceritinib prolonged PFS compared with CT in all patients: median PFS was 16.6 (12.6–27.2) on ceritinib, compared with 8.1 (5.8–11.1) on CT (HR 0·55 (0.42–0.73). The effects of ceritinib were consistent across all subgroups considered, except for the subgroups with previous adjuvant chemotherapy, where the sample size was very small. The treatment benefit in patients with

brain metastases at baseline was numerically smaller that in those without (HR 0.80, compared with 0.45). Median PFS was greatest in patients without brain metastases who were treated with ceritinib (26.3 months).

At the time of the analysis (24 June, 2016), the OS data were immature; only 107 events (42% of the required OS events) had occurred: 48 (25.4%) patients randomised to the ceritinib group had died, compared with 59 (31.6%) randomised to CT. Median OS was 'not reached' in the ceritinib group and was estimated as 26.2 months in the CT group (HR 0.73, p=0.056). A sensitivity analysis that adjusted for crossover of CT patients to ceritinib, after disease progression, had little impact on the result (HR 0.73, 95% CI 0.49 to 1.10), probably due to the limited follow-up data.

The results, both from central and local assessment, favoured ceritinib in terms of tumour response, time to first response and duration of response. The results for intracranial tumour responses in patients with measurable brain metastases at baseline indicated that the intracranial tumour responses to ceritinib and to CT were similar to the whole-body responses. Intracranial outcomes were not assessed in patients without BM at baseline, therefore, the impact of ceritinib in preventing the development of new BM has not been assessed in the CS.

Time to definitive symptom deterioration was assessed using both the LCSS and QLQ-LC13 questionnaires, and the results for both tools demonstrated a statistically significant difference in favour of ceritinib.

In current clinical practice the standard of care for first-line treatment for ALK+ advanced or metastatic NSCLC is crizotinib. Unfortunately, there is no trial that directly compares ceritinib with crizotinib. Two directly relevant trials crizotinib were identified: PROFILE 1040, which was included in the CS, and ALEX, identified by the ERG. Both PROFILE 1040 and ALEX were similar in their population and design to ASCEND-4. However, both crizotinib trials used an older form of CT that did not include pemetrexed maintenance therapy, and which has been shown to be significantly less effective than the CT used in the ASCEND-4 trial. Consequently, these three trials cannot be combined in an indirect analysis through a common comparator. The CS therefore presents a Matching-Adjusted Indirect Comparison (MAIC) of ceritinib and crizotinib using only the ALK inhibitor arm of the ASCEND-4 and PROFILE 1040 trials (MAIC 1). The company then presents a second MAIC using only the ALK inhibitor arm of ASCEND-4 and ALEX (MAIC 2).

The results of these comparisons were that the HR for PFS was [redacted] (MAIC 1) or [redacted] (MAIC 2). The HR for OS was [redacted] (MAIC 1) and [redacted] (MAIC 2).

The ERG notes that the MAIC method was developed as an improvement on standard indirect comparison methods, which use aggregate data only; it was not developed as a method to be used without a common comparator arm. There are significant limitations to this type of analysis. Despite the matching, the analysis can still be subject to the effects of residual confounding due to unobserved differences between the trials. In the present context, the method is being applied in the absence of a common comparator. This means that there is nothing to use as a measure of the success of the matching to reduce confounding. There is a possibility that the adjustment on a small number of observed factors may actually increase the confounding due to unknown factors. Furthermore, as the matching process reduces the amount of data (the sample size of the ceritinib arm), precision is reduced. The ERG also notes that in MAIC 1 the whole ASCEND-4 population was matched to the whole crizotinib population. The ERG believes that this is inappropriate given that only the ceritinib and crizotinib arms were being compared in the analysis; in MAIC 2 only the ceritinib and crizotinib arms were matched.

In summary, whilst the ERG acknowledges that an indirect comparison of individual trial arms was the only option available to compare ceritinib and crizotinib, it is unclear whether the results derived from the matched adjusted analyses are any more reliable than those from the unadjusted data; the comparisons with ceritinib are still observational and subject to a high risk of bias. The OS results are even more uncertain, being the result of an observational comparison of immature highly uncertain data.

The intracranial effects of ceritinib and crizotinib were not compared in the MAIC analyses. The ERG suggests that the data presented in the CS do not provide evidence for a specific intracranial benefit with ceritinib.

Adverse events were common on ceritinib in the ASCEND-4 trial though most could be managed with dose adjustment. Dose adjustment was common: 68% of ceritinib patients required at least one dose reduction and 78% required at least one dose interruption. The median relative dose intensity was 78%. This level of dose adjustment is higher than that seen in the ALEX trial for crizotinib: dose reduction 25%; 19% dose interruption; and dose intensity was 92.4%.[28]

In summary, there is good evidence that ceritinib is effective in prolonging PFS in patients with previously untreated ALK+ advanced or metastatic NSCLC. The effect on OS is as yet uncertain and longer follow-up data are awaited. An observational comparison suggests that ceritinib may be more effective in prolonging PFS than crizotinib, but this comparison is at a high risk of bias and is highly uncertain.

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, Section 3.1 pp 79-81 and Appendix G) and quality-of-life studies (CS, Section 3.4.1 pp 94 and Appendix H).
- A report on the *de novo* economic evaluation conducted by the company. The report outlined the intervention; comparators and patient population; the modelling methods; the resource components and unit costs; data input sources and assumptions; the base-case results; and sensitivity analysis (CS, Section 3, pp 82-123).
- The company's electronic Excel-based *de novo* model.

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 included additional scenario analyses requested by the ERG.

5.1 ERG's comments on the company's review of the cost-effectiveness evidence

The company conducted a systematic literature review to identify economic evaluations of ceritinib and other targeted therapies for the treatment of patients with advanced or metastatic ALK+ NSCLC. The ERG's critique of the systematic review, presented by the company, is given below.

5.1.1 Searches

5.1.1.1 Reporting

The databases used for the cost-effectiveness review are reported as MEDLINE, MEDLINE in Process (via OVIDSP), Embase (via OVIDSP), the Cochrane Library (via OVIDSP) and Tufts Cost-Effectiveness Registry. The Cochrane databases used included: Health Technology Assessment (HTA) Database and NHS Economic Evaluation Database (NHS EED). This is reported in section G.1.1. Published cost-effectiveness studies of the company submission.

The search strategies used in MEDLINE, Embase and the Cochrane Library are fully reproduced in section G.1.3, and the date that they were conducted is given. No information is given about the searches of the Tufts Register, although it is reported in the PRISMA flow diagram that 100 records were identified from this source.

The numbers of records retrieved from the searches matches the number given in the PRISMA diagram on page 74.

The ISPOR conference websites (2014 to 2017) were used to identify potentially relevant posters and abstracts.

5.1.1.2 Strategy

The strategy used in MEDLINE, Embase and the Cochrane Library consisted of the three sections used in the effectiveness review i.e. 1) non-small-cell lung cancer 2) advanced stage and 3) anaplastic lymphoma kinase, combined with the AND search operator, combined with a further set of search statements 4) to identify records about crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib. Finally, limits were then applied in terms of publication type, language (English) and date.

Sections 2 and 3 of the search strategy relied solely on the use of free-text searching of the title and abstract fields, and did not use any subject headings (MeSH or Emtree), although terms were available, e.g., Receptor Protein-Tyrosine Kinases (MeSH) that could have been included in section 3, alongside line 8; similarly, Neoplasm Metastasis (MeSH) could have been included in section 2, alongside line 6.

It is not known whether this limitation could have resulted in any additional studies not being identified.

None of the free-text search statements in sections 1, 2 or 3 made use of the adjacency operator, which has the potential to improve the relevance of the records identified and to increase the overall precision of the search strategy. There are also some potentially relevant phrases that would not be identified by the current line 8, e.g., "anaplastic lymphoma receptor tyrosine kinase". This could be corrected by either using the relevant MeSH term, e.g., *Receptor Protein-Tyrosine Kinases* or by making use of the adjacency operator, e.g., *ALK adj4 rearranged.* Again, it is not known whether this could have resulted in any additional studies not being identified.

5.1.1.3 Use of search filters

The costs filter, used in both the MEDLINE and Embase searches, relies entirely on free-text terms, without the use of any of the relevant thesaurus terms. In MEDLINE, these MeSH terms are available*:* "Costs and Cost Analysis, Cost Allocation, Cost-Benefit Analysis, Cost Control, Cost of Illness, Cost Sharing, Health Care Costs, and Health Expenditure. In Embase, these Emtree terms are available: health economics, economic evaluation, health care cost, and pharmacoeconomics.

It is not known whether potentially relevant records, present in the results set at line 20, could have been removed by using these "costs" search filters.

In the HTA Database and NHS EED (via the Cochrane Library) the search was restricted to the title only rather than using the title, abstract and keyword option. Choosing to search the title only is a very restrictive option and has the potential to miss relevant records. In addition, a search filter (lines 23 to 34) was applied to these searches to limit the results to records about costs and resource use. This was entirely unnecessary as the two databases being searched had already had their content filtered to cover these areas.

This unnecessary use of the filter removed nine potentially relevant records (line 11 and line 22) from the search results at line 34.

The additional restrictions by language and date, in lines 40 and 41, were unnecessary as no records were available at line 39.

There were nine records from the HTA Database that were identified by the search strategy at line 11, but subsequently removed by the inclusion of various limits and filters (listed in Section 10, Appendix).

An alternative approach to searching NHS EED and HTA Databases would have been to use a simple search consisting entirely of drug names, e.g., ("crizotinib":ti,ab,kw or ceritinib:ti,ab,kw or alectinib:ti,ab,kw or brigantinib:ti,ab,kw or lorlatinib:ti,ab,kw). This would have been sufficient to

identify that there were no matching NHS EED records and 14 HTA Database records, including some of those listed above.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria used in the study selection are listed in **Error! Reference source not ound.**.

Table 18: Inclusion/exclusion criteria for study selection (adapted from CS, Table 17, Appendices, p 73)

	Inclusion criteria	Exclusion criteria
Population	Adults aged >18 years of age Patients with advanced or metastatic (stage IIIB or IV) ALK+ NSCLC If the study assessed a mixed population (e.g., early stage and advanced/late stage; ALK+ and wild type), then studies where the outcomes of interest are reported for a subgroup of patients in the included population are included	Not NSCLC disease (e.g. small cell lung cancer) Early stage of NSCLC (i.e. not advanced or metastatic NSCLC or stage IIIB or stage IV NSCLC) Not ALK+ (and no separate subgroup data reported for ALK+ population)
Interventions	Crizotinib or Xalkori (monotherapy or combination therapy) Ceritinib or Zykadia (monotherapy or combination therapy) Alectinib or Alecensa (monotherapy or combination therapy) Brigatinib or Alunbrig (monotherapy or combination therapy) PF-06463922 or Lorlatinib (monotherapy or combination therapy)	Non-medical therapy (supportive care, radiotherapy, surgery)
Comparators	Any	No restriction
Outcomes	Cost utility (ICER, QALY) Cost effectiveness (ICER, LYG) Cost consequences Health equivalent years Health utility index Preference score	No economic model outcomes of interest
Study design	Economic modelling studies	Interventional or observational studies Non-economic modelling studies
Publication type	Systematic reviews or meta-analyses of economic model data will be maintained during database search and during screening in order to identify or confirm selected studies	Case reports Commentaries and letters Recommendations/ guidelines Non-systematic-review articles Methods articles/protocols Clinical trials Non-human studies
Time period	Full-text references published 2007 or later; conference abstracts published 2014 or later	Full-text references published before 2007; conference abstracts published before 2014
Language	English only	Non-English

ALK, anaplastic lymphoma kinase; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NSCLC, non-small cell lung cancer; QALY, quality-adjusted life year

The ERG considers the inclusion and exclusion criteria to be reasonable, apart from the interventions section. The ERG notes that chemotherapy treatments were not included in the interventions list, and this exclusion may have resulted in studies relevant to the NICE scope being missed. However, given that the ERG considers the changes from the scope, made by the company in the decision problem, appropriate, this omission from the inclusion criteria is unlikely to have led to any important studies being missed. The exclusion of non-English studies may have led to some studies being missed, although the ERG does not consider this very likely. Also, the publication type inclusion criteria are confusing, as this was not an inclusion criterion – these studies would not be included in the systematic review, however, this would not lead to any studies being missed.

5.1.3 Studies included and excluded in the cost-effectiveness review

According to the PRISMA flow chart presented in the CS appendices (Appendix G, Figure 2, p 75), a total of 423 potentially relevant records (which included 191 potentially relevant articles and 232 potentially relevant conference abstracts) were identified in the company's review. Of these, 409 records were excluded at the initial screening stage. The remaining 14 records (5 published studies, 8 conference abstracts, and 1 systematic review) were assessed based on their full text. Following full-text screening, 13 articles (5 published studies and 8 conference abstracts) were included in the systematic literature review. The 14th record was a systematic review and so was excluded based on study design. Of the 13 identified articles, seven publications reported information on six cost-effectiveness analyses. Full details of these six economic evaluations are presented in Table 27 of the main CS, pp 80-1, and Tables 20 and 21 in the appendices pp 117-120. Two evaluations included ceritinib as a comparator, and were based in the USA. Another study, which included crizotinib as a comparator, was a UK economic evaluation; this economic evaluation was conducted as part of a previous NICE technology appraisal; TA 296.[37] A summary of these three evaluations is presented in **Error! Reference source not found.** below.

Table 19: Summary of published UK and ceritinib cost-effectiveness studies

Study	Population		Interventions	Model description	Estimated ICER
	Disease subtype	Line of therapy			
Upadhyay 2015[38]	EML4-ALK+ NSCLC	First-line	Ceritinib vs Standard therapy (cisplatin, gemcitabine, pemetrexed, erlotinib)	Decision analytic model with embedded Markov model was used. The health states used were not reported. A lifetime horizon was used.	$21,263 per QALY (ceritinib vs chemotherapy)

Carlson 2017[39]	ALK+ advanced NSCLC	Second-line	Crizotinib vs Alectinib	Partitioned survival methods were used. The time horizon was not reported.	$31,180 (alectinib vs ceritinib)
Morgan 2017[40]	ALK+ advanced NSCLC	First-line	Crizotinib vs Pemetrexed + carboplatin/cisplatin	A partition survival model was used. Lifetime horizon was used.	£47,291 (crizotinib vs chemotherapy
EML4, echinoderm microtubule-associated protein-like 4; ALK, anaplastic lymphoma disease; NSCLC, non-small-cell lung cancer; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year					

The company did not attempt any synthesis of the identified cost-effectiveness studies, which the ERG deems appropriate. The CS states that the UK study (Morgan et al. 2017[40]) was the only study deemed relevant to the current submission and was used to inform inputs for the *de novo* model. The ERG considers this to be, generally, appropriate, however, the other identified economic evaluation of ALK+ could have provided the company with additional information on the input parameters, e.g., second-line treatments, duration of treatments, and utility values. The company presented a table comparing the current appraisal with the Morgan et al. 2017 model, which presented some justifications for the differences (CS, Table 29, p 85).

5.1.4 Conclusions of the cost-effectiveness review

The review highlights the lack of evidence on the cost-effectiveness of ceritinib, as a first-line treatment. The company's review did not identify any studies assessing ceritinib for the first-line treatment of advanced or metastatic NSCLC, in a UK setting. A number of studies were identified, but these were studies evaluating ceritinib in a non-UK setting, or not evaluating ceritinib as one of the comparators. The company's review identified a study evaluating crizotinib, as a first-line treatment, in a UK setting, which was used as the source of evidence on which to base the model developed as part of the current submission.

5.2 ERG's summary and critique of the company's submitted economic evaluation

An overall summary of the company's approach, and signposts to the relevant sections in the company's submission, are reported in Table 20.

Table 20: Summary of the company's economic evaluation (and signposts to the CS)

	Approach	**Source / Justification**	**Signpost (location in the CS)**
Model	A decision model based on a partitioned survival approach. Cycle length was one month and a 20-year time horizon was used.	The submission states that this type of model has been used in many previous NICE submissions to model advanced or metastatic cancers.	Section B3.2.2 pages 82-86

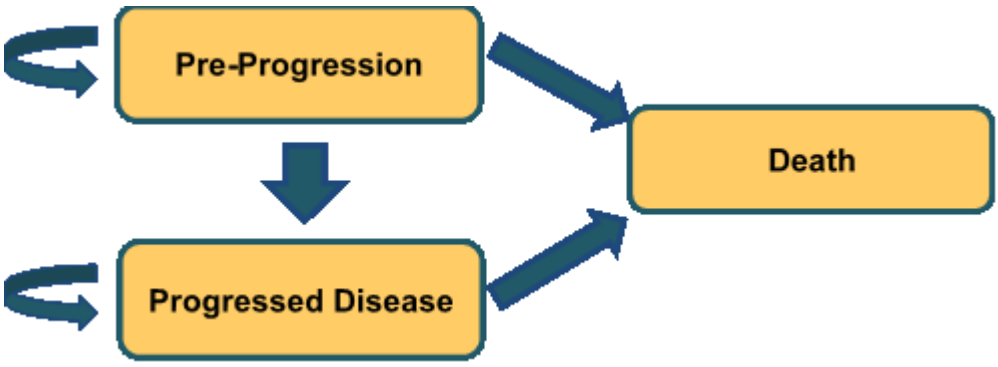
	Approach	**Source / Justification**	**Signpost (location in the CS)**
States and events	The model consisted of three mutually exclusive health stated: (i) progression free (ii) progressed disease (iii) death.	These health states were selected to capture the progressive nature of ALK+ NSCLC and once again are in line with previous NICE submissions which have modelled advanced or metastatic cancers.	Section B3.2.3 pages 83-86
Comparators	The comparator used in the company's model was crizotinib.	Crizotinib is currently the only ALK inhibitor which is approved by NICE for untreated ALK+ NSCLC patients in the UK (TA406)[37] The CS also states that it was the only appropriate comparator as per their clinical experts.	Section B3.2.2 pages 82-86
Subgroups	No subgroup analysis was undertaken.	The provided justification in the CS was that the clinical data indicated that the benefits of ceritinib over chemotherapy were consistent across the entire patient population	Section B3.9 page 120
Treatment effectiveness	Clinical outcomes included were PFS and OS. PFS and OS for ceritinib were derived from the ASCEND-4 trial[30]. PFS and OS for crizotinib were derived from the PROFILE-1014 trial[23]. The relative efficacy of ceritinib vs crizotinib was estimated using the indirect comparison method, MAIC. PFS and OS curves for ceritinib were estimated by fitting parametric functions to patient-level time-to-event data from the ASCEND-4 trial. The HR method was used to estimate PFS and OS curves for the crizotinib arm using the relative efficacy estimated from the MAIC.	The CS considers crizotinib to be the only relevant comparator for this submission. There was no relevant head-to-head RCTs available and so MAIC methods were used to indirectly compare ceritinib and crizotinib using the ASCEND-4 trial and the PROFILE-1014 trial[23, 30].	Section B3.3 pages 87-93
Adverse events	Adverse events for first-line treatments were included if they were grade 3/4 and if they had an incidence rate higher than 5% for either comparator. The resource use associated with adverse events was calculated from previous submissions and was based on clinical expert opinion. Adverse events were not included as disutilities within the model.	Adverse event rates were taken from the ASCEND-4 trial for ceritinib and from the PROFILE-1014 trial for crizotinib.	Section B3.3.3 page 91 Section B3.5.5 pages 103-104
Health-related quality of life	Pre-progression utilities were derived from the EQ-5D data collected in the ASCEND-4 and PROFILE-1014 trials. Post-progression utilities for both ceritinib and crizotinib patients were derived from Chouaid et al (2013)[41].	EQ-5D data were collected from pre-progression ceritinib patients in the ASCEND-4 trial and for crizotinib patients in the PROFILE-1014 trial. EQ-5D data were not collectedly systematically in either ASCEND-4 or PROFILE-1014 for post-progression.	Section B3.4 pages 94-95

	Approach	Source / Justification	Signpost (location in the CS)
Resource utilisation and costs	The cost categories included were: drug and drug administration costs, progression-free health state costs, progressed-disease health state costs, second-line treatment costs, adverse event costs, and terminal care costs.	Drug acquisition costs were sourced from MIMS and eMIT. Resource use items were based on previous NICE submissions and elicited clinical expert opinion. End-of-life care costs were derived from Georghiou and Bardsley (2014)[42]	Section B3.5 pages 96-104
Discount rates	The costs and benefits were discounted at 3.5% per annum.	In accordance with the NICE reference case.	Section B3.2.2 page 83
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic 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 B3.8 pages 110-119
CS, company submission; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; OS, overall survival; MAIC, matching adjusted indirect comparison; HR, hazard ratio; RCT, randomised controlled trial.			

5.2.1 Model structure

The *de novo* analysis, presented by the company, compared ceritinib with crizotinib in patients with untreated advanced/metastatic ALK+ NSCLC. The cost-effectiveness analysis, presented by the company, was based on a partitioned survival model (PSM) or "area under the curve" analysis. This type of model directly uses the time-to-event data from a clinical trial to determine the distribution of patients between the health states. The model structure is depicted in Figure 5. It comprised three mutually exclusive health states: (i) pre-progression or stable disease (including those with objective responses to treatment) (PF), (ii) post-progression or progressive disease (PD), and (iii) death, which is the absorbing state.

Figure 5: Model Structure (CS, Figure 16, p 84)



Transitions between states were not explicitly incorporated into the analysis using probabilities. Instead the proportion of patients in each state was determined by using estimates of OS and PFS based on a parameterisation of the MAIC of Kaplan-Meier (KM) data from the ASCEND-4 trial for ceritinib and the PROFILE 1014 trial for crizotinib (discussed in Section 4.4), with extrapolation of these matched data beyond the trial period. The proportion of patients in the progression-free state was based on estimates of PFS, while the proportion of patients in the death state was 1 minus the estimate of OS. The proportion of patients in the pre-progression state was calculated as the difference between OS and PFS.

The cycle length used in the model was one month. The treatment dosage and duration of therapy, adverse event (AE) rates, and quality of life in progression-free patients used in the economic model were sourced from ASCEND-4 and PROFILE 1014 for ceritinib and crizotinib, respectively (except for crizotinib dose intensity, which, due to a lack of available data, was based on an earlier trial, PROFILE 1007). The remaining inputs were influenced heavily by those used in the economic analysis for first-line crizotinib (TA406),[9] and supplemented by studies identified in the cost-effectiveness review and from other published sources.

Review of the company model identified that a half-cycle correction was incorporated. This method is often used in economic evaluation to provide more accurate outcomes: assuming that the flow of patients between health states is continuous, if the number of patients is measured at the beginning or at the end of each cycle, the costs and QALYs assigned to that cycle may be overestimated or underestimated. To implement this, the company halved the number of patients in the first cycle and the number of patients at the last cycle (resulting in two cycles with half of the original cycle length and the remaining cycles with normal cycle length).

ERG comment

The ERG considers the model structure to be largely appropriate and consistent with previous technology appraisals for NSCLC (TA395, TA406 and TA422) and for advanced cancer in general, as it captured the progressive nature of the disease (patients cannot transition from progressed disease to the progression-free health state[9]. The cycle length was sufficiently granular to allow the model to accurately capture the movement of patients through the states, as well as allowing flexibility in calculating the costs of various drug regimens. The ERG, however, notes a number of issues.

On-treatment

The company's model did not explicitly include health states for patients being on- and off-treatment. Rather, a time-on-treatment curve was estimated for each comparator for the purpose of estimating the

first-line treatment costs. This limits the ability of the company's model to distinguish between costs and quality of life in patients who are on- and off-treatment in the progression-free and post-progression health states, and the current model would require re-structuring to implement these analyses. Distinguishing quality of life between these patients has been discussed and explored further in Section 5.2.8.

RECIST progression criteria

Disease progression in the ASCEND-4 and PROFILE 1014 trials was centrally assessed using the RECIST criteria. 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 are not used to determine disease progression, which instead is determined by the worsening of symptoms. In addition, centrally assessed progression is often more conservative than locally assessed progression. These two factors may imply that the results observed in these two trials are not reflected fully in clinical practice. This may impact on estimates of cost-effectiveness, as patients have different medical costs and quality of life in the pre-progression and progression health states. The ERG notes the limitation of the use of this outcome measure, but no further analyses were undertaken.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 21 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 21: Features of the *de novo* analysis

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether the de-novo evaluation meets the requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice.	Partly	The model largely complies with the NICE scope, but does not consider the listed comparator pemetrexed maintenance therapy. This was considered reasonable - advice from the clinical advisors suggests that pemetrexed is not widely used as first-line therapy in practice.
Type of economic evaluation	Cost-effectiveness analysis.	Yes	NA
Perspective on costs	NHS and PSS.	Yes	NHS and PSS costs were 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 followed a time horizon of 20 years. Few patients remain alive beyond this period.

Synthesis of evidence on outcomes	Systematic review and mixed treatment comparison of relative effects.	Partly	No head-to-head evidence between ceritinib and crizotinib was available. A MAIC was conducted to estimate the relative difference between the two comparators, adjusting for the differences in population. An additional study (ALEX[28]) was identified by the ERG on the comparative evidence for crizotinib, and further incorporated into the economic analysis.
Measure of health effects	QALYs.	Yes	Pre-progression utilities were derived from EQ-5D HRQoL data collected from patients in the ASCEND-4 trial for ceritinib and in the PROFILE 1014 trial for crizotinib. Post-progression utilities were obtained from the published literature(Chouaid 2013)[41].
Source of data for measurement of HRQoL	Reported directly by patients and/or caregivers.	Yes	Utilities for pre-progression were reported directly by patients in the pivotal trials for ceritinib and crizotinib. Post-progression utilities obtained from the Chouaid study were reported directly by patients.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public.	Yes	Utilities were elicited directly from the appropriate patient population.
Discount rate	Annual rate of 3.5% on both costs and health effects.	Yes	Costs and benefits were 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 was applied.
Sensitivity analysis	Probabilistic sensitivity analysis.	Yes	Probabilistic sensitivity analysis was undertaken.
NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal and social services; QALY, quality-adjusted life year; MAIC, matching adjusted indirect comparison; HRQoL, health-related quality of life			

5.2.3 Population

The patient population considered in the base-case analysis was patients with untreated ALK+ advanced NSCLC, which is in line with the population defined in the NICE scope and with the decision problem population considered in this submission. The clinical effectiveness data used in the model were derived from the ASCEND-4 trial for the ceritinib population and from PROFILE-1014 for the crizotinib population. Both these patient populations are in line with the population defined in the NICE scope. As discussed in Section 4.4, no suitable trial was identified to undertake a network meta-analysis, and so a MAIC analysis was undertaken. The methods used for and the limitations of this analysis are discussed in Section 4.4. Owing to the MAIC analysis undertaken, the ceritinib

population in the ASCEND-4 trial were adjusted and weighted to match the crizotinib patients in the PROFILE 1014 trial.

ERG's comments

Although both the patient populations of ASCEND-4 and PROFILE 1014 were in line with the population defined in the NICE scope, there were slight differences in the populations between the two trials. The company attempted to address these differences and their potential bias on the relative treatment effectiveness through the use of a MAIC analysis. The ERG is concerned about the potential to add uncertainty to the model parameters through the use of the MAIC analysis (discussed in Section 4.4, with the potential implications on the modelling of cost-effectiveness in Section 5.2.7.2).

There may also be differences between these trial populations and the real-world population. Table 12 in Section 4.4.1 compares patient characteristics in the two trials alongside a real-world cohort of patients with ALK+ NSCLC. The ERG's clinical advisor expected these patients to be younger and healthier, and that a higher proportion of them would be male, in a real-world setting, compared with the ASCEND-4 and PROFILE-1014 populations. Although the company's clinical experts felt that there was no strong reason to adjust the ASCEND-4 population to match the real-world population, the ERG has some minor concerns that neither trial population was reflective of the real-world population, but on the whole it accepts the generalisability of the trial population and so no further analyses were undertaken. These issues are explored in Section 4.2.1 and Section 4.4.1.

Finally, the ERG's clinical advisor noted that the brain metastases subgroups in the two trials were not consistent: he believes that this is a reflection of how the treatment of brain metastases has moved on, with whole-brain radiotherapy no longer being used. As discussed in Section 4.4.1, the inclusion criteria of the trials, with regards to brain metastases, differed, with the direction of bias difficult to predict. The ERG feels that this is a subgroup that could have been explored in the CS.

5.2.4 Interventions and comparators

5.2.4.1 First-line therapy

The economic model presented in the CS compared ceritinib with crizotinib as first-line treatment for untreated non-squamous advanced NSCLC. The dosing of each therapy was based on the licenced dose of each drug, 750mg and 500mg daily, respectively. Dose reductions due to adverse events, for both treatments, were accounted for by using data on dosing from the ASCEND-4 and PROFILE 1007 trials (PROFILE 1007[43] was used instead of PROFILE 1014 because the relative dose intensity was not reported in PROFILE 1014). Ceritinib was associated with a 77.3% relative dose intensity,

and crizotinib was associated with a 92.0% relative dose intensity. Section 5.2.9 provides further details on the calculations of drug acquisition costs for ceritinib and crizotinib.

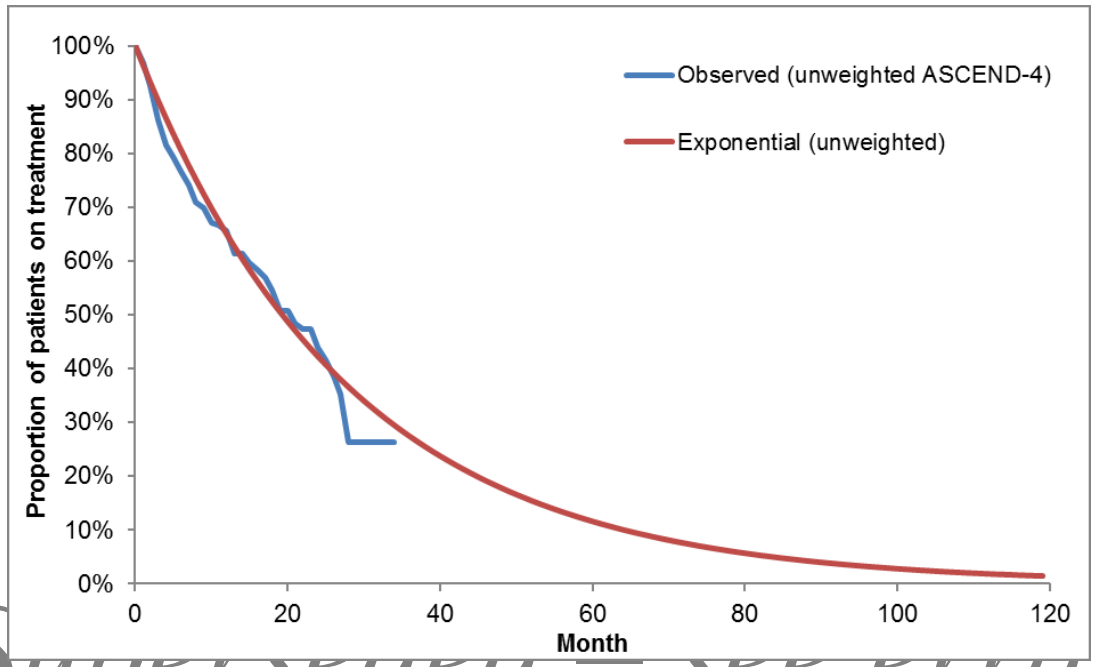
The duration of first-line therapy was obtained from the ASCEND-4 and PROFILE 1014 trials. Ceritinib patients received treatment for longer than ceritinib patients (a median of 15.27 months versus 10.90 months). Details of how treatment duration was modelled in the company model are provided in Section 5.2.7.2.

Platinum doublet therapy (pemetrexed with carboplatin or cisplatin), with or without pemetrexed maintenance treatment was also included in the NICE scope as a potential comparator therapy. This comparator was not included by the company in the analysis. The company justified this decision by stating that more that 90% of ALK+ NSCLC patients would get crizotinib, and therefore crizotinib is the only relevant comparator in this population.

5.2.4.2 Time on treatment

Treatment duration for ceritinib and crizotinib was based on data from the ASCEND-4 trial and from the PROFILE 1014 trial, respectively. Because only summary data and no KM data were available, on the duration of crizotinib, the company was forced to use methods to indirectly estimate the duration of therapy. This approach involved assuming that the duration of treatment followed an exponential curve. Using the summary data reported on the truncated median duration of treatment, the rate parameter (lambda) was estimated for each treatment. The exponential function was selected as it is the only parametric function that can be estimated using a single data point. The truncated median duration for ceritinib in ASCEND-4 was 15.3 months. In PROFILE 1014, the truncated median for crizotinib was 10.90 months. Figure 6: Treatment duration for ceritinib (KM curve vs exponential extrapolation) (Company clarification response, Fig B12.1, p 44) provides a comparison of the treatment duration for ceritinib presenting the Kaplan-Meier curve, based on patient data from ASCEND-4, and the exponential function, estimated from the truncated median duration of treatment.

Figure 6: Treatment duration for ceritinib (KM curve vs exponential extrapolation) (Company clarification response, Fig B12.1, p 44)



The company provided the log-cumulative hazard plot for time to discontinuation for ceritinib in the ASCEND-4 trial (provided in the clarification response). The plot is approximately linear, implying a constant hazard rate of discontinuation, and so supports the use of an exponential function to model treatment duration. Event probabilities were taken directly from the clinical studies – no further adjustment to account for the differences between trials and patient populations was performed.

Acknowledging the uncertainty generated by the lack of KM data on the duration of crizotinib, the company also explored alternative assumptions regarding treatment discontinuation in a number of scenario analyses. In these analyses, patients were treated until *ia*) discontinuation (equivalent duration based on ASCEND-4, using patient-level time–to-event data), *ib*) discontinuation (equivalent duration based on PROFILE 1014, using the truncated median approach as per the base-case), *ii*) progression, and *iii*) until the trial-observed discontinuation or progression (whichever occurred first).

Table 22: Scenario analyses for treatment duration (adapted from CS, Table 32, p 92)

Treatment duration assumption	Mean treatment duration (months)		ICER
	Ceritinib	Crizotinib	
Base-case: Treatment until discontinuation (based on truncated median duration for both ceritinib and crizotinib)	[redacted]	[redacted]	£27,936
Scenario 1a: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on ASCEND-4)	[redacted]	[redacted]	Dominant
Scenario 1b: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on PROFILE 1014)	[redacted]	[redacted]	Dominant
Scenario 2: Treatment until progression	[redacted]	[redacted]	£43,921
Scenario 3: Treatment until discontinuation or progression, whichever occurs first	[redacted]	[redacted]	£28,398
CS, company submission; ICER, incremental cost-effectiveness ratio			

ERG's comments

The ERG has a number of concerns regarding how treatment duration was modelled by the company. Scenario analyses demonstrated that the results were highly sensitive to these assumptions (Table 22). The ERG accepts the need to parameterise and extrapolate the time on treatment, and considers the use of the exponential curve to be the most appropriate, given the lack of data for other distributions, and for its consistency with PFS, with which it is linked. The concerns fall into the following categories:

- The use of the truncated median to estimate treatment duration,
- The population in which treatment duration was modelled,
- The use of individual curves (non-proportional hazards).

Truncated median approach.

The assumptions used in the company base-case, where treatment duration for ceritinib and crizotinib was estimated using the truncated median, appear to underestimate the actual time on treatment. Mean time on treatment for ceritinib was [redacted] as calculated using the individual patient data in the ASCEND-4 trial, compared with [redacted] based on the truncated median method. This seems to indicate that this method is not a reliable way to estimate duration of treatment. Without access to patient-level data for crizotinib, it is not possible to estimate a corresponding comparison, but it is reasonable to expect that the predicted duration of crizotinib therapy is equally poorly estimated. The impact of these assumptions is also likely to be significant as the duration of therapy has a significant impact on total drug acquisition costs, which are the key driver of the incremental costs. Further, while the ERG acknowledges that estimating the duration of treatment for crizotinib is difficult given the limited data available, the ERG questions the validity of adopting an approach that is inconsistent with data they do have on duration of treatment from the ASCEND-4 study. The ERG note that, in the

company base case model, the time on treatment curves fall entirely under the PFS curves, implying that patients do not remain on treatment beyond progression. We know this not to be the case for either ceritinib or for crizotinib, as described in TA406 (where 73% of crizotinib patients received treatment beyond progression for a median of 3.1 months). The ERG carried out further exploratory analysis, considering alternative methods of estimating the duration of treatment, reported in Section 6.

As stated above, the ERG was advised that Pfizer, the manufacturer of crizotinib, was in the process of sharing their patient-level data from PROFILE 1014, including a more recent data cut and full Kaplan-Meier curves for treatment duration. Unfortunately, at the time of writing this report, these data were not available. These data would allow more flexibility in modelling treatment duration, including fitting parametric distributions to the patient-level data for each arm individually, or estimating a more accurate hazard ratio for the relative time on treatment between ceritinib and crizotinib.

Population adjustment.
Fitting exponential curves individually to the treatment duration from each trial does not account for differences in the base-line characteristics of patients enrolled in the ASCEND-4 and PROFILE 1014 trials. Given that the differences in the trial populations were considered large enough to warrant adjustment to the PFS and OS data used in the model, the ERG considers it reasonable that a similar approach should be taken to time on treatment. As such, the ERG requested that the company perform regression analysis to better understand how the base-line characteristics interact with time on treatment, but this was not possible in the time available.

In order for treatment duration to be modelled in the same population, these data from ASCEND-4 would need to be weighted to the crizotinib population in the trial from which the crizotinib data were extracted, using MAIC methods as for OS and PFS (described in Section 4.4). The ERG requested that the company provide a re-analysis of the ceritinib treatment duration from ASCEND-4, adjusting to the crizotinib population in PROFILE 1014 and in the ALEX trial (as described in Section 4.3). Adjusting to the PROFILE-1014 population, resulted in an increased treatment duration for ceritinib (from 15.3 months to [redacted]). The results of the economic model, when these new data were incorporated are presented in Section 6.

Proportional hazards
By fitting curves to each arm individually, the company is relaxing the assumption that the hazard rate is proportional between the ceritinib and the crizotinib arms. However, the implementation of this is not consistent with the method used to model PFS, whereby proportional hazards were assumed and a

hazard ratio for crizotinib was applied to the PFS curve for ceritinib. Given the likely correlation between PFS and treatment duration, the ERG considers it reasonable to apply the same assumption for both parameters. That is, if proportional hazards are assumed for PFS then they should also be assumed for treatment duration, and vice versa. This would also allow for the more accurate patient-level time-to-event data from ASCEND-4 to be utilised and for treatment duration to be more accurately modelled. The ERG explored the impact of applying this assumption in additional analyses, presented in Section 6.

5.2.4.3 Subsequent therapies

Following discontinuation of first-line therapy a proportion of patients were assumed to receive further active therapy. In the base-case model, 40% of patients were assumed to receive no further active therapy, based on advice from the clinical advisor to the company. Of the 60% assumed to receive further active therapy, the treatment distribution of subsequent therapies received in the model was weighted based on the distribution in the ASCEND-4 and PROFILE 1014 trials, in the ceritinib and the crizotinib arm, respectively.

Data on second-line treatment duration, or dose intensity, were not collected or reported in either ASCEND-4 or PROFILE 1014. The duration and dose intensity were instead informed by second-line clinical trials conducted in ALK+ or general NSCLC populations. The dose intensity and dose duration of second-line therapies are provided in Table 23.

The same duration and dose intensity for each second-line therapy was applied, regardless of whether patients initiated on ceritinib or crizotinib. This was justified by the company on the basis that post-progression survival was almost identical for ceritinib and crizotinib in the base-case model.

The distribution, duration and dose intensity of second-line treatment used is presented in Table 23 below. The distribution, duration and dose intensity of second-line treatment did not impact on the clinical parameters used in the model, which were based on the relevant trial data and were, therefore, only used to estimate treatment costs and their associated resource use (e.g., drug administration costs, see Section 5.2.9).

Table 23: Second-line treatment (company base-case analysis) (adapted from CS, Table 40, p 102)

Second-line treatment	Ceritinib arm (% of patients)	Crizotinib arm (% of patients)	Mean duration of therapy (months)	Mean relative dose intensity
No active treatment	40.0	40.0	-	-
Ceritinib	1.9	10.8	11.54	80.9%
Crizotinib	9.4	1.5	10.29	92.0%
Docetaxel	3.8	4.6	3.02	92.6%
Pemetrexed	0.0	0.0	5.97	98.6%
Platinum doublet	45.0	43.1	-	-
pemetrexed	45.0	43.1	2.74	93.0%
+ cisplatin* or	22.5	20.0	2.74	88.0%
+ carboplatin*	22.5	23.1	2.74	88.0%

*options are mutually exclusive

The company also presented a scenario analysis exploring alternative assumptions regarding the distribution of the subsequent line of therapy. The scenario focused on capturing the distribution of the subsequent line of therapy expected in "real world" practice. The proportions used in this scenario were based on clinical expert opinion and are summarised in Table 24.

Table 24: Second-line therapy distribution (real-world scenario) (adapted from CS, Table 41, p 103)

Second-line treatment	Ceritinib arm (% of patients)	Crizotinib arm (% of patients)
No active treatment	40.0	40.0
Ceritinib	0.0	60.0
Crizotinib	0.0	0.0
Docetaxel	0.0	0.0
Pemetrexed	0.0	0.0
Platinum doublet	60.0	0.0
Pemetrexed	60.0	0.0
+ cisplatin, or	30.0	0.0
+ carboplatin	30.0	0.0

In this scenario, all patients initiating on crizotinib were assumed to receive the ceritinib second-line, while patients initiating on ceritinib were assumed to receive pemetrexed doublet. The impact of these assumptions on the cost-effectiveness of ceritinib is significant, and means that ceritinib dominates crizotinib (ceritinib is associated with lower costs and a greater number of QALYs). This is because this scenario assumes that substantially more patients initiating on crizotinib will receive ceritinib second line, and this is a substantially more costly treatment than platinum doublet.

ERG's comments

The ERG is satisfied with the choice of comparators for first-line therapy, how they were modelled, and the decision not to include pemetrexed maintenance therapy as a comparator. The clinical advisor to the ERG confirmed that pemetrexed is not routinely prescribed since the positive recommendation for crizotinib first-line use, except in a small proportion of cases where patients experience rapid deterioration and are too ill for treatment. A discussion on the duration of first-line therapy is provided in Section 5.2.7.2.

The ERG, however, has some serious concerns around how second-line therapy was modelled, both around the distribution of therapies and the duration of therapies. The key points of the critique are as follows:

- Second-line therapy, applied in the model, are inconsistent with the therapies received by patient in the trials, and therefore, with the clinical data used in the model;
- Second-line therapy in the trials is also inconsistent with clinical practice, and as a consequence the clinical data are not externally valid;
- The assumption of an equal duration of second-line therapy is unrealistic.

Inconsistency between the trial distribution and modelled distribution of second-line therapies

The proportion of people receiving second-line therapy in the ASCEND-4 and PROFILE 1014 trials was 35% and 43% respectively. This contrasts with the model, where 60% of patients were assumed to receive subsequent active therapy. This inconstancy is problematic because the clinical data used to populate the economic model was based on the ASCEND-4 and PROFILE 1014 and therefore the costs used in the model are inconstant with the clinical data used in the model. The company's rationale for this inconsistency was that the lower trial-based figures were due to the limited post-progression follow-up time, and that a larger proportion of progressed patients would eventually initiate second-line treatment beyond the data cut-off. The company further argued that the model was not sensitive to the proportion of patients receiving second-line therapy in the additional sensitivity analyses. However, this lack of sensitivity was found when the parameters were varied simultaneously. The ERG accepts the position of the company that a higher proportion of patients may receive subsequent active treatment beyond that in the trials, but notes that these additional treatment costs may not be consistent with the survival benefit beyond progression. As such, the proportion of patients receiving second-line therapy was explored further in Section 6, where the ERG applied the rates of treatment the trials in each arm of the model.

In addition to the points raised above, there were some other small inconsistencies between the number of patients on each subsequent therapy listed for ceritinib, in Table 40 of the CS, and those

described in Section 12.1.4 of the ASCEND-4 patients in the trial, which were due to the company redistributing those treatment options that were considered to be uncommonly used in practice to other treatment options.

Inconsistency between modelled second-line treatment distribution and clinical practice

As stated above, the CS suggests that the distribution of second-line therapies received in the ASCEND-4 and PROFILE 1014 trials was not reflective of clinical practice in the UK and that it was expected that patients initiating on ceritinib would receive platinum doublet chemotherapy and best supportive care following discontinuation of ceritinib. In contrast, patients initiating on crizotinib received ceritinib, platinum doublet chemotherapy, and best supportive care (CS, Figure 3) following discontinuation of therapy. The ERG agrees with the company that this treatment pathway is likely to be more reflective of practice in the UK. This lack of alignment between the clinical data and UK clinical practice, however, implies that the clinical data used in the model is unlikely to fully reflect the relative benefits of ceritinib and crizotinib in UK practice as the second-line therapies will be very different to those received by patients in the ASCEND-4 and PROFILE 1014 trials. The ERG considers this to be a substantial source of uncertainty that is very likely to have a significant impact on the estimated incremental cost-effectiveness ratio (ICER). As stated above, the company carried out a scenario analysis which sought to address this issue by assuming a distribution of subsequent therapies that was more in line with current UK practice. The ERG, however, has several concerns about this scenario analysis.

Firstly, this scenario analysis did not account for how subsequent therapy may have impacted on post-progression survival. These differences are potentially very significant; the economic model developed for the technology assessment (TA395[1]) that evaluated ceritinib as a second-line treatment for NSCLC estimated a gain of 1.35 life years, compared with best-supportive care.

Secondly, the assumption made by the company that 60% of patients would receive active treatment following discontinuation of first-line therapy is inconsistent with advice received by the ERG from its clinical advisor, who suggested that nearer 80% of patients would be expected to receive active treatment after discontinuation of first-line therapy.

Thirdly, the company estimated from the ASCEND-4 trial data that approximately 10% of patients would receive crizotinib after discontinuation of ceritinib. This contradicts the company's assertion that it would not be appropriate for crizotinib, a first-generation ALK inhibitor, to be given after ceritinib, a second-generation ALK inhibitor (CS, Figure 3). The clinical advisor to the ERG also strongly asserted that ceritinib would not be prescribed after the discontinuation of crizotinib.

In conclusion the company's scenario analysis, using a real-world distribution of therapies, should be interpreted with great caution and is likely to underestimate the ICER.

Duration of therapy

The ERG is concerned about the assumption that patients would receive the same duration of therapy irrespective of the first-line treatment. While we accept that there are limited data on the duration of second-line therapies, it is noted that these parameters have a large influence on these costs. The two ALK inhibitors in particular (the two most expensive treatments), are associated with a longer mean duration of therapy (11.54 months and 10.29 months for ceritinib and crizotinib, respectively). The company justified this by noting that patients were in the post-progression health state for the same amount of time, in each arm. The ERG, however, notes that this is a consequence of the extrapolation methods, used by the company (i.e. proportional hazards or parametric model), which the ERG does not consider to be appropriate. If different extrapolation methods are used, patients stay in this health state for different times (e.g., if a Gompertz or Weibull distribution is used to model the overall survival, crizotinib patients in the company base-case model have a greater mean time in the post-progression health state). It is reasonable to assume that if patients are in the post-progression state for longer, then they might be expected to receive second-line therapy for longer. However, given the limited OS data, it is difficult for the ERG to determine whether, in reality, ceritinib patients would remain in the post-progression health state for a longer or shorter time than crizotinib patients, and subsequently what the relative difference in duration of second-line therapy would be.

No additional scenario analyses were undertaken: the ERG considers that the approach taken by the company was the most appropriate, as the costs reflected those of the trial on which the survival benefit was modelled. The modelling of the second-line costs was, however, considered to be a serious limitation of the analysis.

5.2.5 Perspective and time horizon

5.2.5.1 Perspective

The economic perspective taken in the company analysis was that of the National Health Service (NHS) and Personal Social Services (PSS), in accordance with the NICE reference case.

5.2.5.2 Time horizon

The reference case indicates that the time horizon used for estimating the 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 in the company economic analysis was 20 years. Since most patients with advanced NSCLC were expected to die within 20 years of initiating first-line treatment, this timeframe is viewed as being consistent with a lifetime model horizon. In the company

base-case analysis, [redacted]% of ceritinib patients and [redacted]% of crizotinib patients would still be alive at 20 years (with less than 1% of patients being alive, in scenarios exploring alternative methods of overall survival).

ERG's comments

The ERG considers that the time horizon of 20 years was appropriate, as very few patients remained alive at this time. The perspective is also considered to have been appropriate (i.e. there is no additional burden on other sectors).

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. The implementation of discounting in the economic model was carried out appropriately on a continual basis.

5.2.7 Treatment effectiveness and extrapolation

5.2.7.1 Modelling approach

The treatment effectiveness for ceritinib and for crizotinib was measured by overall survival (OS) and progression-free survival (PFS).

Survival data from the ceritinib arm of the ASCEND-4 trial were used to inform the movement between health states for ceritinib (progression-free, post-progression and death), using a partition survival approach. The patient-level time-to-event survival data from ASCEND-4 were parameterised and extrapolated across the model time horizon of 20 years in order to predict survival beyond the trial period. The extrapolation methods are discussed in Section 5.2.7.1.

Since no direct head-to-head data were available for a ceritinib and crizotinib comparison, the company estimated the relative effectiveness of crizotinib using a matched-adjustment indirect comparison. This comparison used data on the effectiveness of crizotinib from the PROFILE 1014 trial and adjusted the OS and PFS estimates to account for differences in the base-line characteristics of patients enrolled in the trials (See Section 4.4 and in 5.2.7.2, below, for further details). This analysis used OS and PFS data that were published in TA 406[37]. The ERG has, however, been advised that Pfizer, the manufacturer of crizotinib, is in the process of making available more recent OS, PFS and time on treatment data from the PROFILE 1014 trial. These new data were not available at the time of writing this report. The remainder of this section is divided into three parts discussing: the extrapolation of survival data used in the model; the estimation of the relative effectiveness of crizotinib using the MAIC; and how adverse events were incorporated into the model.

5.2.7.2 The relative effectiveness of crizotinib

The relative effectiveness of crizotinib was applied in the model by way of a hazard ratio for OS and PFS. The hazard ratios were estimated from the MAIC by matching the baseline characteristics of the ASCEND-4 trial population to the characteristics of the PROFILE 1014 trial population, as the MAIC methodology limits the target population to that of the trial with only summary data. Details of the MAIC methods and their associated limitations are provided in Section 4.4.

The outcomes of the MAIC are presented in Table 25. Matching resulted in a decrease in the hazard ratio for both PFS and OS. The difference in PFS was shown to be significant, however, this was not the case for OS. The immaturity of the datasets were thought to be a factor in this.

Table 25 Outcomes of the MAIC (ceritinib vs crizotinib)

	PFS	**OS**
Before matching	[redacted]	[redacted]
After matching	[redacted]	[redacted]
MAIC, matching adjusted indirect comparison; PFS, progression-free survival; OS, overall survival		

To estimate the relative effectiveness of crizotinib, the HRs estimated from the MAIC were applied to parametric curves estimating the predicted PFS and OS of ceritinib, see section 5.2.7.3 for details of how the parametric curves were selected. This approach makes two assumptions. Firstly, it assumes proportional hazards, i.e. that the treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape. This was assessed by the company through both formal tests and visual inspection of the log-cumulative hazard plots (CS, Figure 15). These statistical tests suggested that the proportional hazards assumption was reasonable and held for PFS (before ([redacted]) and after matching ([redacted])), and OS (before ([redacted]) and after matching ([redacted]). Secondly, this approach assumes that the population modelled is the ASCEND-4 trial population.

ERG's comments

As described in Section 4.4, the estimated benefits of ceritinib are based on an unanchored comparison; however, there are significant limitations associated with comparing two interventions for which there is no head-to-head to evidence. This results in additional levels of uncertainty on the relative efficacy of crizotinib and ceritinib in addition to the immaturity of the OS data. This uncertainty has significant consequences in terms of accurately determining the cost-effectiveness of ceritinib, as the model is very sensitive to the magnitude of the OS hazard ratio. Increasing and decreasing the hazard ratio for OS by 10% results in the ICER varying between £21,763 and £44,925 (28% lower and 38% higher, respectively). The ERG, however, acknowledges that, to their

knowledge, there are no alternative statistical methods suitable for improving the accuracy of estimating the relative effectiveness of ceritinib and crizotinib given the currently available data. The ERG, however, considers this uncertainty as a substantial weakness in the company's submission and it means that the estimated ICER is subject to considerable uncertainty.

Proportional hazards

As stated above, the approach taken by the company assumes proportional hazards - that the hazard would remain constant over the model time horizon. This was justified by the company given the similarities between the treatment arms in terms of therapeutic class, route of administration, and treatment duration rules. The company also presented log-cumulative hazard plots (CS, Figure 15), which appear to be relatively parallel, supporting this assumption. The ERG, however, considers that there is some remaining uncertainty regarding the appropriateness of this assumption, and notes that the proportional hazards assumption can often have a substantial impact on the estimated effectiveness. In order to explore this further, the ERG created some additional scenarios that relax this assumption in the model. The results of these scenarios are presented in Section 6.

Population adjustment

In the company's base-case analysis, the ERG noted an inconsistency in the population that was selected to model survival. The hazard ratio was estimated by matching patient-level ceritinib data from the ASCEND-4 trial to the summary statistics from the PROFILE 1014 trial, therefore, the HR is reflective of the relative efficacy of the two treatments, specifically when administered within the PROFILE 1014 population. The hazard ratio was then applied to the ceritinib survival curve from the ASCEND-4 trial, which reflected survival in the ASCEND-4 population. The ERG requested that the company provide survival curves for ceritinib, adjusted to the PROFILE 1014 population, so that the population, for which the hazard ratio in the MAIC was estimated, and the survival curve for ceritinib, to which it was applied, were consistent. The results of this analysis, and the subsequent impact on the cost-effectiveness results when they are incorporated into the economic model, are provided in Section 6. In the MAIC, the ceritinib data was also matched to the whole population of PROFILE 1014 (including patients in the pemetrexed comparator arm) instead of the crizotinib arm of PROFILE 1014, which the ERG believes to be inappropriate as discussed in Section 4.4.1.

ALEX trial

As stated in Section 4.4, the ERG identified an additional trial providing relevant data for crizotinib (ALEX)[28], which was considered by the ERG as a suitable alternative to PROFILE 1014 as a source of data for modelling crizotinib. In the ALEX trial, described in Section 4.4, crizotinib had a median PFS of 10.4 months and an [redacted] one-year survival rate (Table 14). The impact of using this alternative source of data in the economic model is also explored, by the ERG, in Section 6.

5.2.7.3 The extrapolation of survival data

In the base-case analysis, an exponential function was selected to model both progression-free survival and overall survival. The company also tested the fit of other parametric distributions, including Weibull, Gompertz, log-logistic and log-normal, and selected from exponential, Weibull and Gompertz, since these were able to incorporate the method used by the company to estimate the relative survival of crizotinib (to allow for proportional hazards). The company stated that goodness-of-fit criteria (AIC and BIC) and expert opinion on clinical plausibility were considered when selecting the most appropriate parametric model. Fully fitted curves were considered (no consideration was given to the application of a piecewise approach).

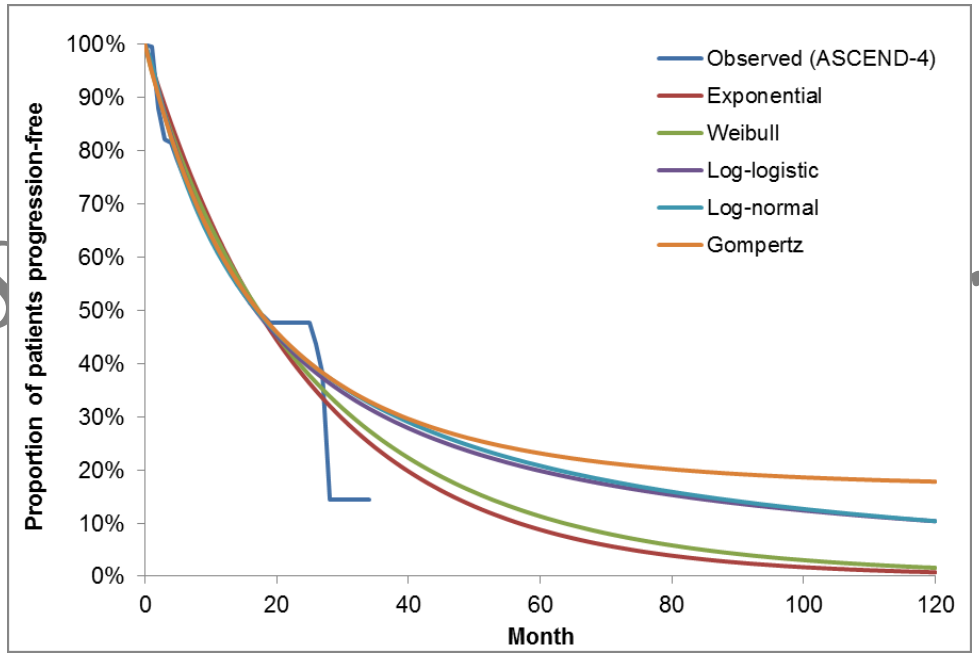
Table 26: Predicted survival by treatment – base-case analysis

Timeframe	Progression-free survival		Overall survival	
	Ceritinib (%)	Crizotinib (%)	Ceritinib (%)	Crizotinib (%)
5 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]

Progression-free survival

For PFS, while the Gompertz function demonstrated the best fit statistically, the long-term predictions provided by the exponential function were considered to be more clinically plausible.

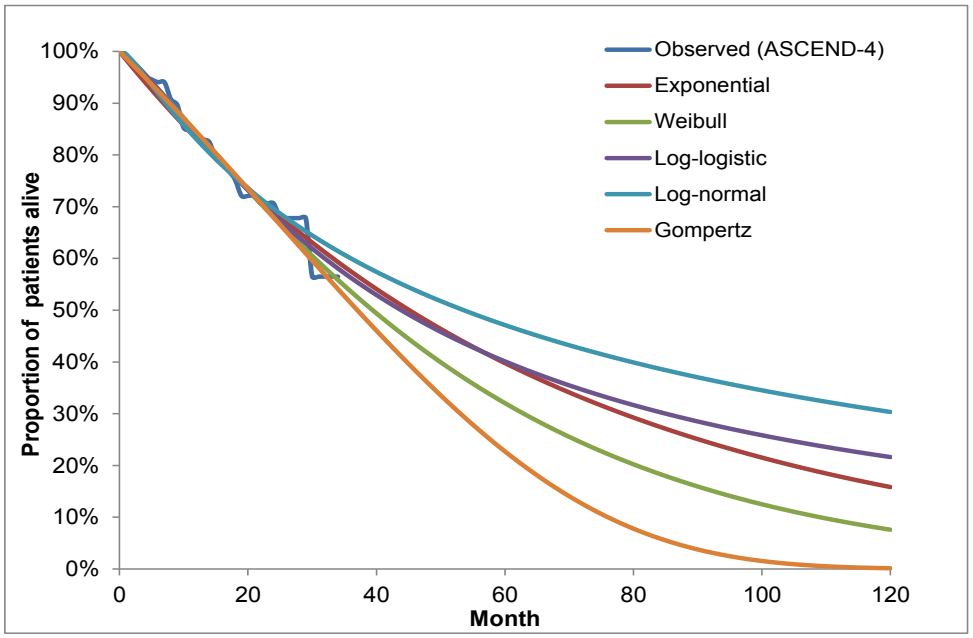
Figure 7: Observed and predicted PFS for ceritinib patients (CS, Figure 17, p 89)



Overall survival

The exponential curve demonstrated the best statistical fit to the available OS trial data, and the log-cumulative hazard plot was linear in shape (supporting a constant hazard of death consistent with an exponential model). The company also stated that their clinical advisors supported the choice of this distribution (although it was not clear, from the CS, how this was determined).

Figure 8: Observed and predicted OS for ceritinib (CS, Figure 18, p 90)



The company acknowledged that the exponential function for OS yielded higher long-term survival predictions that might be observed in clinical practice, so conducted a series of scenario analyses in which the Weibull and Gompertz curves were used to extrapolate OS. In both these scenarios the ICER varied substantially indicating that the model is very sensitive to this parameter, see Section 5.2.10 for further details.

Table 27: Estimated survival at five years for ceritinib, by parametric distribution

Distribution	Progression-free at five years	Alive at five years
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

ERG's comments

The selection of the exponential function appears to have been reasonable for PFS and produces predictions that are consistent with the OS evidence; the ERG notes that after a certain time point, the Gompertz curve yielded estimates of progression that were higher than any one of the OS survival curves.

With respect to OS, the ERG, however, has some concerns about the distribution selected. The ERG notes that the exponential function for OS provides among the most optimistic long-term estimates of survival, compared with the other distributions (Table 27). The choice of this survival function also results in there being no difference in time spent in the post-progression health state in each arm, which appears to lack face validity within the present context, given the different treatment pathway post-progression (discussed in Section 5.2.4). Furthermore, the exponential curves produce predictions about the duration of OS that are inconsistent with the clinical experience of ALK inhibitors; the exponential curve predicts that [redacted] of ceritinib patients and [redacted] of crizotinib patients would be alive after 5 years. The clinical advisor to the ERG suggested that 20% survival at 5 years would be more reasonable, which more closely corresponds with estimates from the Gompertz distribution. The ERG, therefore, considers the use of alternative distributions to model OS within scenario analyses presented in Section 6. Should the more recent OS data for crizotinib from PROFILE 1014 become available later in the process, it would aid in validating the assumptions around extrapolating OS.

In Section 4.2, the ERG noted an additional study identified in their review, a retrospective cohort study assessing treatment patterns and outcomes in patients with ALK+ advanced NSCLC in a

European population treated with crizotinib in regular clinical practice[29]. Figure 9 (adapted from the poster) presents overall survival in crizotinib patients by line of therapy. From crizotinib initiation, median OS was [redacted] in first-line initiators ([redacted]). The study authors commented that the outcomes for median OS for first-line crizotinib initiators aligned with expectations based on previous trials. While it is not possible to ascertain the robustness of the data at later time points (numbers at risk not reported), the long-term data may be useful to determine an appropriate method for extrapolating the ASCEND-4 and PROFILE 1014 data. At three years, approximately [redacted] of patients remained alive, further supporting the ERG's belief that the exponential function overestimates OS in the model.

Figure 9 [redacted]

[redacted]

Further to the above, the ERG would also make the more general comment that the OS data available for both ceritinib and crizotinib are immature, and that median OS was not reached for either treatment. This makes extrapolation of the OS data much more difficult and means that there is

inherently more uncertainty about the relative effectiveness of ceritinib and crizotinib. This is particularly important as the model is very sensitive to the differences in OS benefits. The uncertainty in the clinical evidence, used to populate the model, therefore, means that there is considerable uncertainty in the predicted cost-effectiveness estimates.

5.2.7.4 Adverse events

The adverse events (AEs) associated with first-line treatment were captured in the company's model, with event probabilities based on the safety profile in the ASCEND-4 trial and PROFILE 1014 trial for ceritinib and crizotinib, respectively. All-cause event rates were extracted from the safety population, and were included if they affected ≥5% of patients on treatment and were Grade 3 or above.

The adverse event probabilities incorporated into the model are presented in Table 28. These were based on the number of patients experiencing each type of event during the on-treatment period in the respective clinical trials. Patients experiencing multiple instances of a particular adverse event were only counted once. Event probabilities were taken directly from the clinical studies – no further adjustment to account for differences between trials and patient populations was performed.

Table 28: Grade 3/4 adverse events in the model (CS, Table 31, p 91)

Adverse events, % of patients	Ceritinib	Crizotinib
Neutropenia	0.5	11.1
Diarrhoea	5.3	2.3
Pulmonary embolism	0.0	6.4
Vomiting	5.3	1.8
Hyperglycaemia	6.3	0.0
Alanine transaminase (ALT) elevation	30.7	14.0
Aspartate aminotransferase (AST) elevation	16.9	0.0
Gamma-glutamyltransferase increased	28.6	0.0
Blood alkaline phosphatase increased	7.4	0.0
CS, company submission; ALT, Alanine transaminase; AST, Aspartate aminotransferase		

Adverse events related to subsequent therapy were not included in the economic model. This issue was raised with the company, at the clarification stage, and the ERG requested that AEs associated with subsequent therapy be added to the model. The company's response stated that they would expect the inclusion of these events to have little impact on the base-case results, given the limited potential for differences in second-line adverse event rates between the two arms, due to the proportion of patients on treatment and the large degree of overlap between the distributions of second-line treatments, across the two arms.

Adverse events can have an impact on quality of life and costs through the treatment of the event itself, and with dose interruptions and subsequent reductions in costs of the active therapy. The costs, and disutility, associated with adverse events in the model are discussed in Section 5.2.9 and Section 5.2.8.3, respectively.

ERG's comments

The ERG considers that the use of safety data from the two trials and the selection of events to include in the model were broadly appropriate for modelling AEs in this analysis. The selection of AEs to include in the model was appropriate, as these were those which were considered to be associated with a more substantial impact on costs and quality of life. The ERG, however, does note a number of small issues (described below). These were considered to be minor and unlikely to impact on the outcomes of the economic analysis, and as such were not explored further.

Multiple events

The company model modelled Grade 3+ adverse events using the proportion of patients experiencing an event from the trials. The total cost of treating AEs would be underestimated, in each arm, if patients experience more than one event of a particular type; however, the company was not able to provide the total number of events. It is difficult to determine the extent of any underestimation, but it is likely to be small. The event with maximum severity was recorded for patients who experienced multiple episodes of a particular event, so this would only result in an underestimation in treatment costs if both events were of Grade 3 severity or above.

Population adjustment

Given that survival estimates were adjusted for differences in the trial population, by the MAIC, the ERG queried whether the rates of adverse events for ceritinib and crizotinib might also vary within different patient populations (for example, whether patients with brain metastases have a different safety profile on ceritinib, compared with those without). The ERG accepts that the current approach appears to be adequate and that further adjustment is unlikely to make much different to the ICER: the proportion of patients with AEs was shown to be, generally, consistent across a range of patient characteristics, through subgroup analyses, presented in the ASCEND-4 CSR[44], and deterministic sensitivity analyses, presented by the company, demonstrated that the model results were not sensitive when varying the costs of AEs from zero to twice their base-case values.

Half-cycle correction

The ERG noted an error in the calculation of AE costs, details provided in Section 5.2.12.

Second-line therapy

When asked to justify why the safety profile of each second-line therapy was not modelled, the company stated that there was limited potential for differences in second-line adverse event rates between the two arms. In the company's base-case analysis this assumption is relatively justifiable because it is assumed that patients were equally likely to receive second-line therapy, with a similar treatment distribution and duration of time. However, as discussed in Section 5.2.4, the assumption that ceritinib and crizotinib patients receive the same second-line therapies, and for the same duration of time, is not well supported by the evidence from the ASCEND-4 and PROFILE 1014 trials, and is unlikely to occur in clinical practice. If, as was observed in the trials, ceritinib patients are less likely to receive second-line therapy, the exclusion of AEs associated with subsequent therapy will overestimate the ICER. This is because there is lower opportunity for ceritinib patients to experience AEs associated with second-line therapy, and to incur the costs and disutility that go with them. On the other hand, we would expect that in practice, ceritinib would be followed by pemetrexed, and crizotinib would be followed by ceritinib and subsequently pemetrexed: with pemetrexed associated with a more favourable safety profile than second-line ceritinib, the exclusion of second-line AEs would bias in favour of crizotinib (patients initiating on crizotinib would be expected to experience more events on second-line therapy). On balance, it is difficult to predict the impact of these two factors and they are unlikely to be key drivers of the analysis.

5.2.8 Health-related quality of life

The effectiveness measures in the analysis included life-years (LYs) and quality-adjusted life-years (QALYs). Health state utility values were used to weight LYs and estimate QALYs in each arm. The utility values for the PF health state were obtained from ASCEND-4 and PROFILE 1014 for ceritinib and crizotinib, respectively. Details are provided in Section 5.2.8.1 below.

The utility value for the PD health state was obtained from the published literature, since the required data were not collected in the clinical trials. To identify the utility value for the post-progressed health state, a systematic review was performed, by the company, to identify published HRQoL values for patients with advanced or metastatic NSCLC. The review found 24 studies that met its inclusion criteria (details reported in the CS, Appendix H). Of the 24 studies identified, 18 studies elicited utility values using a variant of the EQ-5D questionnaire (the preferred method for economic evaluations conducted for NICE). These 18 studies were conducted in cohorts of patients undergoing treatment for NSCLC. Studies were excluded on the basis of a number of factors, including the use of a valuation method other than EQ-5D, a relatively small sample size, being conducted in a patient population specific to a country other than the UK, not reporting the utility values corresponding to

the PD health state, or not adequately capturing the utility values of patients following progression on second-line therapy.

Table 29 provides a summary of the utility values used in the company's model.

Table 29: Base-case health state utilities (CS, Table 33, p 95)

Health state	Utility value	Source
Ceritinib		
Progression free (stable disease or objective response)	0.81	ASCEND-4 CSR[44]
Progressed disease	0.64	Chouaid *et al.,* 2013[41]
Crizotinib		
Progression free (stable disease or objective response)	0.81	PROFILE 1014[45]
Progressed disease	0.64	Chouaid *et al.,* 2013[41]
CS, company submission; CSR, clinical study report Source: ASCEND-4 CSR		

5.2.8.1 Progression-free utilities

The utility value for the progression-free health state, in the ceritinib arm, was estimated from EQ-5D utilities collected in the ASCEND-4 trial for ceritinib patients while on treatment. The PROFILE 1014 trial collected the equivalent data for crizotinib. Repeated-measures mixed-effects analyses were performed on each dataset individually, to compare overall scores between treatments, controlling for baseline utility, between-patient variability and other patient variables.

No further adjustments were considered to the base-case PF health state utility, to allow for differences in the patient population, for different treatment response rates, or for whether the patient was on treatment or not.

ERG's comments

The ERG noted that the utility value for progression-free patients in each arm was very similar (within two decimal places). This appears plausible given the similar mode of action, safety profiles, and mode of administration, and based on advice from the clinician consulted by the ERG during the appraisal.

The ERG, however, notes that the quality of life for progression-free patients might be expected to vary within populations with different patient characteristics, and, therefore it may have been appropriate to adjust the utility values using a similar method to that used in the MAIC for survival. The ERG also consider that the model design could have incorporated differentiated between treatment responders and non-responders; the ERG's expert clinician advised was a key determinant of quality of life. The ERG is, however, satisfied that the simpler modelling adopted by the company

is likely to implicitly have captured the proportion of responders, and that adjustment for differences in patient characteristics is unlikely to have had significant impact on the utility values used. The ERG is, therefore, satisfied with the company's approach.

5.2.8.2 Progressed-disease utilities

For the progressed-disease health state the company used data from a study by Chouaid et al.[41] This was a multi-national cross-sectional study, which was conducted in patients receiving any treatment for advanced NSCLC in a real-world setting. EQ-5D data were collected from 263 patients, with the scores transformed into utility values using UK-population weights.

The mean utility used by the company was calculated as being 0.64, and was based on a weighted average of the different utilities estimated in the study (details in Table 30). The study reported utility values that were stratified by progression status (progression free or progressed disease), and by line of therapy. To estimate the utility for progressed-disease patients in their model, the company used the utility value from first-line progressed-disease patients, and from second-line and third-line patients (progression-free and progressed-disease) from the study. The mean utility values in these patient categories were weighted by the number of observations, in each category, to estimate an overall weighted average utility. The same utility value was applied to post-progressed patients in each arm of the model.

Table 30 Utility values used to estimate post-progression utility

Treatment	***n***	**Mean utility value**
First-line PD	26	0.67
Second-line PF	44	0.74
Second-line PD	17	0.59
Third/fourth-line PF	24	0.62
Third/fourth-line PD	21	0.46
Overall PD (weighted average)	**-**	**0.641**
PD: progressed disease. PF: progression free Source: Chouaid[41].		

ERG's comments

The ERG has some concerns around the use of the Chouaid utility values to estimate the post-progression utilities within the context of this decision problem. These concerns lie with the generalisability of the dataset, and with how the utility values were calculated and applied within the model. These issues are discussed, in turn, below.

Generalisability
While it is likely to be the most applicable study in the systematic review, the population within it was not considered to be fully representative of that set out in the decision problem. The study was not specific to ALK+ NSCLC patients, who are thought to be younger and fitter and expected to have better quality of life than ALK-negative (ALK-) NSCLC patients, as discussed in Section 0. The study was undertaken in a variety of countries, and the study patients might have had different baseline characteristics to those in the UK, and received different treatments for each line of therapy to those recommended by NICE (chemotherapy was not reported and could not be assessed for relevance). Furthermore, the dataset was elicited in 2010 to 2011, before ALK inhibitors were widely used. A commonly used second-line therapy at present is ceritinib: second-line ceritinib patients are also thought to have a better quality of life, compared with patients on other second-line chemotherapy options (in TA422, second-line crizotinib had a higher utility value of 0.810, compared with patients on docetaxel [0.740], pooled chemotherapy [0.747] and best supportive care [0.690])[1, 46].

The application and estimation of the utilities
The ERG identified a number of important issues that raised concerns about whether the values extracted from the Chouaid study were applied appropriately.

Firstly, the ERG questions whether it was appropriate to apply the same post-progression utility in each arm. This is considered to lack face validity both within the context of the modelled scenario, where patients received a different mix of chemotherapy treatments in each arm, and the "real world" scenario where post-progression crizotinib patients would be expected to start ceritinib therapy (as discussed in Section 5.2.4). The ERG considers it plausible that second-line chemotherapy patients and second-line ceritinib patients would have different values for quality of life, e.g., due to different safety profiles, and different modes of action[1, 46]. Sensitivity analysis, in the model, showed that varying this parameter resulted in negligible changes to the ICER. However, these scenarios varied the utility values of patients initiating on ceritinib and crizotinib simultaneously: this finding is unsurprising given that, in the base-case, patients were in the PD state for the same amount of time.

Secondly, the utility value for the PD health state was thought to be underestimated, as it did not accurately capture the quality of life of patients remaining on first-line treatment after progression. A clinician may continue treating patients beyond progression if they perceive a continued benefit to a patient's quality of life, by limiting the speed of disease progression. To reflect that large proportion of patients in the ASCEND-4 and PROFILE 1014 trials continued treatment, the company included data from the Chouaid study to reflect the quality of life for these first-line patients within their calculation for the utility value in the PD state. Chouaid estimated the utility value of these patients as 0.67. Given the concerns about the generalisability of the Chouaid study population to the current decision problem, and the fact that ALK inhibitors were not on the market at the time of the study, the

ERG expects that this value is too low, especially in comparison to second-line progression-free patients, in the same study, who experienced a higher quality of life (0.74). As such, the use of this value, within the calculation for the utility value in this health state, may underestimate it, possibly to a different extent in each treatment arm.

On the basis of the issues discussed above, the application of arm-specific post-progression health state utilities (accounting for the difference in quality of life in second-line patients, and allowing for the benefit associated with continuing treatment beyond progression), was explored further in scenario analyses presented by the ERG, in Section 6.

5.2.8.3 HRQoL associated with adverse events

A utility decrement associated with adverse events was not applied in the company's model. The use of trial-based HRQoL data implicitly captures any treatment-related disutility (i.e. related to mode or frequency of administration) and the disutility for AEs; any additional modelling of disutility would double-count this effect.

The disutility values for any adverse events experienced while on second-line therapy were not modelled.

ERG's comments

The ERG considers the assumption, made in the company's base-case, of no disutility adjustment, to be appropriate, given the continual nature of administration of treatment and the fact that any adverse events are likely to fall near to an EQ-5D measurement (unlike the case with chemotherapy administered in cycles).

The exclusion of specific disutilities from second-line therapy is considered unlikely to be an issue within the company's base-case analysis, given that they are likely to be captured within the progressed-disease health state utility, since the value reflects a patient's experience in a range of possible post-progression health states. This may be more of an issue within the context of a "real world" scenario analysis, where patients initiating on crizotinib would receive very different treatment, after discontinuation, to that of ceritinib patients. The ERG did not consider this a major issue and so did not explore further.

5.2.9 Resources and costs

The CS provided a description of the resources and associated costs required to provide first-line and subsequent treatment to patients with advanced NSCLC. The CS presented a description of the following resources and costs:

- Drug acquisition and administration costs for ceritinib, crizotinib and second-line therapies;
- Resources and costs associated with treatment whilst patients are in the progression-free health state;
- Resources and costs associated with treatment for patients following disease progression;
- Resources and costs associated with adverse events;
- Resources and costs associated with terminal care.

A discussion on the cost of ALK-testing was also presented.

To identify the cost and resource-use data, to inform the model, the company carried out a review of recent NICE submissions, but did not carry out a formal systematic review of studies containing cost and resource-use information. The ERG considers that a formal systematic review would have been more appropriate, but that the approach taken by the company was unlikely to have missed any major resource-use items, given the three recent appraisals of ALK inhibitors for NSCLC.

5.2.9.1 Drug acquisition costs

First-line therapy

In the CS base-case model, the drug cost per month was calculated for ceritinib and crizotinib as the first-line therapies. The drug cost per month were calculated for each, based on their unit cost per package, which was derived from MIMS. The company applied the mean relative dose intensity estimates from ASCEND-4 for ceritinib and from PROFILE 1007 for crizotinib[30, 43]. The drug costs included in the company's model are presented in Table 31 below.

Table 31: Unit drug costs, doses, and dose intensity (adapted from CS, Table 34, p 96)

Treatment	Cost per package, £	Package size	Strength, mg	Dosing schedule	Relative dose intensity (%)	Drug cost per month, £
Ceritinib	4,923.45	150 capsules	150	750 mg orally once daily	77.3	3,861.33
Crizotinib	4,689.00	60 capsules	250	250 mg orally twice daily	92.0	4,376.79
CS, company submission						

ERG's comments

The ERG accepts the calculations of the drug costs per month and have no concerns with the calculations and derivations of the unit costs. The ERG also acknowledges that the relative dose intensity estimates were derived from the most relevant clinical trials. The relative dose intensity for crizotinib was not derived from PROFILE 1014 (which assessed crizotinib as a first-line therapy) and,

instead, was derived from a trial which assessed crizotinib as a second line therapy. However, the figure used in the model can be externally validated as appropriate, by the ALEX trial[28], where the relative dose intensity for crizotinib within the ALEX trial was 92.4%. However, the ERG is concerned that, in a real-world setting, the full cost saving owing from the relative dose intensity would not be realised, due to the wastage of surplus doses. The removal of the relative dose intensity assumption, and assuming that the relative dose intensity for both drugs is equal (at the lower rate) significantly increases the ICER for ceritinib (£61,070 and £47,561, respectively). Therefore, the ERG is concerned that the company's model is underestimating the drug costs that would be incurred by the NHS.

A previous submission (TA406[9]) accepted the relative dose intensity calculations, but removed the half-cycle correction, thereby allowing for drug wastage as a result of discontinuation of treatment. TA406 stated that it would be reasonable to assume that any surplus drug prescribed at the beginning of the cycle would be wasted should a patient discontinue treatment within that cycle. This seems like a legitimate assumption, for this submission, given the similarities between ceritinib and crizotinib; ceritinib comes in a 150-tablet pack, which lasts 30 days, while crizotinib comes in a 60-tablet pack, also lasting 30 days. This scenario will be explored in Section 6.

Subsequent therapies

Once patients have entered the disease-progression health state, they begin to incur the cost of second-line treatments. As stated in Section 5.2.4, only 60% of patients were assumed to receive further active therapy, with the distribution of second-line treatment derived from the ASCEND-4 and PROFILE-1014 trials and reweighted, accordingly. The second-line treatments included in the model, along with their estimated costs, are presented in Table 32. The relative dose intensity estimates were derived from the same source for crizotinib, and from ASCEND-3 for ceritinib[47]. Drug costs were based on the unit costs per package from MIMS for ceritinib and crizotinib, and from eMIT for the chemotherapies.

Table 32: Costs of second-line treatment regimens (CS, Table 37, p 101)

PD treatment	Relative dose intensity (%)	Drug cost per month, £	Drug administration costs per month, £		Treatment duration, months		Total drug + administration costs, £
			First month	Subsequent months	Median	Mean	
Ceritinib	80.9	4,041.16	14.26	14.26	8.00	11.54	46,805.89
Crizotinib	92.0	4,376.79	14.26	14.26	7.13	10.29	45,164.18
Docetaxel	92.6	28.09	403.75	495.66	2.09	3.02	1,489.42
Pemetrexed	98.6	2,046.49	395.67	486.09	4.14	5.97	15,034.72
Platinum doublet							
pemetrexed +cisplatin, or	93.0	1,930.26	395.67	486.09	3.22	2.74	6,529.92
carboplatin	88.0	18.08	0.00	0.00	3.22	2.74	49.54
	88.0	29.52	0.00	0.00	3.22	2.74	80.88
CS, company submission; PD, progressed disease							

The CS states that the currently available post-progression treatments differ from those used in ASCEND-4 and PROFILE-1014. Therefore, using medical expert opinion, real-world distribution estimates of second-line treatment were provided. The trial distribution and the real-world distributions, provided in the CS, are presented in Table 33. The estimated progressed-disease treatment cost is also presented for each comparator, in this table.

Table 33: Trial-based and "real world" distribution estimates of second-line treatment (adapted from CS, Tables 40 and 41, pp 102-3)

	Trial-based distribution estimates		Real-world distribution estimates	
Second-line Treatment	**Ceritinib (%)**	**Crizotinib (%)**	**Ceritinib (%)**	**Crizotinib (%)**
Ceritinib	1.9	10.8	0.0	60.0
Crizotinib	9.4	1.5	0.0	0.0
Docetaxel	3.8	4.6	0.0	0.0
Pemetrexed	0.0	0.0	0.0	0.0
Platinum doublet	45.0	43.1	60.0	0.0
pemetrexed +	45.0	43.1	60.0	0.0
cisplatin, or	22.5	20.0	30.0	0.0
carboplatin	22.5	23.1	30.0	0.0
No active treatment	40.0	40.0	40.0	40.0
Total PD treatment costs	£8,135.41	£8,645.67	£3,957.08	£28,083.54
CS, company submission; PD, progressed disease				

ERG's comments

The ERG accepts the calculations of the drug costs per month, for second-line treatment. ASCEND-3 is likely to have been an appropriate source for the relative dose intensity of ceritinib, as roughly two thirds of its population were previously treated with an ALK inhibitor; PROFILE 1007 is an appropriate source, given that this study's population were receiving second-line treatment.

However, the ERG has major concerns regarding the distributions, of the second-line treatments, assumed in the model. As discussed in Section 5.2.4, the trial-based distributions are not reflective of current practice and are likely to underestimate the costs that will be incurred by the NHS. The ERG agrees that the assumptions around the "real world" distributions used in the scenario analysis, in the CS, are likely to be more reflective of the costs incurred in practice. However, the true cost is still uncertain. The company's "real world" assumptions appear to be conservative, they assumed that 60% of patients in the ceritinib arm receive crizotinib, where the ERG's clinical advisor believes it could be closer to 80%. This "real world" distribution estimate has a major cost implication within the model: as can be seen in Table 33. Implementing the trial-based distribution produces a second-line treatment cost estimate of £8,645.67, while using the "real world" distribution produces an estimate of £28,083.54, and so the company's scenario analysis may be underestimating the ICER. Therefore, the ERG is very concerned about the large uncertainty surrounding this important cost category.

In addition, not only are these assumptions increasing the uncertainty being incorporated into the model, but the resource-use data being used in the model also do not correspond to the clinical efficacy data being used. The ERG believes that the base-case analysis in the CS (using the trial-based distributions) is likely to be the most appropriate option, to allow for consistency between the costs and the clinical data in the model. However, the ERG wants to highlight the lack of external validity for this option.

Not only does the distribution of treatments differ, but the model also assumes that the same proportion of patients receive active therapy post-progression in each arm of the trial (60%). Again this is based on clinical expert opinion, and this proportion is much higher than those reported in the trials (35% in ASCEND-4 and 43% in PROFILE 1014). In the points for clarification (PFC), the ERG asked the company to justify this assumption. In response, the company presented sensitivity analysis showing that this assumption does not make a large difference to the ICER. However, the ERG would like to note that combining this assumption with using the "real world" drug distribution estimates significantly increases the costs associated with the crizotinib arm. Therefore, not only are these assumptions reducing the external validity of the model and increasing the uncertainty within the model, but they are also benefiting the ceritinib arm, over the crizotinib arm, of the model.

5.2.9.2 Treatment administration costs

First-line treatment administration costs

Given that ceritinib and crizotinib are both oral medications, the CS assumed that the only administration cost that was required would be a pharmacist's time to dispense the medications. This cost was calculated at £14.26 per month.

ERG's comments

The ERG is concerned that the first-line treatment administration costs have been underestimated in the CS. Although, as stated in the CS, this cost is in line with the previous ceritinib submission (TA395[1]), it does not take account of the administration costs required to implement the relative dose intensity assumed for the first-line treatment costs. The ERG does not agree that a pharmacist would have the authority to adjust prescriptions based on the medication still available, in hand, to the patient. The ERG believes that the administration costs included in the crizotinib submission (TA406[9]) are more appropriate to implement the relative dose intensity assumption. TA406 assumed an initial treatment administration cost of a nurse's appointment, to go through the dosage instructions of the treatment. In that submission, the ERG also assumed that this cost would be incurred every month for the duration of first-line treatment. For this submission, the ERG considers that the inclusion of this monthly cost would cover the time required for altering prescriptions sufficiently to uphold the relative dose intensity assumption. This monthly cost is included in the ERG's model, in Section 6.

Second-line treatment administration costs.

As with first-line treatment, only the pharmacist's time was included as an administration cost within the model. For the chemotherapy treatments, an administration cost for initial and subsequent infusions was provided and included in the model.

ERG's comments

As with first-line treatment administration costs, the ERG is concerned that the second-line treatment administration costs have been underestimated, in the CS, for ceritinib and crizotinib. The same adjustments within this cost category will be undertaken in Section 6.

The NHS reference cost code used in the CS is consistent with previous submissions. However, the unit cost, presented in the CS, does not match any of the costs presented for that code in the NHS reference costs. However, the cost included in the model is an average of the reference cost within the code, and so altering it is unlikely to have a significant effect on the ICER.

5.2.9.3 Health state costs

The three health states in the model are: progression free, progressed disease and death – the model includes those costs associated with patients being in each of these health states.

Progression-free costs

The monthly costs associated with patients being in the progression-free health state are presented in Table 34 below. These costs include those relating to healthcare provider visits, and tests and procedures required to monitor patients. The total cost of this health state was estimated at £184.42 per month.

Table 34: Monthly progression-free health state costs (adapted from CS, Table 35, pp 97-98)

Resource	Unit cost, £	Frequency of use	Cost per month, £
Healthcare provider visits			
Cancer nurse	69.20 per visit	20% of patients (1 visit)	13.84
Outpatient visit	151.12 per visit	0.75 visits	113.34
GP visit	31.00 per visit	10% of patients (1 visit)	3.10
Tests and procedures			
Full blood count	3.10 per test	All patients, 0.75 per month	2.33
Computerised tomography scan	125.49 per scan	30% of patients, 0.75 per month	28.24
X-ray	30.26 per X-ray	All patients, 0.75 per month	22.70
Serum chemistry	1.18 per test	All patients, 0.75 per month	0.89
Total cost per month			**184.42**
CS, company submission; GP, general practitioner			

ERG's comments

The ERG has no major concerns with the progression-free health state costs included in the model, apart from an error identified in the implementation of the half-cycle correction of this cost category.

The costs included are in line with previous submissions and appear to include the relevant costs which would be incurred in this health state.

Progressed-disease costs

The drug costs associated with progressed disease (i.e. costs incurred when patients are receiving second-line treatment in the progressed-disease health state) are presented below.

Table 35: Resource use in the progressed-disease health state (adapted from CS, Table 36, pp 99-100)

Resource	Unit cost, £	Frequency of use	Cost per month, £
Healthcare provider visits			
Cancer nurse	69.20 per visit	10% of patients (1 visit)	6.92
Outpatient visit	151.12 per visit	All patients (1 visit)	151.12
GP visit	31.00 per visit	28% of patients (1 visit)	8.68
Medications			
Steroids (dexamethasone)	0.146 per 0.5mg	50% of patients, 0.5mg x 160	11.68
NSAIDS (ibuprofen)	0.006 per 200mg	30% of patients, 200mg x 60	0.11
Morphine	0.710 per 60mg	75% of patients, 60mg x 7	3.73
Bisphosphonate (alendronate)	0.022 per 5mg	7.5% of patients, 5mg x 28	0.05
Dietary supplement	3.54 per 350g	40% of patients, 350g x 20	28.34
Tests and procedures			
Full blood count	3.10 per test	All patients, 1 per month	3.10
Serum chemistry	1.18 per test	All patients, 1 per month	1.18
Computerised tomography scan	125.49 per scan	5% of patients, 0.75 per month	4.71
Home oxygen	203.91 per event	20% of patients, 1 per month	40.78
X-ray	30.26 per X-ray	30% of patients, 0.75 per month	6.81
Total cost per month			**267.19**
CS, company submission; GP, general practitioner; NSAID, nonsteroidal anti-inflammatory			

ERG's comments

The ERG has no major concerns with the progressed-disease health state costs included in the model. The costs are in line with previous submissions and appear to include the relevant costs which would be incurred in this health state. Some additional costs were included, the medication costs and the cost of home oxygen, compared with previous ALK inhibitor submissions, however, these costs seem reasonable and are unlikely to favour either comparator in the model. The progressed-disease health state costs were reviewed by the ERG's clinical advisor, who considered them reasonable, but noted that radiotherapy may be given to patients with brain metastases and, therefore, should potentially be added to the model. This is consistent with the clinical advice, received by the company, which suggested that radiotherapy would be given to approximately 15% of patients with brain metastases. This potential omission of the costs of radiotherapy would have had, however, only a very minor impact on the ICER, due to the small number of patients who would incur this cost. As such, the ERG has not undertaken any additional analysis to address this issue.

End-of-life costs

The CS model calculated a one-off cost to account for terminal care incurred in the last 90 days before death. Upon entering the death health state, patients incur this terminal care cost within the model. The costs included in the model are presented in Table 36. This estimation is in line with the previous crizotinib appraisal (TA406[9]).

Table 36: Terminal care costs (CS, Table 44, p 104)

Terminal Care Costs	**Average cost, £**
District Nurse	298.40
Nursing and residential care	1,073.36
Hospice care – inpatient	590.35
Hospice care – final three months of life	4,830.14
Marie Curie nursing service	536.68
Total terminal care costs	7,328.93
CS, company submission	

ERG's comments

The ERG notes that the end-of–life (EOL) costs used were not specific to cancer patients, and notes that the costs of GP consultations were not included. The ERG has some minor concerns regarding the source and composition of the EOL costs. The ERG, however, notes that the model is very insensitive to this parameter (because the OS benefits of ceritinib are relatively small) and, therefore, the uncertainty around this parameter is not explored further.

5.2.9.4 Adverse event costs

As with the crizotinib submission (TA406), adverse events of grade 3/4 were considered in the model if reported in ≥ 5% of patients for at least one treatment. AE rates for ceritinib were based on those reported in the ASCEND-4 trial, and for crizotinib were based on those in the PROFILE-1014 trial. The adverse events that were included as costs in the model, based on these criteria, were:

- Neutropenia
- Diarrhoea
- Pulmonary embolism
- Vomiting
- Hyperglycaemia
- Alanine transaminase (ALT) elevation
- Aspartate Aminotransferase (AST) elevation

- Gamma-glutamyltransferase increased
- Blood alkaline phosphatase increased

The unit costs associated with each AE were derived from the National Schedule of Reference Costs for 2015 to 2016. Similarly to previous submissions (crizotinib), the adverse events were applied as one-time events and, within the CS model, the costs occurred in cycle 0 and cycle 1. The adverse event costs included for ceritinib were £340.27 and for crizotinib were £218.23. Only adverse events associated with the first-line treatments were included in the CS model.

ERG's comments

The ERG does not identify any areas of concern regarding the company's derivation of the adverse event costs for first-line treatment – apart from their half-cycle correction which might underestimate the cost. The ERG's clinical advisor thought that the costs may be a little underestimated, however, when the ERG doubled the unit costs of the various adverse events presented in the CS, the ICER went up by only 0.74%, the ERG did not explore this parameter any further.

However, the ERG has some concerns because the adverse events associated with the second-line therapies were not included in the model. In the points for clarification, the ERG asked the company to justify why the safety profile for second-line therapy was not modelled and to present a scenario including these costs.

The company responded that second-line adverse events costs were not modelled as these costs were considered to have a limited impact on the ICERs. The justification provided for this was that the deterministic analysis of the ICERs, when varying the first-line adverse event costs, made little difference to the ICER (going from £27,709 to £28,163) and it was expected that second-line adverse events would have an even smaller impact on the ICER. Therefore, the scenario analysis requested by the ERG was not undertaken. The ERG accepts the logic presented by the company, but would have welcomed the inclusion of these costs in the model, so as to remove the uncertainty.

5.2.9.5 ALK Testing

The company did not include ALK testing in their base-case analysis. The CS states that the base-case analysis assumes that ALK testing is a routine cost for both ceritinib and crizotinib and, therefore, does not need to be included.

ERG's comments

The ERG considers the omission of ALK testing to be appropriate, even though there may be some uncertainty around which test is most commonly used and in which sequence. As stated by the CS,

ALK testing would be equally applied to both ceritinib and crizotinib and so is a common cost for both treatment pathways, which would not affect the choice between the two comparators.

5.2.10 Cost-effectiveness results

Both ceritinib and crizotinib have a confidential patient access scheme (PAS), comprising a simple discount. For ceritinib, this is [redacted]. The results in this section reflect the outcomes of the analysis *i)* when neither PAS was applied and *ii)* when the PAS for ceritinib was applied. The confidential appendix presented the results including both the ceritinib and crizotinib PAS.

The CS estimated that the base-case ICER for the comparison of ceritinib and crizotinib was £27,936 per QALY when no PAS were applied (Table 37). When the PAS for ceritinib was applied, the CS estimated that ceritinib would dominate crizotinib: ceritinib was associated with a higher number of QALYs, at a lower cost. These initial results indicated that ceritinib is a cost-effective use of NHS resources, using a £30,000 per QALY gained threshold.

Table 37: Base-case results (Adapted from CS, Table 47 and Table 48, p 109)

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without ceritinib PAS							
Ceritinib	106,954	4.51	3.22	14,985	0.66	0.54	27,936
Crizotinib	91,970	3.85	2.68	-	-	-	-
With ceritinib PAS							
Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Crizotinib	89,714	3.85	2.68	-	-	-	-
CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; PAS, patient access scheme							

Table 37 presents the base-case analysis of ceritinib. It shows that ceritinib was associated with increased costs (cost difference £14,985 without PAS applied; [redacted] with ceritinib PAS applied) and was more effective (gain of [redacted]), compared with crizotinib.

The CS also presented the disaggregated costs and QALY and LY gains in each arm, by health state (progression free and progressed disease) (CS, Table 49). The primary impact of applying the ceritinib PAS was to reduce the drug and drug administration costs for first-line treatment in the ceritinib arm. The application of the PAS for ceritinib also, however, reduced the drug and drug administration costs for second-line treatment in both the ceritinib and crizotinib arms. This is because patients in both arms are able to receive ceritinib after progression.

The disaggregated costs are presented in Table 38, the primary differences in costs were as follows:

- First-line drug and drug administration costs were the largest component of the total costs for both ceritinib (75.1% without PAS and [redacted]% with ceritinib PAS) and crizotinib (71.87% without PAS and [redacted]% with ceritinib PAS). Ceritinib patients spent a longer time on treatment, hence the higher cost; although the difference was reduced due to the relative dose intensity adjustments made, where ceritinib was associated with a lower dose intensity compared with crizotinib.
- Pre-progression medical costs were noticeably higher for ceritinib, compared with crizotinib (34.35%). This was due to ceritinib patients spending longer on treatment.

Table 38: Cost categories (adapted from CS, Table 49, and from the company's model)

	Without PAS			With PAS for ceritinib		
	Ceritinib	**Crizotinib**	**Ceritinib vs Crizotinib**	**Ceritinib**	**Crizotinib**	**Ceritinib vs Crizotinib**
Costs, £						
Drug and drug administration costs, first-line treatment	80,325	66,097	14,229	[redacted]	[redacted]	[redacted]
Drug and drug administration costs, second-line treatment	7,641	8,261	-620	[redacted]	[redacted]	[redacted]
Treatment-associated AE costs	333	211	122	[redacted]	[redacted]	[redacted]
Medical costs	18,655	17,401	1,254	[redacted]	[redacted]	[redacted]
PF costs	4,245	2,787	1,458	[redacted]	[redacted]	[redacted]
PD costs	8,320	8,307	13	[redacted]	[redacted]	[redacted]
Terminal care costs	6,089	6,307	-218	[redacted]	[redacted]	[redacted]
Total costs	106,954	91,970	14,985	[redacted]	[redacted]	[redacted]

CS, company submission; PAS, patient access scheme; AE, adverse event; PF, progression-free; PD, progressed-disease

In the base-case analysis, ceritinib generated both higher QALYs and higher LYs, compared with crizotinib. These results are presented in Table 39. Ceritinib generated nearly all of its additional QALYs and LYs within the progression-free health state; post-progression QALYs and LYs were approximately equal to those with crizotinib.

Table 39: Effectiveness categories (adapted from CS, Table 49, and from the company's model)

	Ceritinib	Crizotinib	Ceritinib vs Crizotinib
Total QALYs	3.22	2.68	0.54
QALYs: PF	1.55	1.02	0.53
QALYs: PD	1.66	1.66	0.00
Total LYs	4.51	3.85	0.66
LYs: PF	1.92	1.26	0.66
LYs: PD	2.59	2.59	0.00
CS, company submission; QALYs, quality-adjusted life-years; PF, progression-free; PD, progressed-disease; LYG, life-years gained			

5.2.11 Sensitivity analysis

The following sections present the sensitivity analyses undertaken by the company.

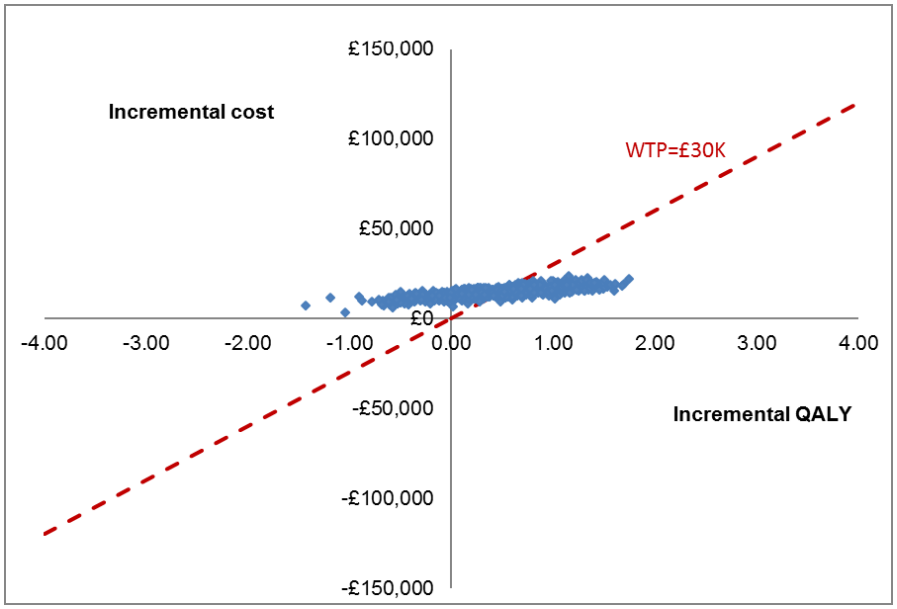
5.2.11.1 Deterministic Sensitivity analysis

The CS presented the results of a variety of one-way deterministic sensitivity analyses to highlight the uncertainty around different individual model parameters and how this impacts on the ICER. Within the deterministic sensitivity analyses (DSA) undertaken, each parameter was varied between an upper and lower limit. The base-case analysis resulted in the ICER varying from £13,758 to £61,070 per QALY. The company also presented a tornado diagram of the results of the DSA (CS, Figure 23, p 117), which suggests that the parameters with the largest effects on the ICER were the drug dose intensity estimates, drug costs, post-progression treatment assumptions and treatment discontinuation assumptions.

5.2.11.2 Probabilistic Sensitivity analysis

The CS undertook a probabilistic sensitivity analysis, in which a Monte-Carlo simulation, with 1,000 iterations, was undertaken. The CS presented the specific distributions used for the model inputs, from which random estimates were drawn for each iteration. The probabilistic ICER for the comparison of ceritinib and crizotinib was £29,239 per QALY, which was similar to, although slightly higher than, the base-case ICER. Figure 10 presents the incremental cost-effectiveness plane for ceritinib compared with crizotinib, resulting from the probabilistic sensitivity analysis.

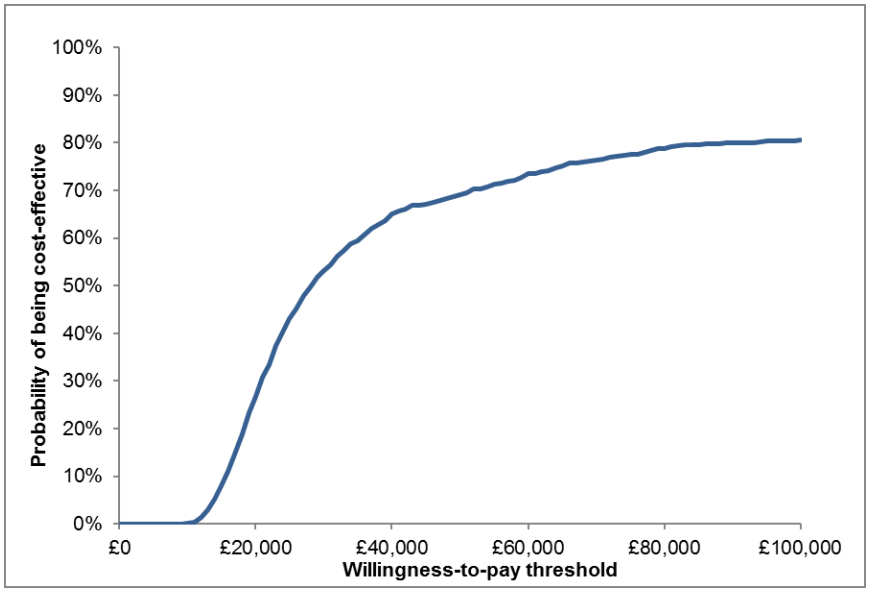
Figure 10: Incremental cost-effectiveness plane for ceritinib vs crizotinib (CS, Figure 21, p 113)



As can be seen from Figure 10, the probabilistic sensitivity analysis estimated that ceritinib was associated with higher costs in all iterations, compared with crizotinib and was associated with higher QALYs in 87% of iterations.

The CS also presented a cost-effectiveness acceptability curve (CEAC), which is presented in Figure 11. This figure illustrates the probability of ceritinib being cost-effective at different threshold values. As illustrated in the CEAC, the probability of ceritinib being cost-effective, using thresholds of £20,000, £30,000 and £50,000 per QALY, was 26.2%, 53.6%, and 71%, respectively.

Figure 11: Cost-effectiveness acceptability curve for ceritinib vs crizotinib (CS, Figure 22, p 114)



When the probabilistic sensitivity analysis was undertaken with the PAS for ceritinib included, ceritinib continued to dominate crizotinib. Figure 12 presents the incremental cost-effectiveness plane for ceritinib, compared with crizotinib, resulting from the probabilistic sensitivity analysis (PSA) undertaken with the ceritinib PAS included.

Figure 12: Cost-effectiveness acceptability curve for ceritinib vs crizotinib, with ceritinib PAS included (Figure from submitted model)

[redacted]

As can be seen from Figure 12 the probabilistic sensitivity analysis estimated that ceritinib was associated with lower costs in all iterations, compared with crizotinib, and was associated with higher QALYS in 87% of iterations. The PSA also indicated that the probability of ceritinib being cost-effective, when the PAS price is used, was [redacted]; that is, [redacted] of the values fell in the south-east quadrant of the cost-effectiveness acceptability curve.

5.2.11.3 Scenario analysis

The company undertook some scenario analyses. Although these scenarios are described throughout the ERG report, Table 40 collates these analyses and presents their impact on the ICER for ceritinib vs crizotinib, both with and without the PAS price for ceritinib included. As with the other results presented in this section, it is important to note that these results do not include a PAS which is in place for crizotinib.

Table 40: Scenario analyses reported throughout the CS with or without a PAS for ceritinib (not including the PAS for crizotinib) (adapted from CS, Table 51, p 117)

Base-case assumption	Scenario	ICER for ceritinib vs crizotinib (£/QALY) – without PAS	ICER for ceritinib (with PAS) vs crizotinib (£/QALY)
Base-case		£27,936	Dominant
Time horizon of the model is 20 years	Time horizon of the model is set to 5 years	£41,407	Dominant
Time horizon of the model is 20 years	Time horizon of the model is set to 10 years	£33,593	Dominant
Time horizon of the model is 20 years	Time horizon of the model is set to 15 years	£29,440	Dominant
Annual discount rate of costs and QALYs is 3.5%	Annual discount rate of costs and QALYs set to 0%	£26,196	Dominant
Annual discount rate of costs and QALYs is 3.5%	Annual discount rate of costs and QALYs set to 6%	£28,934	Dominant
First-line treatment until discontinuation (based on truncated median duration data reported in the ASCEND-4 and PROFILE 1014	Treatment until discontinuation (assuming equivalent time of treatment for ceritinib and crizotinib, with both based on ASCEND-4)	Dominant	Dominant
First-line treatment until discontinuation (based on truncated median duration data reported in the ASCEND-4 and PROFILE 1014	Treatment until discontinuation (assuming equivalent time of treatment for ceritinib and crizotinib, with both based on PROFILE 1014)	Dominant	Dominant
First-line treatment until discontinuation (based on truncated median duration data reported in the ASCEND-4 and PROFILE 1014	Treatment until progression	£43,921	Dominant
First-line treatment until discontinuation (based on truncated	Treatment until discontinuation or progression, whichever occurs first	£28,398	Dominant

median duration data reported in the ASCEND-4 and PROFILE 1014			
Post-progression treatment distribution based on those used in ASCEND-4 and PROFILE 1014	"Real world" distribution, estimated based on consultation with clinical experts	Dominant	Dominant
CS, company submission; PAS, patient access scheme; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years			

5.2.11.4 Subgroup analysis

No subgroup analysis was undertaken in this submission. The CS justified this by stating that their clinical data indicated that the clinical benefits of ceritinib over chemotherapy were consistent across the entire patient population.

ERG's comments

The ERG agrees that Figure 12 (CS, p 52) indicates that the clinical benefit was consistent across the entire population. However, this figure also shows that the median PFS for patients with and without brain metastases was quite different (25.3 for without, and 10.7 for with, brain metastases at screening). Given this difference in an important parameter within the model, the ERG thinks that a subgroup analysis of patients with and without brain metastases present at screening would have been useful.

5.2.11.5 Revised economic model results

After reviewing the original model, the ERG requested that the company provide additional information around some of the assumptions made, in their analysis, and include some additional analyses in their model. The requests for clarifications and their rationale are summarised in Table 41.

The ERG acknowledges that there was no direct evidence on the effectiveness of ceritinib and crizotinib. However, the ERG was particularly concerned with the reliability of the MAIC analysis, given the importance of its results within the model. Consequently, to explore the underlying uncertainty in the model, due to the MAIC results, the ERG requested several scenario analyses, which included an alternative source of data to estimate the relative effectiveness of crizotinib with the MAIC. The ERG also requested additional information and analysis around the clinical data for ceritinib, adverse events included, the time-on-treatment estimates, cost categories included in the model, and post-discontinuation care for patients in both comparators.

Table 41: Points for Clarification

ERG request [PFC number]	Rationale for request	Company response	Action in new company model
A re-analysis so that the base-case models the population in PROFILE 1014 trial population. [B1 (i)]	An alternative scenario analysis to assess the reliability of the MAIC analysis.	The company modified the base-case analysis by refitting the parametric functions of PFS and OS for ceritinib to match the PROFILE 1014 population. The truncated median time on treatment was similarly re-calculated.	The model was updated to incorporate this alternative method.
Using the analysis from B1 (i) fit the parametric curves to the Kaplan Meier data independently.	To test the assumption of proportional hazards used in the base-case analysis.	The company modified the analysis undertaken above as requested.	The model was updated to incorporate this alternative method.
Re-run the MAIC analysis using clinical data from the ALEX trial, rather than the PROFILE 1014 trial, for crizotinib. [B2 (i)]	An alternative scenario analysis to assess the reliability of the MAIC analysis.	The company undertook a MAIC analysis using data on crizotinib from the ALEX trial, using the same approach that was used in the previous MAIC undertaken in the CS.	Alternative MAIC results were presented, which the ERG was able to incorporate in the model. No action in the model was undertaken.
Re-run the MAIC analysis using clinical data from the ALEX trial combined with the PROFILE 1014 trial, for crizotinib. [B2 (ii)]	An alternative scenario analysis to assess the reliability of the MAIC analysis.	The company stated that they were unaware of any methodology to facilitate this analysis.	None taken.
The analysis from B2 to be incorporated into the model. [B3]	To assess these additional scenario analyses' effect on the ICER.	The company stated that they did not have time to incorporate these analyses in the model but did provide the necessary information required for the ERG to undertake the inclusion.	Parameter values were presented but no action in the model was undertaken.
Further exploration of the weighting used to match the IPD from ASCEND-4 to PROFILE-1014. [B4]	The CS states that only mild weighting was required to match these data but the process of matching had a large impact on median survival with ceritinib.	The company stated that although the median changed, the 95% CI did not changed substantially.	A comparison of QALYs and LYs before and after the MAIC re-weighting was undertaken. No action in the model was undertaken.
Further exploration of the impact of baseline characteristics on time on treatment. [B5]	Time on treatment is a key driver of costs and the ERG wanted to understand how differences in baseline characteristics may affect this parameter.	The company conducted additional scenario analyses using the MAIC-adjusted time–on-treatment estimates for ceritinib.	None taken.
Present population – adjusted estimates of time on treatment using methods similar to those used to estimate PFS and OS in the base-case analysis. [B6]	Time on treatment for the two comparators is estimated from two different trial populations. The ERG suggests that these differing populations	The MAIC methodology was used to estimate time on treatment for people on ceritinib adjusted to the crizotinib population and a hazard ratio for time on	Parameter values were presented but no action in the model was undertaken. Instructions on how to replicate the analyses were provided.

ERG request [PFC number]	**Rationale for request**	**Company response**	**Action in new company model**
	influence the estimated time on treatment.	treatment in the crizotinib population was estimated.	
Include subgroup analysis within the MAIC analysis. [B7]	The rates of adverse events for ceritinib and crizotinib may differ within different patient populations, such as those with brain metastases. The inclusion of these varying outcomes may affect the outcome of the model.	The proportion of patients with AEs was similar across subgroups and so adjusting for this would have minimal impact on the ICER.	None taken.
Some discrepancies were noted between the data in the CS and in the ASCEND-4 CSR [B8]	Clarifications of the correct data.	Adverse event definition and sources were confirmed.	None taken.
Clarification on the difference between adverse event definitions and rationale for their inclusion/exclusion in the model. [B9]	To ensure that all appropriate adverse events were captured in the model.	Additional information on the adverse event definitions was provided. Deterministic sensitivity was also presented to highlight the lack of impact of SAEs and 3/4 serious AEs had on the results.	None taken.
Clarification around the instances of AEs per patient. [B10]	To ensure that all appropriate adverse events were captured in the model.	Clarification provided.	None taken.
Provide a scenario where the safety profiles of the second-line therapies were included in the model. [B11]	The ERG expects that the number of adverse events would differ in each arm, based on the different distributions of treatments provided after discontinuation.	The company believes that this cost component would have little impact on the model results.	None taken.
Provide information on the number of patients who continued treatment with ceritinib, post-progression. Provide further information on the exponential curve used and information on any other curves used. [B12]	Time on treatment for ceritinib as calculated from the exponential function appears to underestimate the actual time on treatment.	Additional information was provided.	None taken.
Include quality of life estimates for patients on ceritinib and crizotinib, including sub-groups such as patients with brain metastases, in the MAIC analysis. [B13]	The inclusion of this outcome within the analysis may have an effect on the outcome of the model.	The company believes this outcome is already included in their analysis.	None taken.
Provide additional information on how EQ-5D	To ensure that all appropriate quality of life	Additional information was provided.	None taken.

ERG request [PFC number]	**Rationale for request**	**Company response**	**Action in new company model**
data were collected within the ASCEND-4 trial. [B14]	estimates were captured in model.		
Clarification on why drug and drug administration and pre-progression costs were half in the first cycle of the model. [B15]	To ensure that all costs were appropriately captured in the model.	The company explained their half-cycle corrections.	None taken.
Justify the application of the same post-progression costs for both comparators. [B16]	To ensure that all costs were appropriately captured in the model.	Justification and clarification were provided.	None taken.
Justify why radiotherapy was not included in the health state costs in the model. [B17]	To ensure that all costs were appropriately captured in the model.	Justification was provided.	None taken.
Justify why the same proportion of patients received active therapy post-discontinuation in each arm of the model. [B18]	To ensure that all costs were appropriately captured in the model.	Justification was provided and an additional scenario analysis was undertaken.	None taken.
Justify the assumption that the duration of each second-line therapy is the same for both treatment arms. [B19]	To ensure that all costs were appropriately captured in the model.	Justification was provided.	None taken.
Clarify if the duration of second-line therapies was recorded in the ASCEND-4 trial. [B20]	To ensure that all costs were appropriately captured in the model.	Confirmation that these data were not collected.	None taken.
ERG, evidence review group; PFC, points for clarification; PFS, progression-free survival; OS, overall survival; MAIC, matching adjusted indirect comparison; CS, company submission; IPD, individual patient data; CI, confidence interval; QALY, quality-adjusted life year; LY, life year; AE, adverse event; ICER, incremental cost-effectiveness ratio; CSR, clinical study report			

In their response, the company provided some additional information, justifications and analysis to address the concerns of the ERG. Some of the additional analyses resulted in revised results, based on the scenario analyses requested. These results, along with the point for clarification (PFC) to which they relate, are presented in Table 42 below.

Table 42: Revised results, based on PFC adjustments

PFC Number	Scenario	ICER for ceritinib vs crizotinib (£/QALY) – without PAS	ICER for ceritinib (with PAS) vs crizotinib (£/QALY)
B1 (i)	Re-adjustment of base-case to population in PROFILE 1014	£29,149	Dominant
B1 (ii)	Using adjustment in B1 (i) and fit the parametric curves to the Kaplan Meier data independently	£38,534	Dominant
B3 (i)	Base analysis where the clinical data is derived from a MAIC analysis using ALEX data for crizotinib	£32,386	Dominant
B3 (ii)	Using adjustment in B3 (i) and re-fitting the parametric functions of ceritinib PFS and OS	£31,766	Dominant
B6	Using MAIC-weighted population –adjusted estimates of time on treatment using methods similar to those used to estimate PFS and OS in the base-case analysis	£37,344	Dominant
PFC, points for clarification; MAIC, matching adjusted indirect comparison; PFS, progression-free survival; OS, overall survival			

5.2.12 Model validation and face validity check

5.2.12.1 Validation carried out by the company

The company stated that three expert clinicians were consulted to evaluate the key model parameters and inputs. The following issues/areas were discussed (as per their summaries of the meetings):

- Model structure
- Including crizotinib as the sole comparator
- Including ALK-testing costs in the model
- The indirect comparison methods used
- Efficacy estimations
- Post-progression treatment
- Target population
- Time on treatment
- Utilities
- Overall response rate
- Cross-over in OS data
- Post-progression resource use
- Sensitivity analysis
- Overall response rate definition

- Subgroup analyses

The feedback from these clinical experts was similar to that from our clinical advisor.

5.2.12.2 Validation carried out by the ERG

The ERG undertook a review of the company's base-case and sensitivity analyses. This included the use of a checklist to carry out a series of black-box tests to evaluate the internal validity of the model.

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 main calculation sheets, with a view to understanding how the QALYs and costs accumulated in the model.

- The ERG noted a number of errors in how the half-cycle correction was implemented in the model, specifically for attributing costs to adverse events and to drugs.
- AE costs were applied as a one-off event at the beginning of the model. The company inappropriately applied a half-cycle correction, where the costs of half of these events were applied in the first cycle and half in the second cycle. In the second cycle, costs were applied to patients who were still living. The inclusion of such an adjustment would not be necessary given that the AE rates were taken from the whole on-treatment period and reflect the survival in each arm. As such, the ERG removed the half-cycle correction.
- The discount rate applied per cycle corresponded to the cycle number and was not adjusted for cycle length (for example, the costs incurred in cycle 2, corresponding to month 2, were discounted with rate t=2 rather than t=2/12).

Section 6 provides base-case results, adjusted for all the calculation errors identified by the ERG.

5.3 Conclusions of the cost-effectiveness section

A limited number of cost-effectiveness analyses of ceritinib and other targeted therapies were identified in the systematic review presented in the CS. One of these studies was considered relevant to the current submission: a cost-effectiveness analysis of crizotinib, taking a UK perspective and designed to be consistent with the NICE reference case.

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 base-case ICER presented in the CS was £27,936 per QALY; including the PAS for ceritinib (but not the PAS for crizotinib) resulted in ceritinib dominating crizotinib (with lower costs and more QALYs). The ICER when the PAS for crizotinib is applied was provided in a confidential appendix.

The ERG identified that the electronic economic model, submitted by the company, contained a small number of minor errors. These were in relation to how the half-cycle correction and discounting were applied. As a consequence, the ICER presented in the CS is slightly overestimated but is largely reliable. In addition to these interval validity issues, the ERG identified a number of uncertainties surrounding the assumptions made in the company's model, which limit the credibility of the company's results.

1. Reliability of OS data

Overall survival data from the ASCEND-4 trial, for ceritinib, and the PROFILE 1014 trial, for crizotinib, were immature, and so the extrapolation of the trial data was associated with considerable uncertainty.

2. Extrapolation of OS data

The choice of parametric model for OS was demonstrated to have a large impact on the model results. The company appears to have made their selection of survival curve for OS on the basis of statistical fit (AIC/BIC), and it does not appear that clinical plausibility was taken into account. The clinical advisor to the ERG suggested that the long-term survival estimates, based on the exponential curve, were implausibly high. The company's base-case model provides the most optimistic estimate of cost-effectiveness for ceritinib in this respect.

3. The MAIC to estimate the relative treatment effectiveness

The relative treatment effect was based on a MAIC, due to the lack of direct head-to-head evidence of the two comparators. The results of the MAIC are highly uncertain, and so the results of the cost-effectiveness analysis should be interpreted with caution.

4. Adjustment of clinical data

The hazard ratios for OS and PFS, used to estimate the relative effectiveness of crizotinib, were calculated using ceritinib data adjusted to the PROFILE 1014 population; however, they were applied to unadjusted survival curves for ceritinib (i.e. they reflected the outcomes in the ASCEND-4 population). The ERG is concerned with this discrepancy of the populations in which survival was modelled.

5. The assumption of proportional hazards

The company also assumed that the proportional hazards assumption holds, and justified this by inspecting the log-cumulative hazard plots for both PFS and OS. The ERG, however, considers that the rationale for proportional hazards is not sufficiently compelling and, given that the model is largely sensitive to these inputs, considers that the more conservative method of relaxing this assumption may be more appropriate.

6. Selection of second-line therapies

The modelling of second-line treatment in the ceritinib and crizotinib arms was based on what was received in the ASCEND-4 and PROFILE 1014 trials, respectively. There were inconsistencies between the model and the trial treatment distributions, however, specifically that a greater proportion of patients in the model were assumed to receive subsequent therapy. The distributions were also not considered to be reflective of general practice, which casts doubt on the face validity of the survival data. The company did not account for patients receiving multiple subsequent lines of therapy (real-world practice is expected to be platinum doublet followed by best supportive care, after ALK inhibitors). The assumption of equal duration and dose intensity of second-line therapy is also considered to be unrealistic.

7. Treatment duration

Time on treatment was estimated from the truncated median treatment duration in each trial, since patient-level data were not available for crizotinib. This method underestimated the treatment duration. Treatment duration was not adjusted for population differences between the ASCEND-4 and PROFILE 1014 trials (as it was for OS and PFS). The use of individual curves to model each arm was also inconsistent with how PFS was modelled, and it is considered to be more reasonable for these to be modelled in the same way. Modelling treatment duration for crizotinib relative to ceritinib would allow for the use of more accurate patient-level data from the ASCEND-4 trial to estimate the treatment duration.

8. Quality of life for progressed-disease patients

The progressed-disease utilities were not collected consistently in the trials and so were identified through a literature review. The study used was not fully generalisable, in that it was not specific to ALK+ patients and was conducted before ALK inhibitors were in routine use. Additionally, the same utility was applied to both ceritinib and crizotinib progressed-disease patients, which appears unreasonable, considering that patients would, in practice and in the model, receive a different mix of

therapy with either treatment. The PD utility was based on a weighted average utility of patients on different lines of therapy from the study, but is not considered to represent patients who remained on first-line therapy after progression (underestimates the utility). The utility value of patients remaining on first-line treatment after progression was also not captured, with the quality of life of these patients not collected in the utility study.

9. Drug wastage

No drug wastage was assumed for ceritinib or crizotinib. The dose intensity of ceritinib was substantially lower than that for crizotinib, which significantly lowers the cost of ceritinib in the model. This mean estimate may be unrealistic in a real-world setting and this price reduction would not be realised, due to wastage of surplus doses.

10. Administration cost

The treatment administration costs may be underestimated, as it seems implausible that the treatments could be administered by a pharmacist alone. Given that patients on ceritinib are on treatment for longer, they would be expected to have higher administration costs. The company's model, therefore, biases the cost-effectiveness results in favour of ceritinib.

In summary, the ERG considers the manufacturer's base-case ICERs to be overly optimistic towards ceritinib. Additional analyses undertaken by the ERG are presented in Section 6, and they 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 assumptions 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 errors identified in ERG's validation of the executable model. Section 6.3 details a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The analyses presented in Section 6.3 focus on exploring the following issues and uncertainties:

- Assumptions around the modelling of clinical data (PFS, OS and treatment duration);
- Alternative source of effectiveness data for crizotinib;
- Modelling the proportion of patients on second-line therapy;
- Alternative scenarios for modelling quality of life in post-progression patients;
- Drug wastage and administration cost for first-line and second line therapy.

In Section 6.4, based on a combination of the exploratory analyses presented in Section 6.3, the ERG presents an alternative ERG base-case that the ERG's considers to be more reflective of the cost-effectiveness of ceritinib. Section 6.5 presents a brief conclusion summarising the ERG's additional analyses.

The results in this section do not include the PAS for the comparator therapy crizotinib. Results for the company's base-case and all analysis carried out by the ERG with the PAS for crizotinib applied are instead presented in a separate confidential appendix.

6.2 ERG corrections and adjustments to the company's base case model

A small number of errors were identified by the ERG in the company model, see Section 5.2.11 for details. The impact of these corrections to the base-case results was small, with the ICERs (without ceritinib PAS) decreasing by about 6%.

Table 43: Results of the ERG-corrected company base case model

	Mean Costs	Mean QALYs	Incremental Costs	Incremental QALYs	ICER
CS base case					
Without PAS					
Ceritinib	106,954	3.22	14,985	0.54	27,936
Crizotinib	91,970	2.68	-	-	-
CS base case - with PAS for ceritinib					
Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Crizotinib	89,714	2.68	-	-	-
ERG-corrected base case					
Without PAS					
Ceritinib	115,116	3.69	16,133	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
ERG-corrected base case - with PAS for ceritinib					
Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Crizotinib	68,816	3.02	-	-	-

Please note that these results do not incorporate the confidential PAS for crizotinib. Please refer to the confidential appendix for results applying the PAS for both ceritinib and crizotinib.

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CS, company submission; PAS, patient access scheme

6.3 Additional ERG analyses

6.3.1 Effectiveness and extrapolation

The ERG conducted a series of analyses, exploring alternative assumptions around the modelling of the clinical data (namely, overall survival, progression-free survival and treatment duration for ceritinib and crizotinib). The exploratory analyses included:

- Adjustment of ceritinib clinical data from ASCEND-4 (OS, PFS and treatment duration) to the PROFILE 1014 population;
- Estimating time on treatment for ceritinib using patient-level data from ASCEND-4 and estimating the relative time on treatment for crizotinib using a hazard ratio;
- Alternative survival models to extrapolate overall survival.

All scenarios were applied within the context of the ERG corrected company model.

Proportional hazard of treatment discontinuation

As described in Section 5.2.4.2 the company's approach to modelling time on treatment underestimated the time on treatment for ceritinib patients and was inconsistent with the approach used to model PFS and OS. Table 44 presents the results of this analysis, which the ERG considers more consistent with the approach to modelling PFS and OS and which more accurately estimates duration of treatment on ceritinib. This approach also attempts to account for any differences in the base-line characteristics of crizotinib and ceritinib patients. The steps used to estimate treatment duration for ceritinib and crizotinib are as follows: (1) the KM for time on treatment for ceritinib is adjusted using the MAIC method; (2) median time on treatment is estimated from the adjusted KM curve; (3) the adjusted median for ceritinib and median time on treatment reported in PROFILE 1014 are then used to estimate a hazard ratio for treatment discontinuation for ceritinib versus crizotinib ([redacted]); (4) this hazard ratio is applied to the ceritinib time on treatment curve estimated from ASCEND-4 patient-level time-to-event data, fitted with an exponential curve. Time on treatment for ceritinib is therefore base on the extrapolated patient level data and time on treatment for crizotinib is estimated using the hazard ratio. The mean duration of first-line treatment using this methods for ceritinib was [redacted], and [redacted] for crizotinib (compared with [redacted] and [redacted] in the company base case for ceritinib and crizotinib respectively).

Table 44: Results of ERG analysis of proportional hazard of treatment duration

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	115,116	3.69	16,133	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
Proportional hazard of treatment duration					
Ceritinib	137,017	3.69	23,234	0.67	34,743
Crizotinib	113,783	3.02	-	-	-

Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CS, company submission; PAS, patient access scheme

As can be seen in Table 44, this alternative approach to estimating time on treatment results in increase in the ICER. This because the mean duration of treatment with ceritinib increases by a greater amount than for crizotinib, which results in an increase in incremental drug acquisition costs.

Population adjustment

Table 44 presents the results of an exploratory analysis where ceritinib clinical data from ASCEND-4 (OS, PFS and treatment duration) were adjusted to reflect outcomes in the PROFILE 1014 population. The ERG considers this a more consistent approach because the hazard ratios for OS and PFS were estimated using ceritinib data adjusted to the PROFILE 1014 population and therefore the sake of consistency the population modelled should be the PROFILE 1014 population.

Weighting the ASCEND-4 data to match PROFILE 1014 patient characteristics caused a slight upward shift in the parametric functions of PFS and OS compared to the base case (Figure 13). The company provided a population-adjusted time on treatment from ASCEND-4 for people on ceritinib adjusted to the PROFILE 1014 population, using a MAIC. This increased the median time on treatment from 15.27 months to [redacted].

Figure 13: Predicted OS and PFS for ceritinib base case and re-weighted curves (based on exponential distribution)

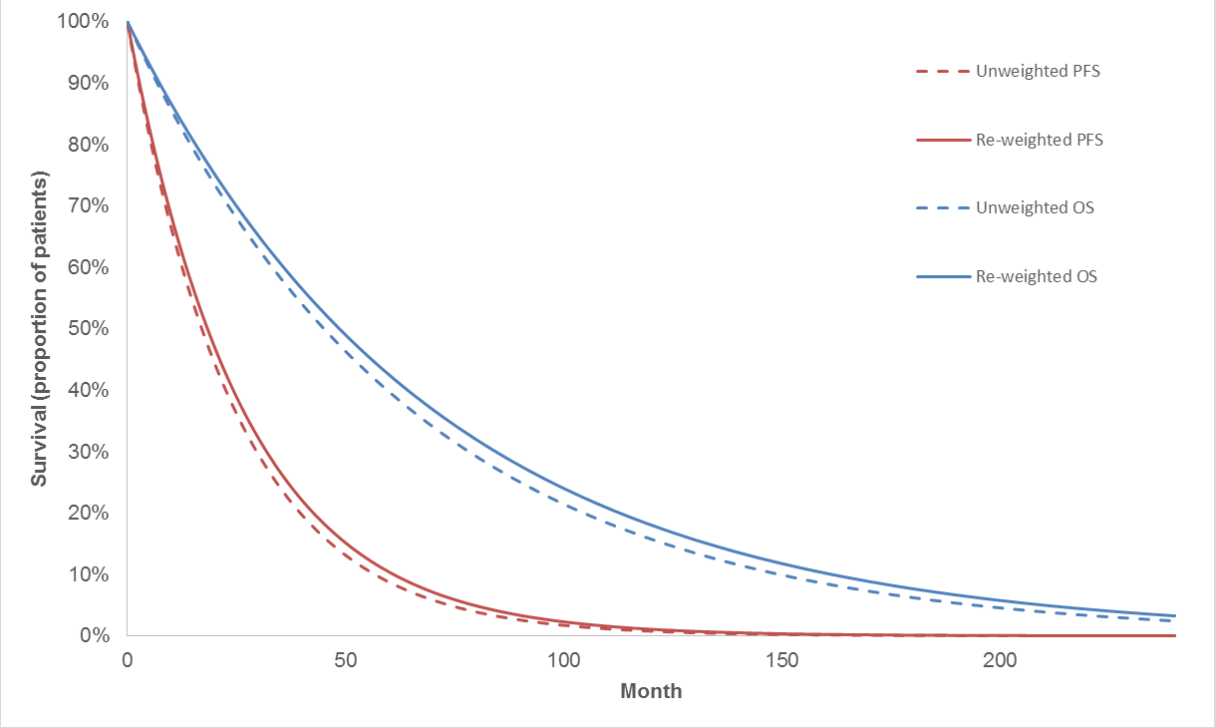


Table 45: Results of ERG analysis of clinical data matched to the PROFILE 1014 population

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	115,116	3.69	16,133	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
Clinical data matched to the PROFILE 1014 population					
Ceritinib	117,531	3.94	19,169	0.70	27,202
Crizotinib	98,362	3.24	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

This scenario resulted in a small increase to the ICER. The ERG felt that it was important for populations to be consistent and the PROFILE 1014 population was felt to be equally as representative as the ASCEND-4 population, but constraints of the MAIC methodology meant that the trial with only summary data available was the target population of the analysis.

Extrapolation of OS data

Alternative parametric models for overall survival to the exponential model used in the company base case were then explored. Other models explored were Weibull and Gompertz. Results of the scenarios are presented in Table 46.

The company provided a range of OS curves for ceritinib, re-analysed so that estimations were in the PROFILE 1014 population. For consistency, time on treatment was also modelled in the PROFILE 1014 population. Predicted OS with each parametric model are presented in Figure 14.

As with the exponential curve, weighting the ASCEND-4 data to match PROFILE 1014 patient characteristics caused a slight upward shift in the OS parametric functions. The shape of the different parametric functions, and their relative ranking in terms of fit with the observed data, was similar to the base-case parametric functions. The exponential function demonstrated the best fit with the observed data based on AIC/BIC statistics (but implausible results).

Figure 14: Predicted OS for ceritinib using different parametric functions (after applying MAIC weights to match PROFILE 1014 baseline characteristics) (Response B1 from PfC)

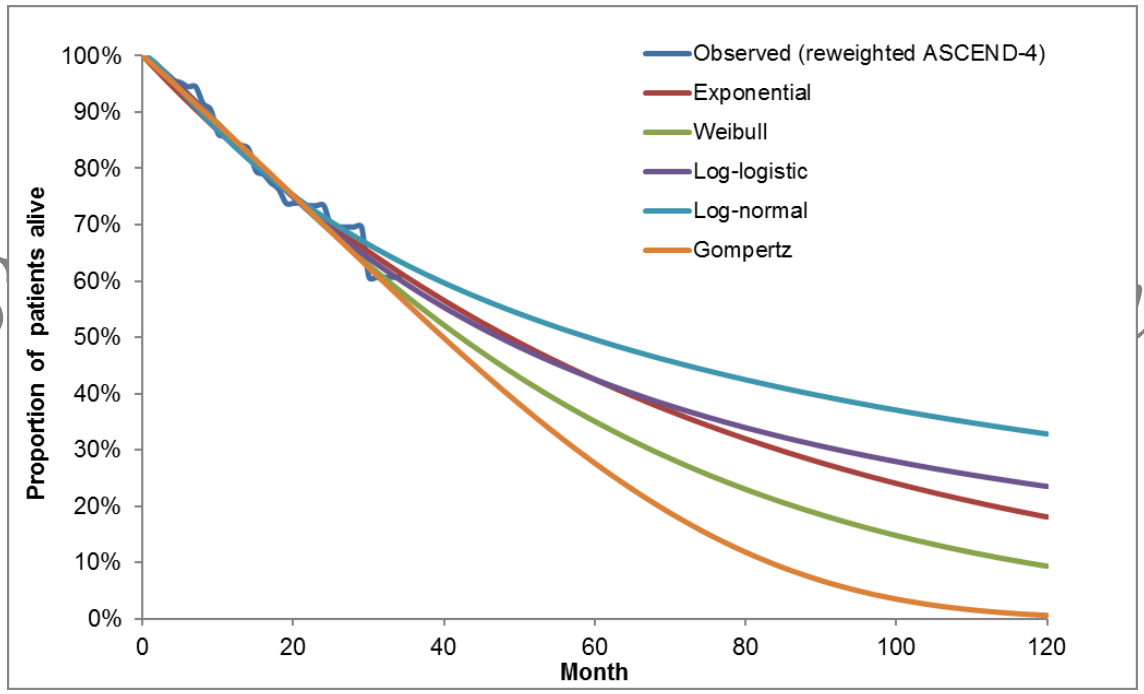


Table 46 Results of ERG exploratory analyses on alternative survival models for OS

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	115,116	3.69	16,133	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
Weibull curve to model OS					
Ceritinib	114,283	3.25	18,553	0.56	33,034
Crizotinib	95,730	2.69	-	-	-
Gompertz curve to model OS					
Ceritinib	111,454	2.66	17,775	0.39	45,257
Crizotinib	93,679	2.27	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied					

Both scenarios results in similar total costs but lower QALYs and an increase in the ICER compared to the ERG-corrected base case scenario. The company appears to make their selection of survival curve for OS on the basis of statistical fit (AIC/BIC), and it does not appear that clinical plausibility

was taken into account. The clinical advisor to the ERG suggested that long-term survival estimates based on the exponential curve were implausibly high. A later cut of data from Pfizer for PROFILE 1014 would help to determine the most appropriate set of assumptions for OS.

6.3.2 Alternative source of clinical data (ALEX trial for crizotinib)

The ERG have noted some concerns about the reliability of the effectiveness estimated derived from the MAIC analysis. The ERG considered that ALEX provided a relevant alternative source of data for the crizotinib patient population to PROFILE 1014.

To explore the impact on the cost-effectiveness analysis of this new MAIC analysis, the ERG requested that the company undertake the following two scenarios:

1. Using the data derived from the MAIC analysis, which used the crizotinib population from ALEX, where the population is adjusted to the ASCEND-4 study as per the company's base-case
2. Using the data derived from the MAIC analysis, which used the crizotinib population from ALEX, model the population to that the data is adjusted to the ALEX trial population.

In order to implement the first scenario, the company provided the ERG with the information presented in Table 47, which was based on the updated MAIC analysis requested.

Table 47: Hazard ratios of PFS and OS and truncated median duration of crizotinib under Scenario B3.i in the PfCs (Company response to PFCs)

Parameter	Parameter value under Scenario B3.i
Hazard ratio of PFS with crizotinib vs. ceritinib	[redacted]
Hazard ratio of OS with crizotinib vs. ceritinib	[redacted]
Truncated median time on treatment for crizotinib	10.7 months
PFS, progression-free survival; OS, overall survival; PfCs, points for clarification	

The effect of using the crizotinib population from the ALEX trial rather than the PROFILE 1014 trial is to increase the ICER of ceritinib vs. crizotinib from £26,354 to £30,212. The use of the ALEX trial data causes the total costs for crizotinib to reduce and the total QALYs to increase the. These results are presented in Table 48.

The second scenario required the analysis undertaken in the first scenario to be further modified, by re-fitting parametric functions of ceritinib PFS and OS, after weighting the ASCEND-4 data to match the base-line characteristics from the ALEX trial. This scenario also required the truncated median

time on treatment to be re-calculated for ceritinib after weighting the ASCEND-4 population to match the ALEX trial population, ([redacted]).

The effect of using the crizotinib population from the ALEX trial rather than the PROFILE 1014 trial, with the ASCEND-4 population being adjusted to match the ALEX trial population is presented in Table 48. Once again, the scenario increases the ICER of ceritinib vs. crizotinib, from £26,354 to £30,189. In this instance, the use of the ALEX trial data causes the total costs crizotinib to reduce, the total costs of ceritinib to increase and the total QALYs for both comparators to increase, compared the ERG's corrected base-case results. As with the previous scenario the ICER for ceritinib vs. crizotinib increases.

Table 48: Results from ERG exploratory analyses using ALEX trial data for crizotinib

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	115,116	3.69	16,133	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
ALEX for crizotinib effectiveness, ceritinib data in ASCEND-4 population*					
Ceritinib	115,116	3.69	18,841	0.62	30,212
Crizotinib	96,275	3.06	-	-	-
ALEX for crizotinib effectiveness, ceritinib data in ALEX population*					
Ceritinib	115,643	3.76	19,044	0.63	30,189
Crizotinib	96,599	3.13	-	-	-

Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.

*these results differ slightly (taking account of the ERG corrections) from those presented by the company. This was due to the company providing rounded parameter values, rather than formally incorporating these scenario analyses in the submitted, updated model. These rounded parameters resulted in slightly different ICERs being derived in the ERG's analysis, pre ERG correction. The ERG are not concerned with these slight differences.

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

These additional analyses show that the use of PROFILE 1014 within the MAIC analysis appears to be underestimating the ICER for ceritinib vs. crizotinib compared to using ALEX within the MAIC analysis. This scenario shows the inherent uncertainty of using the MAIC to estimate the relative effectiveness of ceritinib and crizotinib, with this adjustment increasing the ICER by approximately

12%. The ERG considers the use of the ALEX trial as source of effectiveness data for crizotinib equally valid to using PROFILE 1014.

6.3.3 Proportion of patients on second-line therapy

The ERG conducted a scenario analysis where the proportion of patients receiving second-line therapy was explored further. In the company base-case analysis, it was assumed that 60% of patients would receive further active therapy following discontinuation from ceritinib or crizotinib, based on clinical advice. This was larger than what was received in the ASCEND-4 and PROFILE 1014 trials, which was 35% and 43% respectively. In this scenario, the ERG explored the impact when the proportion of patients receiving second-line therapy in the model reflected that of the trials.

The results of this scenario are presented in Table 49. Use of the trial-based rates of therapy result in a decrease in total costs: the decrease is greater in the ceritinib arm (consistent with the lower rate of patients receiving second-line therapy), and subsequently incremental costs and the ICER decrease.

Table 49: Results of ERG exploratory analysis for distribution of second-line therapy

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	115,116	3.69	17,624	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
Trial-based second-line treatment distribution					
Ceritinib	111,744	3.69	16,692	0.67	24,961
Crizotinib	95,052	3.02	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

While the distribution of treatments in this analysis is less reflective of clinical practice, the ERG believe that this adjustment provides estimates that are more consistent with the costs that would be incurred in the trials, and that the company's base-case ICER is overestimating the incremental costs of ceritinib when compared with crizotinib in this respect.

6.3.4 Quality of life

The ERG conducted two scenario analyses around the progressed disease utility: In the first scenario models post-progression utility values were selected to reflect the real world treatment pathway, where patients initiating on crizotinib are expected to receive ceritinib as second-line ceritinib. In the

second scenario models post-progression utility values were selected to better reflect the trial-based treatment pathway, by accounting for the fact that significant proportion of patients receive first-line treatment beyond progression. In each scenario, two amendments were made. Table 50 presents the utility values from Chouaid[41]which were used to estimate post-progression utility in the base case, accompanied by a description of the amendments made to the calculation of the utilities used in the scenario analysis.

Table 50: Utility values used to estimate post-progression utility

Treatment	*n*	*Mean*	ERG comments
First-line PD	26	0.67	Corresponds to ALK patients who continue after progression – this is expected to be too low as it is based on patients on chemotherapy agents (not as effective as ALK inhibitors[9]) Remove this from the weighted average PD utility and replace with the sustained utility adjustment Sustained utility estimated as the midpoint of pre-progression utility (0.81) for both crizotinib and ceritinib) and post-progression utility (see below).
Second-line PF	44	0.74	Corresponds to patients within the PF health state (patients who discontinue ALK inhibitors before progression) Remove this from the weighted average PD utility
Second-line PD	17	0.59	Trial scenario: Appropriate for calculations in both arms Real world scenario: Appropriate for calculation for ceritinib arm For crizotinib arm, second-line would be ceritinib – this value is expected to be too low. Alternative utility estimated to be 0.66 from Blackhall et al (value was redacted from the STA for second-line ceritinib, but notes that the values derived from their mapping exercise of ASCEND-2 utilities are consistent with the findings of the Blackhall study)
Third/fourth-line PF	24	0.62	Appropriate for calculation
Third/fourth-line PD	21	0.46	Appropriate for calculation
ALK, anaplastic lymphoma kinase; PD: progressed disease. PF: progression-free; STA, single technology appraisal			

In order to implement these scenarios, in meaningful way it was necessary to use the alternative method of estimating duration of first-line treatment outlined in 6.3.1. This is because in the company's base-case no patients are assumed to receive treatment beyond progression. To apply a sustained utility for patients receiving first-line treatment beyond progression an additional health

state was created, using the difference between the time on treatment curve and the PFS curve. Utility values used in the exploratory analyses undertaken by the ERG are presented in Table 51.

Table 51: Utility values in the ERG scenario analysis

Health state	Scenario 1: Trial scenario	Scenario 2: Real world scenario
Ceritinib		
Progression-free	0.81	0.81
Disease progression	0.56	0.56
Sustained utility on progression	0.68	0.68
Crizotinib		
Progression-free	0.81	0.81
Disease progression	0.56	0.58
Sustained utility	0.68	0.69
ERG, evidence review group		

Results of the scenario analyses are presented in Table 52. In each of the company-presented scenarios, the total number of QALYs accumulated in each arm were reduced when the alternative set of utility values were used. In the trial scenario, the same utility values were applied in each arm and this resulted in this scenario having a very similar number of incremental QALYs to the base-line scenario (the amended base case), and subsequently a smaller increase in the ICER. The real world scenario, however, resulted in a greater number of QALYs in the crizotinib arm compared with the trial scenario, reflecting that this scenario accounted for the improved quality of patients in the PD health state in this arm due to second-line ceritinib therapy. Therefore, this scenario had lower incremental QALYs and a higher ICER than the trial scenario. The ERG felt that the trial scenario was more defendable in this analysis despite the fact that it was considered to be less reflective of quality of life we might expect in clinical practice. This is because the OS benefits associated with second-line ceritinib were not mirrored in the clinical trial data, where only a small proportion of patients receive this treatment.

Table 52: Results of ERG exploratory analysis with alternative utility values for post-progression

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	115,116	3.69	17,624	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
Base line scenario (base case utility values alternative method of estimating time on treatment)					
Ceritinib	137,017	3.69	23,234	0.67	34,743
Crizotinib	113,783	3.02	-	-	-
Scenario 1: Trial scenario					
Ceritinib	137,017	3.03	23,234	0.53	43,894
Crizotinib	113,783	2.50	-	-	-
Scenario 2: "Real world" scenario					
Ceritinib	137,017	3.03	23,234	0.48	48,178
Crizotinib	113,783	2.55	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

6.3.5 Resource use and costs

The ERG conducted two scenario analyses to take account of the relative dose intensity assumptions applied to drug costs within the model, and to allow for some drug wastage to occur.

As discussed in Section 5.2.9, the ERG accept the relative dose intensity assumptions included in the CS model. However, in line with previous ERG submissions (TA406) the ERG consider it unreasonable to also include half cycle corrections for drug costs. Removing this correction allows for drugs prescribed at the beginning of the cycle to be wasted should a patient discontinue treatment within that cycle. This adjustment still allows for drug wastage as a result of discontinuation of treatment to effectively be treated as a cost-saving within the model. The impact of this adjustment is presented in Table 53. When compared to the ERG corrected base case, the ICER for ceritinib vs. crizotinib is reduced when the half-cycle correction is removed. This is because this scenario increases the total costs for both ceritinib and crizotinib.

The second scenario analysis relates to administration costs for the oral chemotherapies (ceritinib and crizotinib) in both first-line treatment and in subsequent treatment following progression. In Section 5.2.9, it was discussed that including a pharmacist's time for dispensing prescriptions is likely to be underestimating the treatment administration costs for the oral chemotherapies. The ERG also believe

that pharmacist's time cost does not take account of the administration costs required to implement the relative dose intensity assumptions included in the company's model. An outpatient administration cost, SB11Z, which is labelled as "Deliver oral exclusively oral chemotherapy" was included in the economic model. This cost was derived from NHS reference costs, 2015-2016 and is in line with the additional administration cost included in the previous appraisal of crizotinib (TA406). The monthly unit cost for this additional administration cost is £181. The results, when this cost is included, are presented in Table 53. In this instance, the total costs for ceritinib are increased to a larger degree compared with crizotinib and the resulting ICER increases to £29,676.

Table 53: Results of ERG exploratory analysis for drug and drug administration costs

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	115,116	3.69	17,624	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
Scenario 1 – remove half-cycle correction for drug cost					
Ceritinib	120,756	3.69	16,949	0.67	25,345
Crizotinib	103,807	3.02	-	-	-
Scenario 2 – additional administration cost included					
Ceritinib	123,263	3.69	19,845	0.67	29,676
Crizotinib	103,418	3.02	-	-	-
Scenario 3 – both scenarios incorporated					
Ceritinib	129,084	3.69	19,171	0.67	28,667
Crizotinib	109,914	3.02	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

Table 53 also presents the results when both of the scenarios relating to drug and drug administration costs are incorporated. The resulting ICER for ceritinib compared with crizotinib is £28,667. The ERG believe that these adjustments better reflect the costs that would be incurred in clinical practice and that the company's base-case ICER is underestimating the incremental costs of ceritinib when compared with crizotinib.

6.4 ERG preferred base-case analysis

Table 54 presents the ERG's preferred range of scenarios to estimate the cost-effectiveness of ceritinib compared with crizotinib. Based on the assessment of the company analysis and the exploratory analyses conducted in Section 6.3, the ERG considers that there is considerable uncertainty associated with the survival data that is not parameterisable.

The ERG presents two scenarios, and within each scenario an optimistic estimate and a conservative estimate of cost-effectiveness based on different methods to estimate long-term survival. Given the data immaturity from both trials and lack of long-term observational data in these patients to facilitate curve selection, the ERG does not think it is reasonable that one model can be selected confidently over any others.

The scenario is based on the following sets of assumptions:

- ERG resource use and costs (Section 6.3.5)
- Proportion of patients on second-line therapy based on the rates from the ASCEND-4 and PROFILE 1014 trials (Section 6.3.3)
- ERG utilities for post-progression patients, based on the "trial scenario" (Section 6.3.4)
- All clinical data in PROFILE 1014 population (Section 6.3.1)
- Gompertz survival curves for OS (Section 6.3.1).

The ERG considers the alternative scenario presented here to be at least as reasonable as the company base case analysis. Combining these modifications to the company model leads to a considerable increase in the ICER.

Table 54: Results of ERG preferred scenario analyses

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
ERG-corrected company base case					
Ceritinib	115,116	3.69	16,133	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
ERG preferred base case					
Ceritinib	156,083	2.40	25,596	0.37	69,255
Crizotinib	130,487	2.03	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied. Note that when adjusted for population differences and modelled with a hazard ratio, the mean treatment duration of ceritinib was [redacted], and [redacted] for crizotinib					

The ERG notes that these results should be interpreted with caution. Without access to patient-level data for crizotinib treatment duration, there is no way to accurately model crizotinib time on treatment since the truncated median approach underestimates duration. Treatment duration is a key driver of the model (as demonstrated by the results in Section 6.3.1). It is also difficult to validate the outcome of the hazard ratio approach without access to patient-level data.

6.5 Exploration of proportional hazards assumption

The analysis of the clinical data used in both the company's and ERG base-case analysis both make the assumption that the proportional hazards assumption holds i.e. that the hazard remain constant over the model time. In this section, the ERG explores the impact of relaxing the assumption that the hazards of disease progression, death and treatment discontinuation are not constant. To do this, separate parametric models were fitted to the PFS and OS curves. Time on treatment is estimated as per the company base-case suing the truncated median time on treatment. ASCEND-4 ceritinib survival data was re-weighted to match PROFILE 1014 patient characteristics as it is not possible to fit independent parametric curves while modelling the ASCEND-4 population.

Exponential survival functions for PFS and OS

Firstly, the ERG explored the use of the exponential curve when fit to the Kaplan Meier PFS and OS curves for ceritinib and crizotinib independently (B1b of PFC), to provide a comparison analogous to the company base-case.

Predicted PFS and OS used in this analysis are presented in Figure 15 and Figure 16 respectively (with the curve for crizotinib estimated with hazard ratio for comparison). With the exponential function, the two methods used to estimate PFS and OS for crizotinib were very similar, with the curve fit using the hazard ratio producing slightly lower survival estimates.

Figure 15: Predicted PFS for ceritinib and crizotinib using exponential parametric function

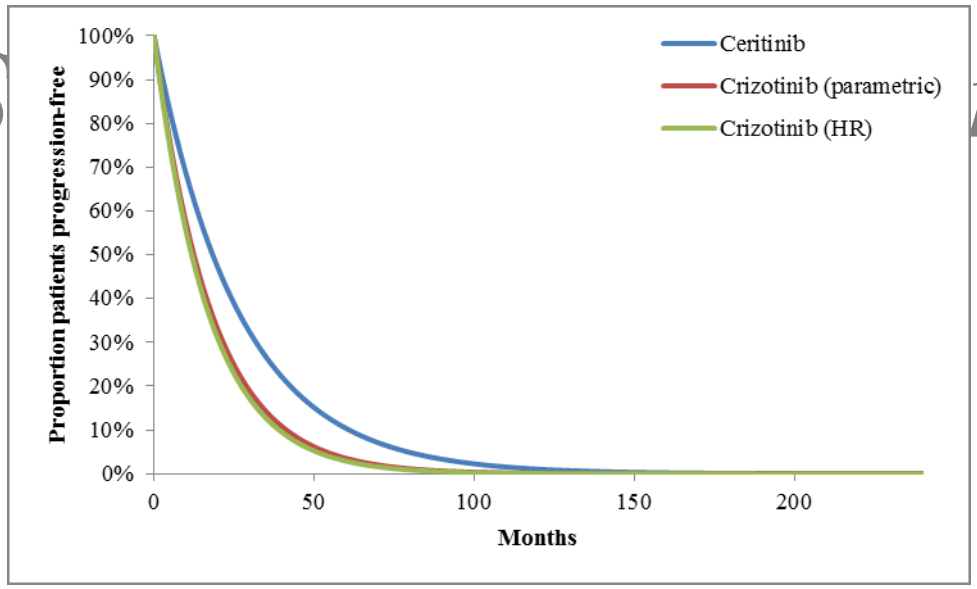
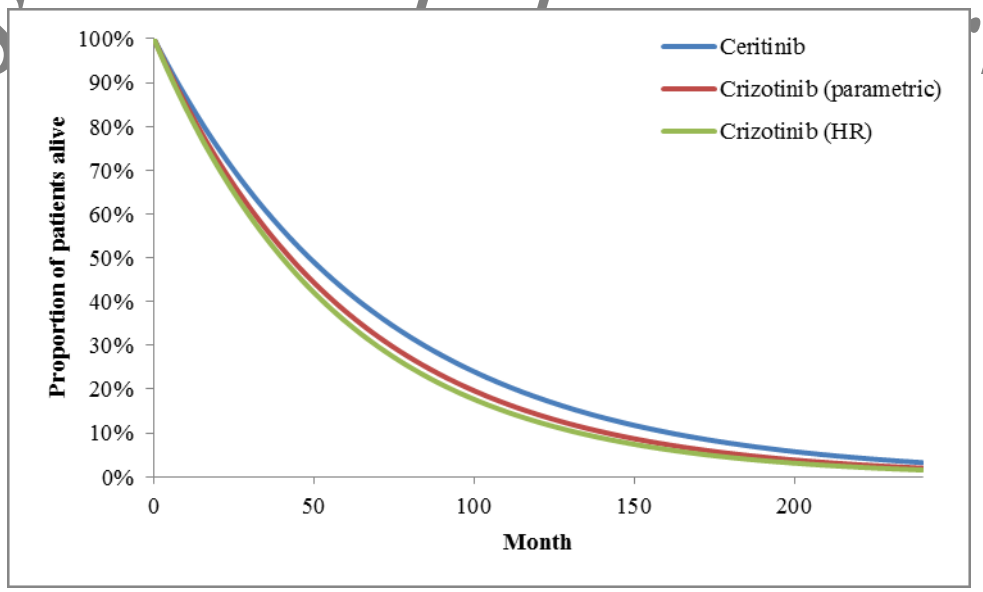


Figure 16: Predicted OS for ceritinib and crizotinib using exponential parametric function



Alternative parametric models for OS

The ERG then explored alternative parametric models for OS. Other models explored were Weibull and Gompertz. The same parametric curve was fitted to both ceritinib and crizotinib KM data , as the

ERG did not consider there sufficient justification for fitting curves of different types (e.g. exponential to the ceritinib arm and Weibull to the crizotinib arm). PFS continued to be modelled with the exponential function as the ERG accepted that this was the most appropriate distribution for this variable.

Predicted overall survival for ceritinib and crizotinib using different survival functions are presented in Figure 17 and Figure 18.**Error! Reference source not found.** According to AIC/BIC statistics, the exponential curve has the best statistical fit for both ceritinib and crizotinib. However, the ERG feels that the exponential curve is likely to overestimate survival for both ceritinib and crizotinib. Given current expectations regarding the long-term survival of patients on ALK inhibitors, the ERG considers the Weibull curve to be the most clinically plausible. Selecting this curve predicts that 35% of patients receiving crizotinib are alive at 5 years. This most closely matches the data available from the Davis study[29], which predicted that a similar proportion of patients would be alive after 3 years. The Weibull curve was also considered by the company in TA406 (first-line crizotinib)[9] to be the most plausible distribution.

Figure 17: Predicted OS for ceritinib using different parametric functions (after applying MAIC weights to match PROFILE 1014 baseline characteristics) (Company response to PFCs)

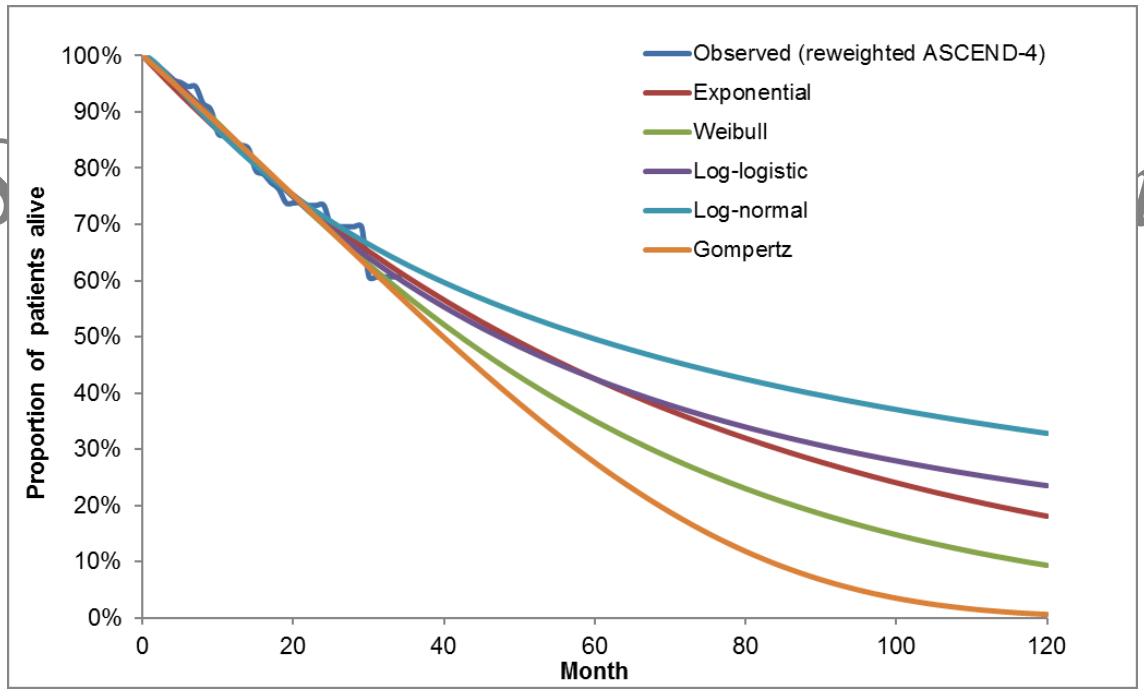
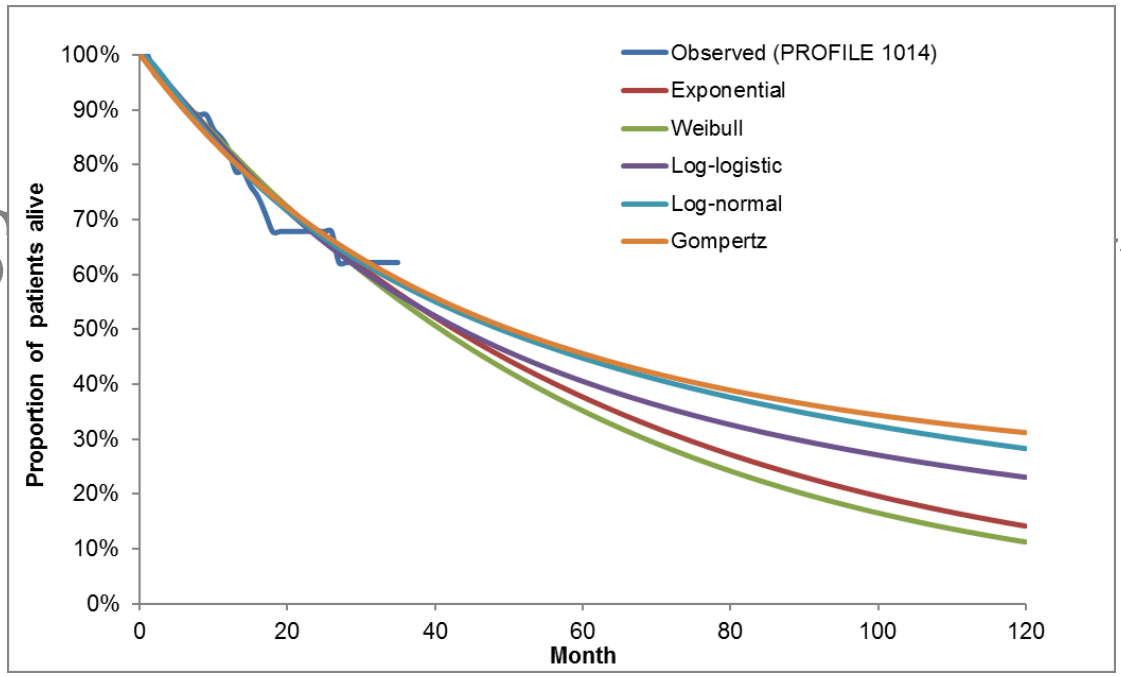


Figure 18: Predicted OS for crizotinib using different parametric functions (separately estimated based on published Kaplan-Meier curves from PROFILE 1014) (Company response to PFCs)



Results of the exploratory analyses

Results of the analyses using the exponential curve and Weibull curve are presented in Table 55. The use of the Weibull curve resulted in very similar estimates of long-term survival between the ceritinib and crizotinib arm, implying that the benefit of ceritinib over crizotinib is to delay progression rather than to extend overall survival. Given the uncertainty in overall survival for both comparators, this scenario could be considered a conservative approach.

Table 55: Results of ERG exploratory analyses of non-proportional hazards

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
ERG-corrected base case					
Ceritinib	115,116	3.69	16,133	0.67	26,354
Crizotinib	97,492	3.02	-	-	-
Exponential survival functions for PFS and OS					
Ceritinib	117,531	3.94	18,402	0.51	35,818
Crizotinib	99,129	3.43	-	-	-
Weibull survival function for OS					
Ceritinib	114,283	3.25	16,243	0.05	301,690
Crizotinib	98,039	3.19	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

Comparing the results of the analogous scenarios in Section 6.3.1, the results are similar in the analysis when exponential curves were used, implying that the assumption of proportional hazards is relatively plausible in this instance. However, the results are very different when the Weibull and curves is used, which may suggest that the assumptions of proportional hazards is inappropriate. The ERG is however, notes that he immaturity of the OS data means fitting independent parametric curves is subject to significant uncertainty. The ERG particularly highlights that predicted survival for patients receiving crizotinib is very high (regardless of curve selected) and substantially higher than reported in the Davis cohort study[29]. The apparent inconsistency in results when fitting independent parametric curves may therefore be the result of poor extrapolation rather the lack of any difference in OS.

The ERG also note there are some limitations to the implementation of independent survival curves (relaxing the proportional hazards assumption) as it means that alternative method of estimating duration of treatment used in 6.3.1 cannot be implemented as this relies on the proportional hazard assumption. Relaxing the proportional hazards assumption also prevents the ERG from implementing their alternative set of utility values (which rely in the creation of a post-progression on-treatment health state within the model).

6.6 Conclusions from ERG analyses

The ERG has presented a number of additional analyses. These analyses were carried out in a number of stages. The first stage addressed a number of minor calculation errors in the company's revised model (Section 6.2). The impact of these changes was to reduce the ICER by a small amount from £27,936 per QALY to £26,354 per QALY without ceritinib PAS applied. When the PAS for ceritinib was applied, ceritinib remained the dominant treatment option.

Using the corrected model, the ERG then presented a number of analyses considering a range of issues raised in Section 5 (Section 6.3). These scenario analyses addressed the following issues:

- Assumptions around how clinical data is modelled:
  - ERG method of estimating treatment duration;
  - The population in which effectiveness is estimated;
  - The extrapolation of OS data.
- Estimating the proportion of patients on second-line therapy from the ASCEND-4 and PROFILE 1014 trials;
- Alternative assumptions around how resource use and unit costs were incorporated, specifically around drug wastage and administration costs;
- How quality of life is modelled in post-progression patients: the use of alternative data sources to estimate health state utilities and alternative patient health states to predict quality of life.

The ERG also identified an additional source of data to model survival of patients receiving crizotinib (Section 6.3.2). The results of the analysis when using data from ALEX instead of PROFILE 1014 are broadly similar; the ICER increases from £26,354 per QALY to £30,189 per QALY.

The most of important these scenarios related to changes made by the ERG to the clinical data. These analyses explored two distinct issues with the assumptions made in the company's analysis; firstly the selection of survival curve to extrapolate overall survival, and secondly the method used to estimate time on first-line treatment. The results of this analysis demonstrated that these issues have a significant impact on the ICER, which is due in part to the immaturity of the OS data which leads to considerable uncertainty around the extrapolation. This exploration of alternative modelling assumptions was concluded with the ERG presenting a preferred set of assumptions.

The ERG presents a range of plausible ICERS to aid the Committee in determining whether ceritinib is cost-effective compared with crizotinib. The ERG's analyses suggests that the ICER for ceritinib compared with crizotinib may be £69,255 per QALY. These scenarios are 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 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 from ASCEND-4 and PROFILE 1014, which leads to considerable uncertainty around the extrapolation. Using the same parametric functions fitted in the company's base where proportional hazards is assumed and that provided the best statistical fit, this analysis resulted in an ICER of £35,818 per QALY. When using the Weibull parametric function which had the most conservative estimate of long-term survival for crizotinib the ICER increased to £301,690.

Based on the ERG's base-case analysis, there is considerable uncertainty around whether ceritinib is likely to represent good value to the NHS considering typical willingness to pay thresholds.

Superseded – see erratum

7 End of Life

Not applicable

Superseded – see erratum

8 Overall conclusions

The section should focus on any difference(s) of opinion between the company and the ERG that might influence the size of the ICER. Priority should be focussed on discussing information that will be useful to the Appraisal Committee including strengths, weaknesses and remaining uncertainties. Further summary of evidence is not required in this section.

There is reliable evidence that ceritinib has a beneficial effect on PFS when compared with pemetrexed/cisplatin plus pemetrexed maintenance therapy. There is no direct comparative evidence for ceritinib versus the current standard of care, crizotinib.

The presented comparison of ceritinib with crizotinib is based on a MAIC analysis, an observational comparison. The size of the PFS treatment difference generated by this analysis is uncertain.

The OS data from the RCT is immature; follow-up was too short for a definitive assessment of OS. The MAIC results for the OS treatment effect difference between ceritinib and crizotinib are highly uncertain, being the result of an observational comparison of immature data.

The economic evidence presented by the company primarily consisted of a *de novo* model. The company's model used a partition survival model approach which utilised parameterised data from the ASCEND-4 trial to determine the distribution of patients between the health states over time. The company found ceritinib to be more costly (cost difference of £14,985, without any PAS discounts applied) and more effective (0.54 QALY gain) compared with crizotinib. The deterministic base-case ICER (without any PAS discounts applied) was £27,936 per QALY, and the mean probabilistic ICER (without PAS) was £29,239 per QALY.

The ERG considers the company's assessment of cost-effectiveness of ceritinib to be uncertain with respect to a number of assumptions used in the model. These concerned the reliability of clinical inputs based on the MAIC comparison of ceritinib and crizotinib; the selection of survival model to parameterise and extrapolate overall survival; the method used to estimate duration of first-line treatment; the distribution and proportion of patients receiving second-line therapy; and, the inclusion of additional drug administration costs.

The ERG attempted to address some of the key issues and uncertainties by conducting a series of explanatory analyses exploring alternative assumptions and addressing the uncertainties identified in the company's model. The ERG base-case analysis estimated ceritinib to be more costly (cost difference £25,596, without PAS applied) and more effective (0.37 QALY gain) compared with

crizotinib. This suggests that the ICER for ceritinib compared with crizotinib, without any PAS applied, is £69,255 per QALY.

The ERG also carried out further exploratory analysis around the assumption of proportional 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. Using the same parametric functions fitted in the company's base and that provided the best statistical fit, the ICER was £35,818 per QALY (without PAS). When using the function in which best aligned with real world data on the benefits of ALK inhibiters, the ICER increased to £301,690 (without PAS).

8.1 Implications for research

Mature OS data for ceritinib and crizotinib are needed.

A RCT directly comparing ceritinib and crizotinib in untreated advanced ALK+ NSCLC is required to reliably evaluate the true difference in effect between these two treatments.

Superseded – see erratum

9 References

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10 Appendices

10.1 Additional records identified by ERG for review of cost-effectiveness studies

Record #1 of 9

ID: HTA-32015000583

TI: Diagnostic fluorescence in situ hybridisation (FISH) testing for Anaplastic Lymphoma Kinase (ALK) in advanced non-small cell lung cancer (NSCLC) to determine eligibility for crizotinib treatment (co-dependent). (Resubmission) (Structured abstract)

SO: Health Technology Assessment Database YR: 2014 NO: 4

PB: Medical Services Advisory Committee (MSAC)

Record #2 of 9

ID: HTA-32016000369

AU: NIHR HSRIC

TI: Alectinib for advanced ALK-positive, non-small cell lung cancer ? first line (Structured abstract)

SO: Health Technology Assessment Database YR: 2015 NO: 4

PB: NIHR Horizon Scanning Research&Intelligence Centre

Record #3 of 9

ID: HTA-32015000107 AU: NIHR HSC

TI: Crizotinib (Xalkori) for ALK-positive, locally advanced or metastatic, non-small cell lung cancer - first line (Structured abstract)

SO: Health Technology Assessment Database YR: 2015 NO: 4

PB: NIHR Horizon Scanning Centre (NIHR HSC)

Record #4 of 9

ID: HTA-32015001163

AU: Calderón M, Bardach A, Pichon-Riviere A, Augustovski F, García Martí S, Alcaraz A, Ciapponi A, López A, Rey-Ares L

TI: Ceritinib for the treatment of ALK-positive metastatic non-small cell lung cancer (Structured abstract)

SO: Health Technology Assessment Database YR: 2015 NO: 4

PB: Institute for Clinical Effectiveness and Health Policy (IECS)

Record #5 of 9

ID: HTA-32016000857

AU: NIHR HSRIC

TI: Ceritinib (Zykadia) - non-small cell lung cancer: locally advanced or metastatic; anaplastic lymphoma kinase (ALK) positive ? first line (Project record)

SO: Health Technology Assessment Database YR: 2016 NO: 4

PB: NIHR Horizon Scanning Research&Intelligence Centre

Record #6 of 9

ID: HTA-32015000435

TI: Diagnostic fluorescence in situ hybridisation (FISH) testing for Anaplastic Lymphoma Kinase (ALK) in advanced non-small cell lung cancer (NSCLC) to determine eligibility for crizotinib treatment (co-dependent) (Structured abstract)

SO: Health Technology Assessment Database YR: 2013 NO: 4

PB: Medical Services Advisory Committee (MSAC)

Record #7 of 9

ID: HTA-32016000370

AU: NIHR HSRIC

TI: Alectinib for locally advanced or metastatic ALK-positive, non-small cell lung cancer following failure of crizotinib (Structured abstract)

SO: Health Technology Assessment Database YR: 2015 NO: 4

PB: NIHR Horizon Scanning Research&Intelligence Centre

Record #8 of 9

ID: HTA-32013000355

AU: NIHR HSC

TI: LDK378 for ALK-activated advanced non-small cell lung cancer ? second and subsequent lines (Structured abstract)

SO: Health Technology Assessment Database YR: 2013 NO: 4

PB: NIHR Horizon Scanning Centre (NIHR HSC)

Record #9 of 9

ID: HTA-32013000256

AU: Semlitsch T, Jeitler K

TI: Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) (Structured abstract)

SO: Health Technology Assessment Database YR: 2013 NO: 4

PB: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID1117]

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

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 13 October 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

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

Contents

ERG model errors

Issue 1 Double application of the ERG's additional drug administration cost

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In scenarios that apply an additional drug administration cost of £181/month, the ERG's model mistakenly applies this cost twice per month that patients remain on first-line treatment: Within the trace for each treatment arm, this cost is first applied in the "undiscounted" cost column AL. It is then applied an extra time in the "discounted" cost column AM, which already reflects any cost components that were included in the undiscounted column.	Revise formulas in the discounted drug cost column of each trace, as described in the Technical Appendix.	Duplicate inclusion of the additional drug administration cost is a clear calculation error and results in bias against ceritinib. The company reiterates that the inclusion of a £181/month cost in the first place already represented double-counting; the ERG's extra inclusion of this cost now constitutes triple-counting. The model captures routine treatment monitoring costs through the monthly medical costs associated with progression-free survival, which is longer in the ceritinib arm.	The ERG apologises for this error and thanks the company for spotting it. The model has been amended so that the monthly oral chemotherapy administration cost is only incurred once each cycle.

Issue 2 Erroneous correction of the company's discounting formulas

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG erroneously corrected the company's application of discounting in the model, stating that the discount rate was not	The erroneous correction of discounting in the ERG's model should be reversed. Details of the proposed changes are included in the Technical Appendix.	Correction of inaccuracy in reporting and in the ERG's model calculations	The ERG apologises for this error and thanks the company for spotting it. Corrected in model. The validation section of the ERG report has been

adjusted for cycle length (e.g., pg. 116). To clarify, discounting in the company's model already accounted for cycle length. Namely, the annual discount rates of 3.5% for costs and 3.5% for effectiveness were first converted into monthly discount rates of ~0.29% and ~0.29%, which were then applied within the trace for each treatment arm.	The report text and results of the ERG's exploratory analyses should be corrected accordingly.		amended. Results relating to the ERG-corrected base case and ERG exploratory analyses have been updated (Section 1, Section 6, Section 8 and the confidential appendix).

Issue 3 Inconsistent discounting of QALYs vs. costs under the ERG's utility scenarios

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Under the ERG's preferred utility scenario, QALYs are more heavily discounted than costs when applying the ERG's "correction" to the company's discounting. Specifically, in the trace tab for each treatment arm: • QALYs in columns AA - AC are correctly discounted at an annual rate of 3.5%, as the formulas refer to the annual discount rate of effectiveness ("disc_eff") • Costs are discounted at a substantially lower rate, as	Reversing the ERG's erroneous discounting correction (as described in the Technical Appendix) should address this issue within the model. Note that the discounting formulas in AA - AC do not require revision. In the report, results and conclusions corresponding to the ERG's utility scenarios should be revised after this issue is addressed.	Inconsistent discounting of QALYs and costs under the ERG's utility scenarios leads to substantial overestimation of the ICER for ceritinib vs. crizotinib (by over £10,000 in the ERG's preferred base case).	Corrected (see Issue 2 above).

the ERG's discounting formula treats the ~0.29% monthly discount rate ("disc_cost2") as if it were an annual discount rate.			

Technical Appendix

Proposed model changes to address double application of additional drug administration cost:

In the trace tab for each treatment arm ("LDK_Summary" and "CRIZ_Summary"), the discounted drug and drug administration costs in column AM should be derived by discounting the corresponding undiscounted costs in column AL. No further cost components should be added in the discounted cost column AM. Please refer to the section below regarding the correct formula for discounting.

Proposed model changes to address erroneous correction of company's discounting:

Within the Excel model, the input cells containing the annual discount rates for costs (3.5%) and effectiveness (3.5%) are named "disc_cost" and "disc_eff", respectively. The model converts these annual discount rates into monthly discount rates, which are referred to as "disc_cost2" (~0.29%) and "disc_eff2" (~0.29%) in the model.

In the trace tab for each treatment arm ("LDK_Summary" and "CRIZ_Summary"), columns containing discounted costs or effects should employ the formula from the company's original submission, i.e., discounted outcome = undiscounted outcome/(1+monthly discount rate)^cycle number. The cycle number should not be divided by 12 in formulas that refer to the monthly discount rates "disc_cost2" or "disc_eff2".

Please note that the discounting formulas in columns AA through AC of each trace do not require revision. The ERG's formulas in these columns divide the cycle number by 12, but refer to the annual discount rate, "disc_eff".

Typographical errors and AIC/CIC mark-up in the ERG report

Issue 4 Redaction is no longer required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Redaction no longer required in following pages of the report: 1. Page 12, paragraph 5 2. Page 34, Table 4 3. Page 37, paragraph 2 and Table 6 4. Page 40, paragraph 2 5. Page 43, Table 9 6. Page 44, paragraph 1 7. Page 49, Table 11 8. Page 50, Table 12 9. Page 55, paragraph 4 and 5 10. Page 56, Table 17 11. Page 58, paragraph 1 12. Page 72, all numbers can be unredacted 13. Page 77, Table 23 14. Page 78, paragraph 3 15. Page 95, Table 32	Redaction can be removed.	No longer CIC/AIC.	On the advice of the NICE technical team The ERG has not implemented these changes (which are not factual inaccuracies in their report)

16. Page 97, Table 32 17. Page 109, Table 40 18. Page 114, Table 42 19. Page 126, paragraph 1 20. Page 127, paragraph 2			

Issue 5 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 44, paragraph 3: "A further difference between ACSEND-4..."	Correct to "ASCEND-4..."		Corrected
Page 72, paragraph 2: "Ceritinib patients received treatment for longer than ceritinib patients (a median of [redacted] months versus [redacted] months)."	Correct to: "Ceritinib patients received treatment for longer than crizotinib patients..."	Typographical errors which may lead to confusion.	Corrected
Page 74, paragraph 2: "[redacted] weeks and [redacted] weeks"	This should be months rather than weeks: "[redacted] months and [redacted] months"		Corrected
Page 79, paragraph 5: "The clinical advisor to the ERG also strongly asserted that ceritinib would not be prescribed after the discontinuation of crizotinib."	This should read: "The clinical advisor to the ERG also strongly asserted that crizotinib would not be prescribed after the discontinuation of ceritinib." Ceritinib treatment can follow crizotinib but ceritinib is unlikely to follow crizotinib.		Corrected
Page 98, paragraph 2: "The company's "real world" assumptions appear to be	The terms "ceritinib" and "crizotinib" need to appear in the reverse order. Ceritinib treatment		Corrected

conservative, they assumed that 60% of patients in the ceritinib arm receive crizotinib, where the ERG's clinical advisor believes it could be closer to 80%."	can follow crizotinib but ceritinib is unlikely to follow crizotinib.		
Page 122, paragraph 1: "Table 44 presents the results of an exploratory analysis where ceritinib clinical data from ASCEND-4 (OS, PFS and treatment duration) were adjusted to reflect outcomes in the PROFILE 1014 population."	"Table 44" should read "Table 45."		Corrected
Page 125, paragraph 5:" The use of the ALEX trial data causes the total costs for crizotinib to reduce and the total QALYs to increase the."	Incomplete sentence. The word "ICER" is missing.		Corrected
Page 139, paragraph 1, final sentence.	Incomplete sentence. The words "per QALY" are missing.		Corrected

Issue 6 Incorrect confidentiality categorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect confidentiality categorisation. 1. Page 74, Table 22, needs changing from CiC (turquoise) to AiC (yellow)	Please change CiC to AiC.	Incorrectly assigned confidentiality categorisation.	On the advice of the NICE technical team The ERG has not implemented these changes

2. Page 74, paragraph 2, needs changing from CiC (turquoise) to AiC (yellow) 3. Page 75, paragraph 4 4. Page 121, paragraph 1 5. Page 125, Table 47			

Issue 7 The PROFILE 1014 study is referred to as a number of other incorrect variants throughout the report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The Phase III trial registrational trial for crizotinib is PROFILE 1014: 1. Page 13, paragraph 5 (twice) 2. Page 14, paragraph 1 3. Page 44, paragraph 3 4. Page 44, paragraph 4 5. Page 45, paragraph 1 6. Page 45, paragraph 3 7. Page 48, paragraph 6 8. Page 49, paragraph 1 (twice) 9. Page 49, Table 11 title 10. Page 50 table 12 11. Page 50, paragraph 3 12. Page 52, Table 14 title 13. Page 53, paragraph 3 14. Page 54 Table 15 15. Page 56, paragraph 1 16. Page 56, Table 17 title and column heading 17. Page 58, paragraph 5 (several)	Please check/ensure this study is referred to as PROFILE 1014, and not 1010, 1040, 4, or other variants.	To minimise confusion with regard to the trial included in the model.	Corrected

Factual errors in the ERG report

Issue 8 Misleading presentation of OS evidence from Davis et al. (2017)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 87-88, the ERG cites real-world OS evidence to validate their alternative base-case OS assumptions, but omits pertinent information about the referenced study and does not acknowledge more recent and highly relevant OS data from PROFILE 1014 (Davis et al. 2017)[1]: "In Section 4.2, the ERG noted an additional study identified in their review, a retrospective cohort study assessing treatment patterns and outcomes in patients with ALK+ advanced NSCLC in a European population treated with crizotinib in regular clinical practice[29]. Figure 9 (adapted from the poster) presents overall survival in crizotinib patients by line of therapy. From crizotinib initiation, median OS was [redacted] months in first-line initiators (n=[redacted]). **The study authors commented that the**	The limitations of using Davis et al. to validate OS assumptions within the model and the availability of more recent data from PROFILE 1014 should be acknowledged: • The real-world population in Davis et al. included a larger percentage of current/former smokers and older patients compared to both the ASCEND-4 and PROFILE 1014 populations. Without any adjustment for these baseline differences, it is difficult to directly compare OS outcomes in this study with the model's trial-based OS extrapolations. • If real-world OS data is to be used to inform base-case OS assumptions, it is inconsistent to combine this approach with trial-based estimates of treatment duration. • Patient numbers at risk should also be included with the KM curves to assess the reliability of the estimates. The Report states that, "**The study authors commented that the outcomes for median**	The presentation of evidence from Davis et al. is potentially misleading and may overstate the applicability of this study to the current decision problem. Data from the Davis paper is used to support the ERG's belief that the Gompertz extrapolation of OS is more appropriate than an exponential extrapolation. However, the numbers of patients at risk are not included in the KM curve (figure 9). This means that the reliability of using data from the very tail end of the KM curve, which may represent very few patients, cannot be adequately assessed and should not be used to draw any firm conclusions.	Additional statements have been added to this section of the report (pages 87-88). "It is good practice to validate long-term predictions of treatment effectiveness against an external dataset, where possible." "However, the ERG acknowledges there are various prognostic factors that influence the response to treatment, and that the differences between the Davis study population and the ASCEND-4 and PROFILE 1014 trial populations may lead to differences in OS. Further, the treatment pathway (specifically, second-line therapy following crizotinib discontinuation) in the real world cohort may differ to that in the clinical trials, which may

outcomes for median OS for first-line crizotinib initiators aligned with expectations based on previous trials. While it is not possible to ascertain the robustness of the data at later time points (numbers at risk not reported), **the long-term data may be useful to determine an appropriate method for extrapolating the ASCEND-4 and PROFILE 1014 data. At three years, approximately [redacted] of patients remained alive, further supporting the ERG's belief that the exponential function overestimates OS in the model**."	**OS for first-line crizotinib initiators aligned with expectations based on previous trials."** However, this is misleading in light of the recently reported long term follow up OS results from PROFILE 1014, presented at the 2017 ESMO Congress.[2] These results predict that 56.6% of patients will be alive at 4 years. This finding is more consistent with the exponential extrapolation of OS as per the manufacturers base case assumption.		also lead to differences in OS." In addition to acknowledge the lack of the ESMO Congress data we have inserted a sentence in the report, "At the time of writing this report this real world data provided the best long-term data that the ERG were aware of." Incorporation of the ESMO Congress data is dealt with under Issues 9.

Issue 9 Use of appropriate evidence on long-term OS with ALK inhibitors.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG's alternative base case OS assumptions relies on evidence that has now been superseded by the availability of long term (median 46 months) follow up data from the PROFILE 1014 study:[2] Page 17, paragraph 1: "The company selected the exponential curve which	Longer-term OS data from the PROFILE 1014 trial is currently available in an abstract published in September 2017, and was presented at the 2017 ESMO Congress. These results should be acknowledged in the ERG's assessment report and due consideration	The ERG's evaluation of the company's base-case OS assumption should be updated to account for the most recent data available from PROFILE-1014.[2] The data show that the median OS has not been reached in patients treated with crizotinib at a median	Long term data for crizotinib were not available to the ERG at the time of analysis. The uncertainty in choice of survival function has been acknowledged in an addendum, where the results of an additional scenario within the ERG base case using the

produces the most optimistic long-term estimates of survival compared with the other distributions within the model, with [redacted] % of patients alive at five years. These estimates are inconsistent with clinical experience of ALK inhibitors and real world data reporting on the survival of patient who had received crizotinib, where a five-year survival rate might be expected to be around 20%."	given to the most plausible OS extrapolation based on these results .	follow up of 46 months. The 4-year OS rate in this final primary analysis is 56.6%.[2] These recent results are more consistent with the manufacturer's base case OS extrapolation assumptions than the ERG's preferred assumptions. It is important that the most recent long-term OS data from PROFILE 1014 are included in the Committee's considerations as to the most plausible extrapolation of OS. Prior to the availability of the most recent OS data, clinical expert opinions were sought on the 5-year survival rates in patients treated with crizotinib. However, these views should be considered with caution, not only in the light of the most recent OS data, but also due to the relatively limited clinical experience of treating patients with crizotinib in the first line setting, even in the context of a clinical trial. This reflects the fact that the EC licence for crizotinib was granted on the 25th November 2015.	exponential curve for OS are presented.
Page 18, paragraph 3: "The main areas of uncertainty in the cost-effectiveness analysis relate to the clinical evidence available to populate the model: the treatment comparison based on the MAIC analysis; the immature OS data and the overly optimistic extrapolation of the OS."			
Page 86, paragraph 3: "With respect to OS, the ERG, however, has some concerns about the distribution selected."			
Page 86, paragraph 3: ""…the exponential curves produce predictions about the duration of OS that are inconsistent with the clinical experience of ALK inhibitors; the exponential curve predicts that [redacted]% of ceritinib patients and [redacted]% of crizotinib patients would be alive after 5			

years. The clinical advisor to the ERG suggested that 20% survival at 5 years would be more reasonable, which more closely corresponds with estimates from the Gompertz distribution. The ERG, therefore, considers the use of alternative distributions to model OS within scenario analyses presented in Section 6. Should the more recent OS data for crizotinib from PROFILE 1014 become available later in the process, it would aid in validating the assumptions around extrapolating OS."			

Issue 10 Incorrect statements regarding the cost of drug administration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The company's consideration of treatment administration/monitoring costs is incorrectly described (see also Issue 1): Page 99, paragraph 2: "The ERG is concerned that the first-line treatment administration costs have been underestimated in the CS. Although, as stated in the CS, this cost is in line with the previous ceritinib submission (TA3951), it does not take account of the administration costs required to implement the relative dose intensity	The company submission accounted for treatment monitoring costs through the monthly cost of routine medical management that patients incur in the pre-progression health state. Application of further administration costs would result in double counting and bias the results in favour of crizotinib. The text and ERG exploratory analyses should be revised based on this clarification.	Correction of reporting inaccuracy and incorrect double counting of treatment monitoring costs in the ERG's preferred base case.	See Issue 1 above.

assumed for the first-line treatment costs." Page 118, paragraph 3: "The treatment administration costs may be underestimated, as it seems implausible that the treatments could be administered by a pharmacist alone. Given that patients on ceritinib are on treatment for longer, they would be expected to have higher administration costs. The company's model, therefore, biases the cost-effectiveness results in favour of ceritinib." Page 17, paragraph 3: "The treatment administration costs are likely to be underestimated, particularly in the light of the low relative dose intensity seen with ceritinib."			

Issue 11 The comparator arm in PROFILE 1014 is represented imprecisely

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The description of the comparator arm in PROFILE 1014 is not correct: 1. Page 13, paragraph 4	"PROFILE 1014 was an open-label RCT of crizotinib, compared with pemetrexed/cisplatin chemotherapy, in previously untreated advanced or metastatic ALK+ NSCLC." should read: "PROFILE 1014 was an open-label RCT of crizotinib, compared with cisplatin or carboplatin and pemetrexed, in previously untreated advanced or metastatic ALK+ NSCLC."	Investigators were permitted a choice of platinum agent.	Corrected

Issue 12 The comparator arm in ASCEND-4 is incompletely and incorrectly described

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The description of the comparator arm in ASCEND-4 is not correct. 1. Page 12, paragraph 1	"ASCEND-4 was an international, multicentre, open-label RCT comparing ceritinib with pemetrexed/cisplatin plus pemetrexed maintenance therapy." should be amended to reflect the fact that investigators had a choice of platinum agent (cisplatin or carboplatin), and that pemetrexed maintenance was only prescribed in those who did not progress during the induction phase.	Investigators were permitted a choice of platinum agent, and pemetrexed maintenance was only prescribed for those patients who did not progress during induction.	Corrected
2. Page 12, paragraph 5	Please correct the CT arm in the following sentence: "The results found that ceritinib prolonged PFS compared with CT in all patients: median PFS was 16.6 (95% CI 12.6–27.2) months on ceritinib compared with 8.1	CT has already been defined, and is cisplatin/carboplatin plus pemetrexed (not pemetrexed/cisplatin).	Corrected

	(95% CI 5.8–11.1) on pemetrexed/cisplatin (CT)...”		

Issue 13 Inaccurate representation of adverse event management

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Only dose adjustment was mentioned: Page 13, paragraph 3: “Adverse events were common on ceritinib in the ASCEND-4 trial though most could be managed with dose adjustment.”	Please clarify the meaning of dose adjustment and include concomitant medication: “dose reduction, dose interruption, and concomitant medication.”	Investigators could manage adverse events with dose reduction, dose interruption and/or concomitant medication (e.g. anti-diarrhoeals, anti-emetics, or fluid replacement for GI toxicity).	No change needed. The following sentence clarifies what is included in the term ‘dose adjustment’ here

Issue 14 Incorrectly reported dose adjustment for crizotinib from the ALEX trial

Description of problem	Description of proposed amendment	Justification for amendment	
The figures quoted from the ALEX trial were incorrectly reported: Page 13, paragraph 3: "This level of dose adjustment is higher than that seen with for crizotinib in the same indication (the ALEX trial see below): dose reduction 25%; 19% dose interruption; and dose intensity was 92.4%."	Please correct the figures as follows: "dose reduction 21%; 25% dose interruption; and dose intensity was 92.4%."	This maintains the accuracy of the data presented.	Corrected
Page 59, paragraph 4: "This level of dose adjustment is higher than that seen in the ALEX trial for crizotinib: dose reduction 25%; 19% dose interruption; and dose intensity was 92.4%.[3]"	Please amend the figures as per the suggestion above (from page 7 of the primary ALEX manuscript). Please also add: "...but 13% of patients in the crizotinib arm of the ALEX trial discontinued treatment due to AEs, whereas only 5% discontinued ceritinib in ASCEND-4 due to AEs."		Numbers corrected. The comment about ceritinib is not a factual inaccuracy

Issue 15 Clarification required for the subgroup data for patients with and without brain metastases at baseline

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The following statement requires clarification: Page 12, paragraph 5: "The treatment benefit in patients with brain metastases at baseline was numerically smaller that in those without (HR 0.80 compared with 0.45)."	Please change the wording to: "The treatment benefit in patients with brain metastases at baseline was numerically smaller than in those without [median PFS, 10.7 vs 7.0 months, HR 0.80, 95% CI 0.50–1.28) compared with 26.3 vs 8.2 months, HR, 0.45 (95% CI 0.32–0.64)]."	To provide sufficient details to understand the relevant subgroup data.	This not a factual inaccuracy – the limited detail is deliberate as this is a summary only

Issue 16 Unclear description of MAIC 1 and 2

Description of problem	Description of proposed amendment	Justification for amendment	
It is unclear which ALK inhibitor the ERG is referring to in the following sentence: Page 14, paragraph 1: "After a request from the ERG, the company then presented a second MAIC using only the ALK inhibitor arm of ASCEND-4 and ALEX (MAIC 2)."	Please change to: "...then presented a second MAIC using the ceritinib arm of ASCEND-4, and the crizotinib arm of ALEX (MAIC 2)."	Both treatments in the ALEX trial are ALK inhibitors, so the initial phrasing was unclear. These amendments describe the comparison more clearly.	Not a factual inaccuracy
Unclear description of the comparisons made in the MAICs: Page 58, paragraph 5: "The CS therefore presents a Matching-	Please amend, to read: "The CS therefore presents a Matching-Adjusted Indirect Comparison (MAIC) of ceritinib and crizotinib using the ceritinib arm of ASCEND-4 and		Not a factual inaccuracy

Adjusted Indirect Comparison (MAIC) of ceritinib and crizotinib using only the ALK inhibitor arm of the ASCEND-4 and PROFILE 1040 trials (MAIC 1). The company then presents a second MAIC using only the ALK inhibitor arm of ASCEND-4 and ALEX (MAIC 2)."	crizotinib arm of PROFILE 1014 (MAIC 1). The company then presents a second MAIC using the ceritinib arm of ASCEND-4 and the crizotinib arm of ALEX (MAIC 2)."		
The comparator for the ALEX trial used in MAIC 2 is incorrect: Page 58, paragraph 5: "However, both crizotinib trials used an older form of CT that did not include pemetrexed maintenance therapy..."	Please replace this statement with: "PROFILE 1014 included a CT comparator arm that did not involve pemetrexed maintenance, but the comparator arm in the ALEX study was alectinib (not CT)."	This is important for demonstrating that there was no common comparator between the three studies, as well as for the factual accuracy of the report.	Corrected

Issue 17 Incomplete reporting of the unmatched hazard ratio for OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Incomplete figures quoted for the unmatched HR estimates of [redacted] for OS: Page 14, paragraph 1: "The two matched HRs for OS were similar ([redacted]) and lower than the unmatched estimate of [redacted]."	Correct to state, "The two matched HRs for OS were similar ([redacted]) and lower than the unmatched estimates of [redacted] for MAIC 1 and 2, respectively."	Accuracy of data reporting.	Not a factual inaccuracy – this is a summary

Issue 18 Critique of the length of follow up for ASCEND-4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The critique of length of follow up does not take into account that two further analyses are planned: Page 14, paragraph 3: "Follow up was also too short for definitive assessment of OS."	Correct to: "Currently the follow up for ASCEND-4 is insufficient to allow for a definitive assessment of OS. Follow up is ongoing until [redacted], and two more analyses are planned for OS."	We acknowledge that the data is currently immature; however, two further analyses are planned for OS and hence follow up is expected to continue until [redacted]. The term "too short" implies an error in the design of the trial, when, in fact, the timings of the first two assessments of OS were determined by the number of PFS events, the primary endpoint of the ASCEND-4 trial (BIRC assessed PFS) at interim analysis.	Not a factual inaccuracy
Page 17, paragraph 6: The follow-up duration in ASCEND-4 at the latest data cut is too short for a reliable assessment of OS.	Correct to: "The duration of follow-up for ASCEND-4 is currently insufficient for a reliable assessment of OS. Two further OS analyses are planned: one after observing 215 deaths, and a final analysis for OS after observing 253 deaths."		Not a factual inaccuracy
Page 57, paragraph 5: "Follow-up was also too short for a definitive assessment of OS."	Change to: The duration of follow-up for ASCEND-4 is currently insufficient for a reliable assessment of OS. Two further OS analyses are planned: one after observing 215 deaths, and a final analysis for OS after observing 253 deaths.		

Issue 19 Inclusion of the ALEX trial in the original submission was unrealistic given the date of publication

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The timing of the ALEX trial publication is not taken into account: Page 14, paragraph 6: "In addition, the ERG believes that the ALEX trial should also have been included in the analysis. The ERG notes the following specific limitations of the MAIC analysis."	Change to: "A further relevant study, the ALEX trial, was published shortly before the submission (June 6th 2017) and after the date for the update of the systematic literature review. A second MAIC using this trial was conducted in response to a request from the ERG. The ERG notes the following specific limitations of the MAIC analysis."	The ALEX trial was published after the date of the SLR update, and close to the submission deadline. The close proximity of publication of the ALEX trial to the submission deadline meant that the results from the ALEX trial were not included in the submission dossier. This was a function of timing and not a deliberate decision to exclude it.	Not a factual inaccuracy
Page 27, paragraph 6: "The ERG believes that one of these trials was the relevant ALEX trial of crizotinib versus alectinib as first-line treatment for ALK+ advanced NSCLC,[3] which the ERG has identified (see Use of search filters, below)."	Please add: "However the ALEX trial was not published within the time frame of the clinical systematic literature review."		Not a factual inaccuracy

Issue 20 Incorrect relative dose intensity

Description of problem	Description of proposed amendment	Justification for amendment	Response
The relative dose intensity is incorrectly represented: Page 72, paragraph 1: "Ceritinib was associated with a 77.3% relative dose intensity, and	Correct to say "mean relative dose intensity" for both, crizotinib and ceritinib.	Accuracy of the data presented.	Corrected

crizotinib was associated with a 92.0% relative dose intensity.”			

Issue 21 Reference to WHO performance status is ambiguous and requires clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Omission of the word “performance” makes this sentence ambiguous: Page 32, paragraph 1: “Pre-planned subgroups were: ... WHO status: 0 or ≥1”	Please insert the word “performance”.	Reduces ambiguity as to the subgroup that is being referred to in this sentence.	Not a factual inaccuracy (and the text was copied directly from CS)

Issue 22 The ERG report incorrectly states that the monitoring of plasma glucose is not detailed within the CS

Description of problem	Description of proposed amendment	Justification for amendment	
The report incorrectly states that fasting plasma glucose prior to commencing ceritinib treatment is not mentioned in the CS: Page 55, paragraph 5: “The SmPC recommends that patients should be monitored for fasting plasma glucose prior to the start of treatment with ceritinib; this is not stated in the CS.”	Please delete: “this is not stated in the CS.”	This monitoring requirement is stated on pages 12-13 and 75 of the CS.	Corrected

Issue 23 The ERG report omits mention of differences in the safety profile of ceritinib and crizotinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report mispresents the comparison of the safety profile for ceritinib and crizotinib by omitting to consider the longer follow-up for ceritinib and differences in the recommendations for monitoring during treatment. Page 56, paragraph 1 "The CS claims that the AE profile for ceritinib is better than that for crizotinib. The ERG is uncertain that this is the case: is it better or just different? Using the data available on the NICE website for crizotinib, from TA406, the ERG compared the rates of AEs in ASCEND-4 and PROFILE 1014 (**Error! Reference source not found.**). There is no clear difference between the rates of AEs."	When comparing the AE profiles for ceritinib and crizotinib from their respective phase 3 trials it should be borne in mind that the duration of treatment was 10.9 months for crizotinib and 66.4 weeks (approximately 16 months) for ceritinib. This may well account for the higher incidence of all-causality grade 3/4 AEs reported for ceritinib vs crizotinib. Furthermore, the much lower incidence of treatment-related grade 3/4 AEs with ceritinib (12.2% vs 35.1%) is clinically meaningful, especially in the context of the longer duration of treatment. These points should be mentioned in the discussion of the AE profile. Another point that should be mentioned in this discussion of the safety profile of ceritinib vs crizotinib is the recommendation for monitoring of full blood counts and renal function and ophthalmological assessment (for patients in whom vision disorders persist or worsen or in whom there is a new onset of severe visual loss) during therapy with crizotinib. Such monitoring is not recommended for ceritinib and reflects clinically meaningful differences in the safety profile of the two drugs.	It is important to accurately characterise the safety profile of both drugs.	The ERG accepts that as presented the brief summary may have appeared to conclusive. It has added the statement, "The ERG recognises this is not a thorough or definitive comparison of the adverse effects profiles of the two agents."

The report omits mention that gastrointestinal toxicity is not solely associated with ceritinib. Page 56, paragraph 1: "Comparison of AEs highlighted in the drugs' respective SmPCs, reveals that hepatotoxicity, interstitial lung disease/pneumonitis, QT-interval prolongation, and bradycardia are associated with both drugs. Vision loss is very rarely associated with crizotinib but not ceritinib; Grade 3 or 4 neutropenia is common with crizotinib but rare with ceritinib. Cardiac failure, gastrointestinal perforation, and renal impairment have been associated with crizotinib, whereas gastrointestinal toxicity, hyperglycaemia and lipase/amylase elevations are associated with ceritinib."	Gastrointestinal toxicity needs to be attributed to both drugs.	Gastrointestinal toxicity is categorised as Very Common in the crizotinib SmPC, also.	

Issue 24 The ERG assessment of the intracranial benefit for ceritinib is understated, and does not take into account the difference in the baseline radiotherapy treatment of brain metastases between the two studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG simplification does not take into account the significant differences in treatment of brain metastases between the two studies, and hence understates	Change to: "The ERG suggests that the data presented in the CS do not provide **conclusive** evidence for a specific intracranial benefit with **ceritinib, although the 1.7 month median PFS benefit seen in the BM subgroup in ASCEND-4, despite only 39%**	Fair representation of intracranial efficacy, given the baseline differences between the two trials, and the subgroup analyses of PFS between the two trials.	Not a factual inaccuracy

the intracranial benefit for ceritinib: Page 53, paragraph 3: "….the ERG suggests that they do not provide evidence for a specific intracranial benefit with ceritinib." Page 59, paragraph 3: "The ERG suggests that the data presented in the CS do not provide evidence for a specific intracranial benefit with ceritinib."	**of BM patients being treated before study entry, suggest a benefit with ceritinib."**		

Issue 25 Incomplete summary in the clinical effectiveness conclusions section

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59, paragraph 2: "… the comparisons with ceritinib are still observational and subject to a high risk of bias."	Change to: "the comparisons with ceritinib are observational and subject to a high risk of bias, but both the adjusted and unadjusted comparisons indicate that ceritinib is associated with a longer PFS than crizotinib."	Fair representation of the data outlined in the clinical effectiveness section in the conclusions.	Not a factual inaccuracy

Issue 26 Data requests for crizotinib KM data for time on treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, paragraph 4: "Treatment duration for ceritinib and crizotinib was based on data from the ASCEND-4 trial and from the PROFILE 1014 trial,	Please add, "This was necessary because KM data for crizotinib were not made available to the company or the ERG following requests made to Pfizer by both parties."	Provides a fuller account of why in the CS time on treatment was not based on KM data and was determined using other methods.	Not a factual inaccuracy

respectively. Because only summary data and no KM data were available, on the duration of crizotinib, the company was forced to use methods to indirectly estimate the duration of therapy."			

Issue 27 The ERG report states that it was unclear how clinical advisor opinions were determined.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The lack of clarity as to how clinical advisor opinions were established is unfounded, since summary reports were provided: Page 85, paragraph 1: "The company also stated that their clinical advisors supported the choice of this distribution (although it was not clear, from the CS, how this was determined)."	Please delete: "although it was not clear, from the CS, how this was determined."	The information was obtained from a clinical validation meeting, for which a summary report was provided.	Corrected

Issue 28 The ERG queried adverse event rates in those with and without brain metastases, but a reference for this had already been provided in the clarification questions.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A reference has already been provided to answer this query: Page 89, paragraph 4: "the ERG queried whether the rates of adverse events for ceritinib and	Please delete this statement.	As stated in the clarification question B7, subgroup analysis of safety by region, age, gender, race, presence or absence of brain	Corrected

crizotinib might also vary within different patient populations (for example, whether patients with brain metastases have a different safety profile on ceritinib, compared with those without)."		metastases, prior adjuvant chemotherapy (yes vs. no), and WHO PS (0 vs. 1-2) at baseline showed that the proportion of patients with AEs was generally consistent across subgroups. These data are described in the ASCEND-4 CSR section 12.5.2.2	

Issue 29 Incorrect representation of PFS data.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The figure quoted below is incorrect: Page 110, paragraph 2: "However, this figure also shows that the median PFS for patients with and without brain metastases was quite different (25.3 for without, and 10.7 for with, brain metastases at screening)."	Change 25.3 to 26.3 months.	Accuracy of the data presented from the primary ASCEND-4 paper.	Corrected

Issue 30 Incomplete summary of company's response regarding second-line treatment distributions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 98, the ERG provides an incomplete summary of the company's clarification response regarding the distribution of second-line treatments, and inaccurately describes the impact of this assumption:	The base-case assumption that 60% of patients receive post-progression therapy is conservative under the base case and in sensitivity analyses other than the real-world second-line treatment scenario. The last sentence of this excerpt should be revised to acknowledge this point.	Correction of reporting inaccuracy.	The ERG has modified this statement by removing the final part of the sentence describing the potential bias to the results.

"…the model also assumes that the same proportion of patients receive active therapy post-progression in each arm of the trial (60%). Again this is based on clinical expert opinion, and this proportion is much higher than those reported in the trials (35% in ASCEND-4 and 43% in PROFILE 1014). In the points for clarification (PFC), the ERG asked the company to justify this assumption. In response, the company presented sensitivity analysis showing that this assumption does not make a large difference to the ICER. However, the ERG would like to note that combining this assumption with using the “real world” drug distribution estimates significantly increases the costs associated with the crizotinib arm. **Therefore, not only are these assumptions reducing the external validity of the model and increasing the uncertainty within the model, but they are also benefiting the ceritinib arm, over the crizotinib arm, of the model**."	(As illustrated in the ERG's exploratory analysis in 6.3.3, the ICER of ceritinib vs. crizotinib slightly decreases when applying the 35% and 43% proportions observed in the trials.)		

Issue 31 Incorrect description of time on treatment figure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 72, paragraph 4, the ERG incorrectly describes a figure provided in the company clarification response: "Figure 6: Treatment duration for ceritinib (KM curve vs exponential extrapolation) (Company clarification response, Fig B12.1, p 44) provides a comparison of the treatment duration for ceritinib presenting the Kaplan-Meier curve, based on patient data from ASCEND-4, and the exponential function, estimated from the **truncated median duration of treatment**."	The exponential curve shown in Figure 6 was fitted to the Kaplan-Meier curve for time to discontinuation of ceritinib, which accounts for the censoring of patients who remained on treatment at the data cut-off date. It is different from the exponential curve used in the company's base case, which was estimated using the truncated median treatment duration.	Correction of reporting inaccuracy; the current excerpt from the ERG report mischaracterises the robustness of the sensitivity analyses undertaken by the company.	The figure has been removed from the report (page 73). Since the ERG does not have the data for Kaplan-Meier curve for treatment duration, it was not possible to replicate the figure using the predictions using the truncated median method.

Issue 32 Incorrect summary of company clarification response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 111, Table 41, the ERG incorrectly states that no action was taken in the new company model in response to clarification questions B5 and B6.	Revise to state: "The model was updated to incorporate this alternative method."	Correction of reporting inaccuracy; this statement mischaracterises the robustness of the updated company model.	The statement regarding B6 has been corrected in Table 41 (page 112), to state that the parameter estimates were included in the model. The statement regarding B5, a request for regression analysis

			exploring the impact of baseline characteristics on time on treatment, has not been updated as no amendments were made to the model as a result of this question.

Issue 33 Misinterpretation of the base-case cost result

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 105, paragraph 1, the ERG states, "Pre-progression medical costs were noticeably higher for ceritinib, compared with crizotinib (34.35%). This was due to ceritinib patients spending longer on treatment." This is inaccurate, as the higher pre-progression medical costs are due to longer progression-free survival in the ceritinib arm.	Revise to state "This was due to the longer PFS among patients treated with ceritinib."	Correction of reporting inaccuracy.	Corrected statement as per the company suggestion.

Issue 34 Inconsistent valuation of the proposed sustained utility progression state utility.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 129, Table 51, the ERG states the utility for the sustained utility health state is valued at 0.68 for both crizotinib and ceritinib in scenario 1.	Revise the sustained utility progression state utility value to between 0.74 and 0.78.	Consistency with previous appraisal of crizotinib in first-line treatment of advanced ALK+ NSCLC where a value of between	Not a factual error.

This is inconsistent with the utility value previously accepted for sustained utility in TA406.		0.74 and 0.78 was accepted by the appraisal committee.	

References

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2. Mok TS, Kim D, Wu YL, al e. Overall Survival (OS) for first-line crizotinib versus chemotherapy in ALK+ lung cancer: updated results from PROFILE 1014. Abstract presented at ESMO 2017, 8-12 September 2017. Available at: http://oncologypro.esmo.org/Meeting-Resources/ESMO-2017-Congress/Overall-Survival-OS-for-First-Line-Crizotinib-Versus-Chemotherapy-in-ALK-Lung-Cancer-Updated-Results-from-PROFILE-1014 Accessed October 2017.
3. Peters S, Camidge D, Shaw A *et al.* Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *New England Journal of Medicine* 2017;377:829-38.

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer

Erratum

Note on pages 13, 14, 44, 45, 48, 49, 50, 52, 53, 54, 56 and 58 PROFILE 1014 was misnamed PROFILE 1040 (or PROFILE 4 on page 13). Individual pages with this correction are not included in this erratum. Nor are those for minor typographical errors

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review of relevant trials. Evidence for the clinical effectiveness of ceritinib was from ASCEND-4, a Phase III company-sponsored trial. ASCEND-4 was an international, multicentre, open-label RCT comparing ceritinib with and cisplatin or carboplatin plus pemetrexed maintenance therapy. The study included patients with advanced or metastatic non-squamous ALK+ NSCLC, untreated with systemic therapy (with the exception of adjuvant or neoadjuvant therapy, if relapse had occurred at least 12 months after the end of therapy). If present, brain metastases were required to be asymptomatic or neurologically stable (including not having required increasing doses of steroids, within the two weeks prior to screening, to manage central nervous system symptoms).

Patients were randomised to receive ceritinib 750 mg, administered orally, once daily (and continuously) in a fasted state, or chemotherapy (CT). CT was pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or (based on the investigator's choice) carboplatin (AUC 5–6), administered every 21 days. Patients who completed four cycles of CT (induction), without progressive disease, subsequently received pemetrexed as single-agent maintenance every 21 days. Patients in the CT group, in the treatment and post-treatment follow-up phases, were allowed to cross over to ceritinib after centrally (blinded independent review committee confirmed – BIRC), RECIST-defined progressive disease.

The primary outcome was median progression-free survival (PFS), defined as the time from the date of randomisation to the date of the first radiologically documented disease progression by central review, or death due to any cause. RECIST 1.1 criteria were used to assess response.

The key secondary objective was overall survival (OS), defined as the time from date of randomisation to date of death due to any cause.

The results found that ceritinib prolonged PFS compared with CT in all patients: median PFS was 16.6 (95% CI 12.6–27.2) months on ceritinib compared with 8.1 (95% CI 5.8–11.1) on CT; HR 0·55 (95% CI 0.42–0.73). The treatment benefit in patients with brain metastases at baseline was numerically smaller that in those without (HR 0.80 compared with 0.45). At the time of the analysis (24 June 2016), the OS data were immature; Median OS was 'not reached' in the ceritinib group and was estimated as 26.2 months in the CT group (HR, 0.73; p=0.056). A sensitivity analysis that adjusted for crossover of CT patients to ceritinib after disease progression had little impact on the result (HR 0.73; 95% CI, 0.49–1.10), probably due to the limited follow-up data.

The results, both from central and local assessment, favoured ceritinib in terms of tumour response, time to first response and duration of response. The results for intracranial tumour responses in patients with measurable brain metastases at baseline indicated that the intracranial tumour responses to ceritinib and to CT were similar to the whole-body responses. Intracranial outcomes were not assessed in patients without BM at baseline, therefore, the impact of ceritinib in preventing the development of new BM has not been assessed in the CS.

Time to definitive symptom deterioration was assessed using both the LCSS and QLQ-LC13 questionnaires, and the results for both tools demonstrated a statistically significant difference in favour of ceritinib.

In ASCEND-4 the median duration of ceritinib exposure was 66.4 weeks (IQR 30.0 to 83.7). The median relative dose intensity was 78.4% (IQR 63.2 to 97.5), with a mean dose of 626.0 mg (SD 124.8). Adverse events were common on ceritinib in the ASCEND-4 trial though most could be managed with dose adjustment. Dose adjustment was common: 68% of ceritinib patients required at least one dose reduction and 78% required at least one dose interruption. This level of dose adjustment is higher than that seen with for crizotinib in the same indication (the ALEX trial see below): dose reduction 21%; 25% dose interruption; and dose intensity was 92.4%.

Comparison of ceritinib with crizotinib

In the CS the evidence for crizotinib was derived from the PROFILE 1014 trial. PROFILE 1014 was an open-label RCT of crizotinib, compared with pemetrexed/cisplatin chemotherapy, in previously untreated advanced or metastatic ALK+ NSCLC. The design and population of PROFILE 1014 was similar to that of ASCEND-4, though there were some differences between the trials. The most important difference was the difference in the comparator: maintenance pemetrexed was included in the chemotherapy treatment protocol for ASCEND-4 but not in PROFILE 1014. Maintenance pemetrexed has been shown to improve survival among patients with advanced NSCLC who have not progressed during pemetrexed-cisplatin induction therapy.

The ERG identified an additional relevant trial of crizotinib: the ALEX trial, which compared crizotinib with alectinib (a third ALK-inhibitor) as first-line treatment in ALK+ advanced NSCLC. This trial provides published, directly relevant data on crizotinib. The characteristics of this trial and those of the ASCEND-4 and PROFILE 1014 are very similar. The ERG concluded that three trials, ASCEND-4, PROFILE 1014 and ALEX, are directly relevant for an indirect comparison of ceritinib with crizotinib in the present assessment. However, as neither of the crizotinib trials use the same comparator as the ASCEND-4, these three trials cannot be combined in an indirect analysis through a common comparator.

Whilst the ERG acknowledges that an indirect comparison of individual trial arms was the only option available to compare ceritinib and crizotinib, it is unclear whether the results derived from the MAIC analyses are any more reliable than that from the unadjusted data.

The MAIC generated results for ceritinib compared with crizotinib for OS are even more uncertain, being the result of an observational comparison of immature, highly uncertain data.

Cost-effectiveness evidence

The main areas of uncertainty in the cost-effectiveness analysis relate to the clinical evidence available to populate the model: the treatment comparison based on the MAIC analysis; the immature OS data and the overly optimistic extrapolation of the OS. There is also uncertainty regarding the distribution of second-line therapies in both the ceritinib and crizotinib arm; the methods used to estimate of duration of first-line treatment; utility values in the post-progression health state; and, the duration of post-progression treatment.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG corrections of calculation errors suggest that the ICER for ceritinib compared with crizotinib is £27,936 per QALY gained (with neither PAS applied). With ceritinib PAS applied, ceritinib dominated crizotinib. The ERG's additional exploratory analyses, using a range of alternative assumptions, indicate that the company's base-case is likely to be overly optimistic and overestimate the benefits of ceritinib.

The ERG conducted a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The most important of these scenarios relate to changes made by the ERG to the selection of survival curve to model overall survival, and the method used to estimate time on treatment. The ERG also presents an alternative base-case based on a combination of a number of these scenario analyses.

The ERG explored the following amendments to the company's revised base-case:

1. Corrections for calculation errors;
2. Adjustment of ceritinib clinical data (OS, PFS and treatment duration) to the PROFILE 1014 population;
3. Estimating time on treatment for ceritinib using patient-level data and estimating the relative time on treatment for crizotinib using a hazard ratio;
4. Alternative survival curves to model OS;
5. Alternative trial data (ALEX study) to model effectiveness of crizotinib;

Table 1 Summary of the relevant amendments to the company's revised base-case and impact of those amendments on the ICER (without PAS)

#	Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
-	***CS base-case[$] (corrected)***	*Ceritinib*	106,962	3.22	14,985	0.54	27,936	**n/a**
		Crizotinib	91,977	2.68	-	-	-	-
1	Proportional hazard of treatment duration	*Ceritinib*	126,171	3.22	19,383	0.54	36,136	+8,200
		Crizotinib	106,789	2.68	-	-	-	-
2	Clinical data matched to the PROFILE 1014 population	*Ceritinib*	108,926	3.41	16,328	0.56	29,149	+1,213
		Crizotinib	92,598	2.85	-	-	-	-
3	Weibull curve to model OS	*Ceritinib*	106,706	2.91	15,943	0.47	34,221	+6,285
		Crizotinib	90,763	2.44	-	-	-	-
4	Gompertz curve to model OS	*Ceritinib*	104,707	2.47	15,428	0.35	44,602	+16,666
		Crizotinib	89,279	2.12	-	-	-	-
5	Data from the ALEX trial to model crizotinib (ceritinib unadjusted data from the ASCEND-4 trial)	*Ceritinib*	106,962	3.22	16,127	0.50	32,345	+4,409
		Crizotinib	90,834	2.72	-	-	-	-
6	Data from the ALEX to model crizotinib (ceritinib data from ASCEND-4 adjusted to the ALEX trial population)	*Ceritinib*	107,373	3.27	16,297	0.50	32,411	+4,475
		Crizotinib	91,076	2.77	-	-	-	-
7	Proportion of patients on second-line treatment from ASCEND-4 and PROFILE 1014	*Ceritinib*	103,778	3.22	14,142	0.54	26,364	-1,572
		Crizotinib	89,636	2.68	-	-	-	-
8	Alternative post-progression utilities (trial scenario)	*Ceritinib*	126,171	3.03	19,383	0.53	36,618	+8,682
		Crizotinib	106,789	2.50	-	-	-	-
9	Alternative post-progression utilities (real world scenario)	*Ceritinib*	126,171	3.03	19,383	0.48	40,192	+12,256
		Crizotinib	106,789	2.55	-	-	-	-
10	Drug wastage for ceritinib and crizotinib	*Ceritinib*	112,593	3.22	14,311	0.54	26,681	-1,255

#	Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
		Crizotinib	98,281	2.68	-	-	-	-
11	Additional administration cost	*Ceritinib*	110,914	3.22	15,970	0.54	29,773	+1,837
		Crizotinib	94,944	2.68	-	-	-	-
12	Drug wastage and administration cost (#9 + #10)	*Ceritinib*	116,635	3.22	15,297	0.54	28,518	+582
		Crizotinib	101,338	2.68	-	-	-	-
13	**ERG preferred scenario (#1 + #2 + #4 + #7 + #8 + #12)**	***Ceritinib***	**139,573**	**2.40**	**19,887**	**0.37**	**58,808**	+30,872
		Crizotinib	**119,687**	**2.03**	**-**	**-**	**-**	**-**
$, all ERG corrections and adjustments implemented to the company's base-case model; CS, company submission; PAS, patient access scheme; ICER, incremental cost-effectiveness ratio; Inc, incremental; n/a, not applicable; QALY, quality adjusted life year; OS, overall survival; ERG, evidence review group								

(Table 2). There is no clear difference between the rates of AEs. It is noteworthy that dose interruption and temporary discontinuation were much more common with ceritinib; this could suggest a more troublesome AE profile, requiring more active management of ceritinib treatment than for crizotinib, or it could be reflective of a better understanding of the potential risks associated with ALK inhibitors during the ASCEND-4 trial, compared with the earlier PROFILE 1014 trial. Comparison of AEs highlighted in the drugs' respective SmPCs, reveals that hepatotoxicity, interstitial lung disease/pneumonitis, QT-interval prolongation, and bradycardia are associated with both drugs. Vision loss is very rarely associated with crizotinib but not ceritinib; Grade 3 or 4 neutropenia is common with crizotinib but rare with ceritinib. Cardiac failure, gastrointestinal perforation, and renal impairment have been associated with crizotinib, whereas gastrointestinal toxicity, hyperglycaemia and lipase/amylase elevations are associated with ceritinib. The ERG recognises this is not a thorough or definitive comparison of the adverse effects profiles of the two agents.

Table 2 Comparison of rates of adverse events for ceritinib (ASCEND-4 trial) with those of crizotinib (PROFILE 1014 trial)

Adverse event, No. of patients (%)	Crizotinib (PROFILE 1014) (n=171)		Ceritinib (ASCEND-4) (n=189)	
	All causality	Treatment-related	All causality	Treatment-related
With AEs	170 (99.4)	168 (98)	189 (100)	184 (97)
With serious AEs	58 (33.9)	18 (10.5)	70 (37.0)	30 (15.9)
With Grade 3 or 4 AEs	97 (56.7)	60 (35.1)	148 (78)	23 (12.2)
Permanent discontinuation	21 (12.3)	8 (4.7)	21 (11.1)	10 (5%)
Dose reduction	11 (6.4)		68%	
Temporary discontinuation	70 (40.9)		148 (78.3)	
Total deaths during treatment, n (%)	20 (12)	None	11 (6)	None

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

4.6 Conclusions of the clinical effectiveness section

Although the NICE scope included chemotherapy as a comparator for this appraisal, since the positive NICE recommendation for crizotinib in the first-line treatment of advanced or metastatic ALK+ NSCLC, crizotinib has become the standard of care for this indication. It is, therefore, appropriate that crizotinib is the sole comparator considered in the CS.

A systematic review was conducted to identify trials of ceritinib and the comparator crizotinib. The methods used were generally appropriate, but because the search filter applied depended heavily on MeSH terms, some relevant records were missed. In particular, one directly relevant trial of crizotinib (comparing it with alectinib in the population of interest) was identified by the ERG.

The evidence for ceritinib was based on a single trial, ASCEND-4. This was a RCT of ceritinib as first-line treatment in ALK+ advanced or metastatic NSCLC. ASCEND-4 was a Phase III, international, multicentre open-label RCT comparing ceritinib with pemetrexed and cisplatin or carboplatin plus pemetrexed maintenance therapy. When this trial was planned this pemetrexed regimen was the latest standard of care in untreated advanced or metastatic NSCLC.

A comparison of the patient characteristics in the ceritinib arm of ASCEND-4 with those from a recently presented retrospective chart review of patients treated with first-line crizotinib in the UK and Europe, indicates that the trial patients were slightly younger, had a higher proportion of females and a lower proportion of former or current smokers, and, as might be expected in a trial, a higher proportion of trial patients were ECOG status 0 or 1. The clinical adviser to the ERG commented that, except that a higher proportion of men might be expected in clinical practice, the trial population can be considered generalisable to NHS practice.

ASCEND-4 was a good-quality trial. Although the open-label treatment administration made it susceptible to bias, this was ameliorated by the primary (PFS) outcome assessment being assessed centrally, and the key secondary outcome of OS being an objective outcome. There was some bias in patient withdrawals, which were higher in the CT arm. For the assessment of OS, a major limitation of the trial design was that patients were allowed to remain on therapy despite disease progression and to switch from CT to ceritinib. This resulted in confounding of the OS outcome. Follow-up was also too short for a definitive assessment of OS.

The results found that ceritinib prolonged PFS compared with CT in all patients: median PFS was 16.6 (12.6–27.2) on ceritinib, compared with 8.1 (5.8–11.1) on CT (HR 0·55 (0.42–0.73). The effects of ceritinib were consistent across all subgroups considered, except for the subgroups with previous adjuvant chemotherapy, where the sample size was very small. The treatment benefit in patients with

brain metastases at baseline was numerically smaller that in those without (HR 0.80, compared with 0.45). Median PFS was greatest in patients without brain metastases who were treated with ceritinib (26.3 months).

At the time of the analysis (24 June, 2016), the OS data were immature; only 107 events (42% of the required OS events) had occurred: 48 (25.4%) patients randomised to the ceritinib group had died, compared with 59 (31.6%) randomised to CT. Median OS was 'not reached' in the ceritinib group and was estimated as 26.2 months in the CT group (HR 0.73, p=0.056). A sensitivity analysis that adjusted for crossover of CT patients to ceritinib, after disease progression, had little impact on the result (HR 0.73, 95% CI 0.49 to 1.10), probably due to the limited follow-up data.

The results, both from central and local assessment, favoured ceritinib in terms of tumour response, time to first response and duration of response. The results for intracranial tumour responses in patients with measurable brain metastases at baseline indicated that the intracranial tumour responses to ceritinib and to CT were similar to the whole-body responses. Intracranial outcomes were not assessed in patients without BM at baseline, therefore, the impact of ceritinib in preventing the development of new BM has not been assessed in the CS.

Time to definitive symptom deterioration was assessed using both the LCSS and QLQ-LC13 questionnaires, and the results for both tools demonstrated a statistically significant difference in favour of ceritinib.

In current clinical practice the standard of care for first-line treatment for ALK+ advanced or metastatic NSCLC is crizotinib. Unfortunately, there is no trial that directly compares ceritinib with crizotinib. Two directly relevant trials crizotinib were identified: PROFILE 1014, which was included in the CS, and ALEX, identified by the ERG. Both PROFILE 1014 and ALEX were similar in their population and design to ASCEND-4. However, PROFILE 1014 used an older form of CT that did not include pemetrexed maintenance therapy, and which has been shown to be significantly less effective than the CT used in the ASCEND-4 trial, and the comparator in ALEX was alectinib. Consequently, these three trials cannot be combined in an indirect analysis through a common comparator. The CS therefore presents a Matching-Adjusted Indirect Comparison (MAIC) of ceritinib and crizotinib using only the ALK inhibitor arm of the ASCEND-4 and PROFILE 1014 trials (MAIC 1). The company then presents a second MAIC using only the ALK inhibitor arm of ASCEND-4 and ALEX (MAIC 2).

The results of these comparisons were that the HR for PFS was [redacted] (MAIC 1) or [redacted] (MAIC 2). The HR for OS was [redacted] (MAIC 1) and [redacted] (MAIC 2).

The ERG notes that the MAIC method was developed as an improvement on standard indirect comparison methods, which use aggregate data only; it was not developed as a method to be used without a common comparator arm. There are significant limitations to this type of analysis. Despite the matching, the analysis can still be subject to the effects of residual confounding due to unobserved differences between the trials. In the present context, the method is being applied in the absence of a common comparator. This means that there is nothing to use as a measure of the success of the matching to reduce confounding. There is a possibility that the adjustment on a small number of observed factors may actually increase the confounding due to unknown factors. Furthermore, as the matching process reduces the amount of data (the sample size of the ceritinib arm), precision is reduced. The ERG also notes that in MAIC 1 the whole ASCEND-4 population was matched to the whole crizotinib population. The ERG believes that this is inappropriate given that only the ceritinib and crizotinib arms were being compared in the analysis; in MAIC 2 only the ceritinib and crizotinib arms were matched.

In summary, whilst the ERG acknowledges that an indirect comparison of individual trial arms was the only option available to compare ceritinib and crizotinib, it is unclear whether the results derived from the matched adjusted analyses are any more reliable than those from the unadjusted data: the comparisons with ceritinib are still observational and subject to a high risk of bias. The OS results are even more uncertain, being the result of an observational comparison of immature highly uncertain data.

The intracranial effects of ceritinib and crizotinib were not compared in the MAIC analyses. The ERG suggests that the data presented in the CS do not provide evidence for a specific intracranial benefit with ceritinib.

Adverse events were common on ceritinib in the ASCEND-4 trial though most could be managed with dose adjustment. Dose adjustment was common: 68% of ceritinib patients required at least one dose reduction and 78% required at least one dose interruption. The median relative dose intensity was 78%. This level of dose adjustment is higher than that seen in the ALEX trial for crizotinib: dose reduction 21%; 25% dose interruption; and dose intensity was 92.4%.[28]

In summary, there is good evidence that ceritinib is effective in prolonging PFS in patients with previously untreated ALK+ advanced or metastatic NSCLC. The effect on OS is as yet uncertai

5.2.4 Interventions and comparators

5.2.4.1 First-line therapy

The economic model presented in the CS compared ceritinib with crizotinib as first-line treatment for untreated non-squamous advanced NSCLC. The dosing of each therapy was based on the licenced dose of each drug, 750mg and 500mg daily, respectively. Dose reductions due to adverse events, for both treatments, were accounted for by using data on dosing from the ASCEND-4 and PROFILE 1007 trials (PROFILE 100743 was used instead of PROFILE 1014 because the relative dose intensity was not reported in PROFILE 1014). Ceritinib was associated with a 77.3% mean relative dose intensity, and crizotinib was associated with a 92.0% mean relative dose intensity. Section **Error! Reference source not found.** provides further details on the calculations of drug acquisition costs for ceritinib and crizotinib.

The duration of first-line therapy was obtained from the ASCEND-4 and PROFILE 1014 trials. Ceritinib patients received treatment for longer than crizotinib patients (a median of 15.27 months versus 10.90 months). Details of how treatment duration was modelled in the company model are provided in Section **Error! Reference source not found.**.

Platinum doublet therapy (pemetrexed with carboplatin or cisplatin), with or without pemetrexed maintenance treatment was also included in the NICE scope as a potential comparator therapy. This comparator was not included by the company in the analysis. The company justified this decision by stating that more that 90% of ALK+ NSCLC patients would get crizotinib, and therefore crizotinib is the only relevant comparator in this population.

5.2.4.2 Time on treatment

Treatment duration for ceritinib and crizotinib was based on data from the ASCEND-4 trial and from the PROFILE 1014 trial, respectively. Because only summary data and no KM data were available, on the duration of crizotinib, the company was forced to use methods to indirectly estimate the duration of therapy. This approach involved assuming that the duration of treatment followed an exponential curve. Using the summary data reported on the truncated median duration of treatment, the rate parameter (lambda) was estimated for each treatment. The exponential function was selected as it is the only parametric function that can be estimated using a single data point. The truncated median duration for ceritinib in ASCEND-4 was 15.3 months. In PROFILE 1014, the truncated median for crizotinib was 10.90 months.

Figure 1: Figure removed post factual accuracy check

The company provided the log-cumulative hazard plot for time to discontinuation for ceritinib in the ASCEND-4 trial when fitted to patient-level data (provided in the clarification response). The plot is approximately linear, implying a constant hazard rate of discontinuation, and so supports the use of an exponential function to model treatment duration. Event probabilities were taken directly from the clinical studies – no further adjustment to account for the differences between trials and patient populations was performed.

Acknowledging the uncertainty generated by the lack of KM data on the duration of crizotinib, the company also explored alternative assumptions regarding treatment discontinuation in a number of scenario analyses. In these analyses, patients were treated until *ia*) discontinuation (equivalent duration based on ASCEND-4, using patient-level time–to-event data), *ib*) discontinuation (equivalent duration based on PROFILE 1014, using the truncated median approach as per the base-case), *ii*) progression, and *iii*) until the trial-observed discontinuation or progression (whichever occurred first).

Table 3: Scenario analyses for treatment duration (adapted from CS, Table 32, p 92)

Treatment duration assumption	Mean treatment duration (months)		ICER
	Ceritinib	Crizotinib	
Base-case: Treatment until discontinuation (based on truncated median duration for both ceritinib and crizotinib)	[redacted]	[redacted]	£27,936
Scenario 1a: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on ASCEND-4)	[redacted]	[redacted]	Dominant
Scenario 1b: Treatment until discontinuation (assuming equivalent time on treatment for ceritinib and crizotinib, with both based on PROFILE 1014)	[redacted]	[redacted]	Dominant
Scenario 2: Treatment until progression	[redacted]	[redacted]	£43,921
Scenario 3: Treatment until discontinuation or progression, whichever occurs first	[redacted]	[redacted]	£28,398
CS, company submission; ICER, incremental cost-effectiveness ratio			

ERG's comments

The ERG has a number of concerns regarding how treatment duration was modelled by the company. Scenario analyses demonstrated that the results were highly sensitive to these assumptions (Table 3). The ERG accepts the need to parameterise and extrapolate the time on treatment, and considers the use of the exponential curve to be the most appropriate, given the lack of data for other distributions, and for its consistency with PFS, with which it is linked. The concerns fall into the following categories:

- The use of the truncated median to estimate treatment duration,
- The population in which treatment duration was modelled,
- The use of individual curves (non-proportional hazards).

Truncated median approach.

The assumptions used in the company base-case, where treatment duration for ceritinib and crizotinib was estimated using the truncated median, appear to underestimate the actual time on treatment. Mean time on treatment for ceritinib was [redacted] as calculated using the individual patient data in the ASCEND-4 trial, compared with [redacted] based on the truncated median method. This seems to indicate that this method is not a reliable way to estimate duration of treatment. Without access to patient-level data for crizotinib, it is not possible to estimate a corresponding comparison, but it is reasonable to expect that the predicted duration of crizotinib therapy is equally poorly estimated. The impact of these assumptions is also likely to be significant as the duration of therapy has a significant impact on total drug acquisition costs, which are the key driver of the incremental costs. Further, while the ERG acknowledges that estimating the duration of treatment for crizotinib is difficult given the limited data available, the ERG questions the validity of adopting an approach that is inconsistent with data they do have on duration of treatment from the ASCEND-4 study. The ERG note that, in the

described in Section 12.1.4 of the ASCEND-4 patients in the trial, which were due to the company redistributing those treatment options that were considered to be uncommonly used in practice to other treatment options.

Inconsistency between modelled second-line treatment distribution and clinical practice

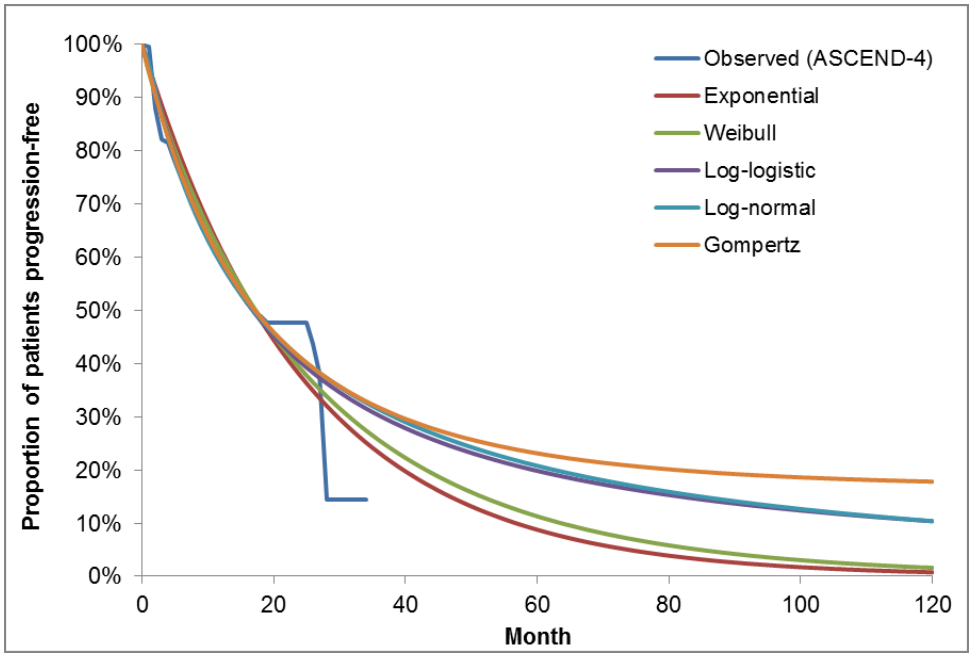
As stated above, the CS suggests that the distribution of second-line therapies received in the ASCEND-4 and PROFILE 1014 trials was not reflective of clinical practice in the UK and that it was expected that patients initiating on ceritinib would receive platinum doublet chemotherapy and best supportive care following discontinuation of ceritinib. In contrast, patients initiating on crizotinib received ceritinib, platinum doublet chemotherapy, and best supportive care (CS, Figure 3) following discontinuation of therapy. The ERG agrees with the company that this treatment pathway is likely to be more reflective of practice in the UK. This lack of alignment between the clinical data and UK clinical practice, however, implies that the clinical data used in the model is unlikely to fully reflect the relative benefits of ceritinib and crizotinib in UK practice as the second-line therapies will be very different to those received by patients in the ASCEND-4 and PROFILE 1014 trials. The ERG considers this to be a substantial source of uncertainty that is very likely to have a significant impact on the estimated incremental cost-effectiveness ratio (ICER). As stated above, the company carried out a scenario analysis which sought to address this issue by assuming a distribution of subsequent therapies that was more in line with current UK practice. The ERG, however, has several concerns about this scenario analysis.

Firstly, this scenario analysis did not account for how subsequent therapy may have impacted on post-progression survival. These differences are potentially very significant; the economic model developed for the technology assessment (TA395[1]) that evaluated ceritinib as a second-line treatment for NSCLC estimated a gain of 1.35 life years, compared with best-supportive care.

Secondly, the assumption made by the company that 60% of patients would receive active treatment following discontinuation of first-line therapy is inconsistent with advice received by the ERG from its clinical advisor, who suggested that nearer 80% of patients would be expected to receive active treatment after discontinuation of first-line therapy.

Thirdly, the company estimated from the ASCEND-4 trial data that approximately 10% of patients would receive crizotinib after discontinuation of ceritinib. This contradicts the company's assertion that it would not be appropriate for crizotinib, a first-generation ALK inhibitor, to be given after ceritinib, a second-generation ALK inhibitor (CS, Figure 3). The clinical advisor to the ERG also strongly asserted that crizotinib would not be prescribed after the discontinuation of ceritinib .

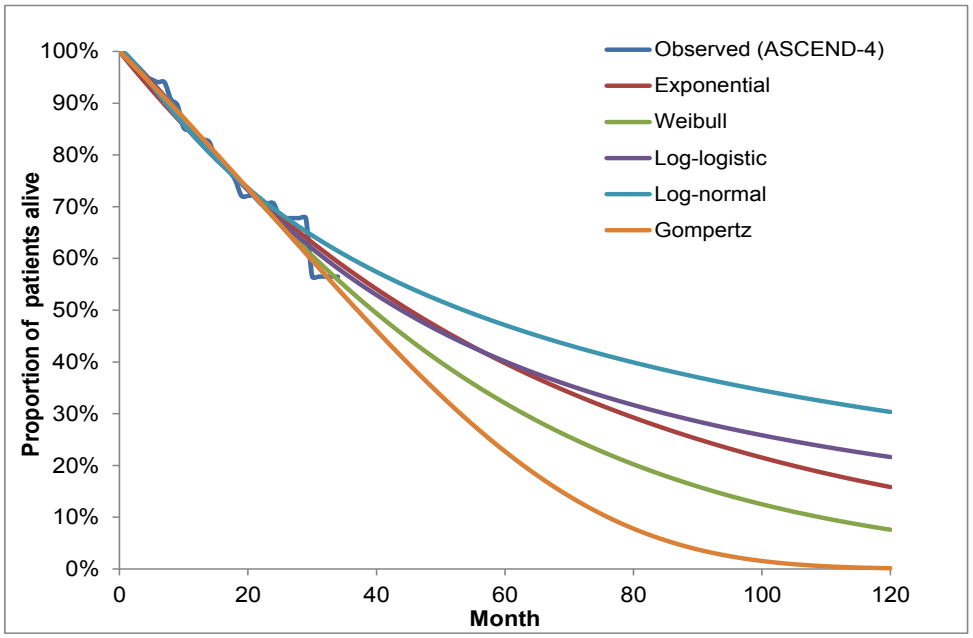
Figure 2: Observed and predicted PFS for ceritinib patients (CS, Figure 17, p 89)



Overall survival

The exponential curve demonstrated the best statistical fit to the available OS trial data, and the log-cumulative hazard plot was linear in shape (supporting a constant hazard of death consistent with an exponential model). The company also stated that their clinical advisors supported the choice of this distribution.

Figure 3: Observed and predicted OS for ceritinib (CS, Figure 18, p 90)



The company acknowledged that the exponential function for OS yielded higher long-term survival predictions that might be observed in clinical practice, so conducted a series of scenario analyses in which the Weibull and Gompertz curves were used to extrapolate OS. In both these scenarios the ICER varied substantially indicating that the model is very sensitive to this parameter, see Section **Error! Reference source not found.** for further details.

Table 4: Estimated survival at five years for ceritinib, by parametric distribution

Distribution	Progression-free at five years	Alive at five years
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

ERG's comments

The selection of the exponential function appears to have been reasonable for PFS and produces predictions that are consistent with the OS evidence; the ERG notes that after a certain time point, the Gompertz curve yielded estimates of progression that were higher than any one of the OS survival curves.

With respect to OS, the ERG, however, has some concerns about the distribution selected. The ERG notes that the exponential function for OS provides among the most optimistic long-term estimates of survival, compared with the other distributions (Table 4). The choice of this survival function also results in there being no difference in time spent in the post-progression health state in each arm, which appears to lack face validity within the present context, given the different treatment pathway post-progression (discussed in Section 0). Furthermore, the exponential curves produce predictions about the duration of OS that are inconsistent with the clinical experience of ALK inhibitors; the exponential curve predicts that [redacted] of ceritinib patients and [redacted] of crizotinib patients would be alive after 5 years. The clinical advisor to the ERG suggested that 20% survival at 5 years would be more reasonable, which more closely corresponds with estimates from the Gompertz distribution. The ERG, therefore, considers the use of alternative distributions to model OS within scenario analyses presented in Section 6. Should the more recent OS data for crizotinib from PROFILE 1014 become available later in the process, it would aid in validating the assumptions around extrapolating OS.

It is good practice to validate long-term predictions of treatment effectiveness against an external dataset, where possible. In Section 4.2, the ERG noted an additional study identified in their review, a retrospective cohort study assessing treatment patterns and outcomes in patients with ALK+ advanced

NSCLC in a European population treated with crizotinib in regular clinical practice[29]. **Error! Reference source not found.** (adapted from the poster) presents overall survival in crizotinib patients by line of therapy. From crizotinib initiation, median OS was [redacted] in first-line initiators ([redacted]). The study authors commented that the outcomes for median OS for first-line crizotinib initiators aligned with expectations based on previous trials. While it is not possible to ascertain the robustness of the data at later time points (numbers at risk not reported), the long-term data may be useful to determine an appropriate method for extrapolating the ASCEND-4 and PROFILE 1014 data. At three years, approximately [redacted] of patients remained alive, further supporting the ERG's belief that the exponential function overestimates OS in the model. At the time of writing this report this real world data provided the best long-term data that the ERG were aware of. However, the ERG acknowledges there are various prognostic factors that influence the response to treatment, and that the differences between the Davis study population and the ASCEND-4 and PROFILE 1014 trial populations may lead to differences in OS. Further, the treatment pathway (specifically, second-line therapy following crizotinib discontinuation) in the real world cohort may differ to that in the clinical trials, which may also lead to differences in OS. [redacted]include in the model was appropriate, as these were those which were considered to be associated with a more substantial impact on costs and quality of life. The ERG, however, does note a number of small issues (described below). These were considered to be minor and unlikely to impact on the outcomes of the economic analysis, and as such were not explored further.

Multiple events

The company model modelled Grade 3+ adverse events using the proportion of patients experiencing an event from the trials. The total cost of treating AEs would be underestimated, in each arm, if patients experience more than one event of a particular type; however, the company was not able to provide the total number of events. It is difficult to determine the extent of any underestimation, but it is likely to be small. The event with maximum severity was recorded for patients who experienced multiple episodes of a particular event, so this would only result in an underestimation in treatment costs if both events were of Grade 3 severity or above.

Population adjustment

Given that survival estimates were adjusted for differences in the trial population, by the MAIC, the ERG queried whether the rates of adverse events for ceritinib and crizotinib might also vary within different patient populations ; the company confirmed that the proportion of patients with AEs was generally consistent across subgroups. The ERG accepts that the current approach appears to be adequate and that further adjustment is unlikely to make much different to the ICER: the proportion of patients with AEs was shown to be, generally, consistent across a range of patient characteristics,

through subgroup analyses, presented in the ASCEND-4 CSR[44], and deterministic sensitivity analyses, presented by the company, demonstrated that the model results were not sensitive when varying the costs of AEs from zero to twice their base-case values.

Half-cycle correction

The ERG noted an error in the calculation of AE costs, details provided in Section **Error! Reference source not found.**.

Second-line therapy

When asked to justify why the safety profile of each second-line therapy was not modelled, the company stated that there was limited potential for differences in second-line adverse event rates between the two arms. In the company's base-case analysis this assumption is relatively justifiable because it is assumed that patients were equally likely to receive second-line therapy, with a similar treatment distribution and duration of time. However, as discussed in Section 0, the assumption that ceritinib and crizotinib patients receive the same second-line therapies, and for the same duration of time, is not well supported by the evidence from the ASCEND-4 and PROFILE 1014 trials, and is unlikely to occur in clinical practice. If, as was observed in the trials, ceritinib patients are less likely

ERG's comments

The ERG accepts the calculations of the drug costs per month, for second-line treatment. ASCEND-3 is likely to have been an appropriate source for the relative dose intensity of ceritinib, as roughly two thirds of its population were previously treated with an ALK inhibitor; PROFILE 1007 is an appropriate source, given that this study's population were receiving second-line treatment.

However, the ERG has major concerns regarding the distributions, of the second-line treatments, assumed in the model. As discussed in Section 0, the trial-based distributions are not reflective of current practice and are likely to underestimate the costs that will be incurred by the NHS. The ERG agrees that the assumptions around the "real world" distributions used in the scenario analysis, in the CS, are likely to be more reflective of the costs incurred in practice. However, the true cost is still uncertain. The company's "real world" assumptions appear to be conservative, they assumed that 60% of patients in the crizotinib arm receive ceritinib, where the ERG's clinical advisor believes it could be closer to 80%. This "real world" distribution estimate has a major cost implication within the model: as can be seen in **Error! Reference source not found.**. Implementing the trial-based distribution produces a second-line treatment cost estimate of £8,645.67, while using the "real world" distribution produces an estimate of £28,083.54, and so the company's scenario analysis may be underestimating the ICER. Therefore, the ERG is very concerned about the large uncertainty surrounding this important cost category.

In addition, not only are these assumptions increasing the uncertainty being incorporated into the model, but the resource-use data being used in the model also do not correspond to the clinical efficacy data being used. The ERG believes that the base-case analysis in the CS (using the trial-based distributions) is likely to be the most appropriate option, to allow for consistency between the costs and the clinical data in the model. However, the ERG wants to highlight the lack of external validity for this option.

Not only does the distribution of treatments differ, but the model also assumes that the same proportion of patients receive active therapy post-progression in each arm of the trial (60%). Again this is based on clinical expert opinion, and this proportion is much higher than those reported in the trials (35% in ASCEND-4 and 43% in PROFILE 1014). In the points for clarification (PFC), the ERG asked the company to justify this assumption. In response, the company presented sensitivity analysis showing that this assumption does not make a large difference to the ICER. However, the ERG would like to note that combining this assumption with using the "real world" drug distribution estimates significantly increases the costs associated with the crizotinib arm. Therefore, these assumptions reduce the external validity of the model and increase the uncertainty within the model.

- First-line drug and drug administration costs were the largest component of the total costs for both ceritinib (75.1% without PAS and [redacted]% with ceritinib PAS) and crizotinib (71.87% without PAS and [redacted]% with ceritinib PAS). Ceritinib patients spent a longer time on treatment, hence the higher cost; although the difference was reduced due to the relative dose intensity adjustments made, where ceritinib was associated with a lower dose intensity compared with crizotinib.
- Pre-progression medical costs were noticeably higher for ceritinib, compared with crizotinib (34.35%). This was due to the longer PFS among patients treated with ceritinib in the model.

Table 5: Cost categories (adapted from CS, Table 49, and from the company's model)

	Without PAS			**With PAS for ceritinib**		
	Ceritinib	**Crizotinib**	**Ceritinib vs Crizotinib**	**Ceritinib**	**Crizotinib**	**Ceritinib vs Crizotinib**
Costs, £						
Drug and drug administration costs, first-line treatment	80,325	66,097	14,229	[redacted]	[redacted]	[redacted]
Drug and drug administration costs, second-line treatment	7,641	8,261	-620	[redacted]	[redacted]	[redacted]
Treatment-associated AE costs	333	211	122	[redacted]	[redacted]	[redacted]
Medical costs	18,655	17,401	1,254	[redacted]	[redacted]	[redacted]
PF costs	4,245	2,787	1,458	[redacted]	[redacted]	[redacted]
PD costs	8,320	8,307	13	[redacted]	[redacted]	[redacted]
Terminal care costs	6,089	6,307	-218	[redacted]	[redacted]	[redacted]
Total costs	106,954	91,970	14,985	[redacted]	[redacted]	[redacted]

CS, company submission; PAS, patient access scheme; AE, adverse event; PF, progression-free; PD, progressed-disease

In the base-case analysis, ceritinib generated both higher QALYs and higher LYs, compared with crizotinib. These results are presented in **Error! Reference source not found.**. Ceritinib generated nearly all of its additional QALYs and LYs within the progression-free health state; post-progression QALYs and LYs were approximately equal to those with crizotinib.

First-line treatment until discontinuation (based on truncated median duration data reported in the ASCEND-4 and PROFILE 1014	Treatment until discontinuation or progression, whichever occurs first	£28,398	[redacted]
Post-progression treatment distribution based on those used in ASCEND-4 and PROFILE 1014	"Real world" distribution, estimated based on consultation with clinical experts	Dominant	[redacted]
CS, company submission; PAS, patient access scheme; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years			

5.2.11.4 Subgroup analysis

No subgroup analysis was undertaken in this submission. The CS justified this by stating that their clinical data indicated that the clinical benefits of ceritinib over chemotherapy were consistent across the entire patient population.

ERG's comments

The ERG agrees that Figure 12 (CS, p 52) indicates that the clinical benefit was consistent across the entire population. However, this figure also shows that the median PFS for patients with and without brain metastases was quite different (26.3 for without, and 10.7 for with, brain metastases at screening). Given this difference in an important parameter within the model, the ERG thinks that a subgroup analysis of patients with and without brain metastases present at screening would have been useful.

5.2.11.5 Revised economic model results

After reviewing the original model, the ERG requested that the company provide additional information around some of the assumptions made, in their analysis, and include some additional analyses in their model. The requests for clarifications and their rationale are summarised in Table 6.

The ERG acknowledges that there was no direct evidence on the effectiveness of ceritinib and crizotinib. However, the ERG was particularly concerned with the reliability of the MAIC analysis, given the importance of its results within the model. Consequently, to explore the underlying uncertainty in the model, due to the MAIC results, the ERG requested several scenario analyses, which included an alternative source of data to estimate the relative effectiveness of crizotinib with the MAIC. The ERG also requested additional information and analysis around the clinical data for ceritinib, adverse events included, the time-on-treatment estimates, cost categories included in the model, and post-discontinuation care for patients in both comparators.

Table 6: Points for Clarification

ERG request [PFC number]	**Rationale for request**	**Company response**	**Action in new company model**
A re-analysis so that the base-case models the population in PROFILE 1014 trial population. [B1 (i)]	An alternative scenario analysis to assess the reliability of the MAIC analysis.	The company modified the base-case analysis by refitting the parametric functions of PFS and OS for ceritinib to match the PROFILE 1014 population. The truncated median time on treatment was similarly re-calculated.	The model was updated to incorporate this alternative method.
Using the analysis from B1 (i) fit the parametric curves to the Kaplan Meier data independently.	To test the assumption of proportional hazards used in the base-case analysis.	The company modified the analysis undertaken above as requested.	The model was updated to incorporate this alternative method.
Re-run the MAIC analysis using clinical data from the ALEX trial, rather than the PROFILE 1014 trial, for crizotinib. [B2 (i)]	An alternative scenario analysis to assess the reliability of the MAIC analysis.	The company undertook a MAIC analysis using data on crizotinib from the ALEX trial, using the same approach that was used in the previous MAIC undertaken in the CS.	Alternative MAIC results were presented, which the ERG was able to incorporate in the model. No action in the model was undertaken.
Re-run the MAIC analysis using clinical data from the ALEX trial combined with the PROFILE 1014 trial, for crizotinib. [B2 (ii)]	An alternative scenario analysis to assess the reliability of the MAIC analysis.	The company stated that they were unaware of any methodology to facilitate this analysis.	None taken.
The analysis from B2 to be incorporated into the model. [B3]	To assess these additional scenario analyses' effect on the ICER.	The company stated that they did not have time to incorporate these analyses in the model but did provide the necessary information required for the ERG to undertake the inclusion.	Parameter values were presented but no action in the model was undertaken.
Further exploration of the weighting used to match the IPD from ASCEND-4 to PROFILE-1014. [B4]	The CS states that only mild weighting was required to match these data but the process of matching had a large impact on median survival with ceritinib.	The company stated that although the median changed, the 95% CI did not changed substantially.	A comparison of QALYs and LYs before and after the MAIC re-weighting was undertaken. No action in the model was undertaken.
Further exploration of the impact of baseline characteristics on time on treatment. [B5]	Time on treatment is a key driver of costs and the ERG wanted to understand how differences in baseline characteristics may affect this parameter.	The company conducted additional scenario analyses using the MAIC-adjusted time–on-treatment estimates for ceritinib.	None taken.
Present population – adjusted estimates of time on treatment using methods similar to those used to estimate PFS and OS in the base-case analysis. [B6]	Time on treatment for the two comparators is estimated from two different trial populations. The ERG suggests that these differing populations influence the estimated time on treatment.	The MAIC methodology was used to estimate time on treatment for people on ceritinib adjusted to the crizotinib population and a hazard ratio for time on treatment in the crizotinib population was estimated.	Parameter values were presented and incorporated in the model.

- Subgroup analyses

The feedback from these clinical experts was similar to that from our clinical advisor.

5.2.12.2 Validation carried out by the ERG

The ERG undertook a review of the company's base-case and sensitivity analyses. This included the use of a checklist to carry out a series of black-box tests to evaluate the internal validity of the model.

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 main calculation sheets, with a view to understanding how the QALYs and costs accumulated in the model.

- The ERG noted an error in how the half-cycle correction was implemented in the model, specifically for attributing costs to adverse events.
- AE costs were applied as a one-off event at the beginning of the model. The company inappropriately applied a half-cycle correction, where the costs of half of these events were applied in the first cycle and half in the second cycle. In the second cycle, costs were applied to patients who were still living. The inclusion of such an adjustment would not be necessary given that the AE rates were taken from the whole on-treatment period and reflect the survival in each arm. As such, the ERG removed the half-cycle correction.
-

Section 6 provides base-case results, adjusted for all the calculation errors identified by the ERG.

5.3 Conclusions of the cost-effectiveness section

A limited number of cost-effectiveness analyses of ceritinib and other targeted therapies were identified in the systematic review presented in the CS. One of these studies was considered relevant to the current submission: a cost-effectiveness analysis of crizotinib, taking a UK perspective and designed to be consistent with the NICE reference case.

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 base-case ICER presented in the CS was £27,936 per QALY; including the PAS for ceritinib (but not the PAS for crizotinib) resulted in ceritinib dominating crizotinib (with lower costs and more QALYs). The ICER when the PAS for crizotinib is applied was provided in a confidential appendix.

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 assumptions 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 errors identified in ERG's validation of the executable model. Section 6.3 details a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The analyses presented in Section 6.3 focus on exploring the following issues and uncertainties:

- Assumptions around the modelling of clinical data (PFS, OS and treatment duration);
- Alternative source of effectiveness data for crizotinib;
- Modelling the proportion of patients on second-line therapy;
- Alternative scenarios for modelling quality of life in post-progression patients;
- Drug wastage and administration cost for first-line and second line therapy.

In Section 6.4, based on a combination of the exploratory analyses presented in Section 6.3, the ERG presents an alternative ERG base-case that the ERG's considers to be more reflective of the cost-effectiveness of ceritinib. Section 6.5 presents a brief conclusion summarising the ERG's additional analyses.

The results in this section do not include the PAS for the comparator therapy crizotinib. Results for the company's base-case and all analysis carried out by the ERG with the PAS for crizotinib applied are instead presented in a separate confidential appendix.

6.2 ERG corrections and adjustments to the company's base case model

A small number of errors were identified by the ERG in the company model, see Section 5.2.11 for details. The impact of these corrections to the base-case results was negligible.

Table 7: Results of the ERG-corrected company base case model

	Mean Costs	Mean QALYs	Incremental Costs	Incremental QALYs	ICER
CS base case					
Without PAS					
Ceritinib	106,954	3.22	14,985	0.54	27,936
Crizotinib	91,970	2.68	-	-	-
CS base case - with PAS for ceritinib					
Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Crizotinib	89,714	2.68	-	-	-
ERG-corrected base case					
Without PAS					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
ERG-corrected base case - with PAS for ceritinib					
Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Crizotinib	89,721	2.68	-	-	-
Please note that these results do not incorporate the confidential PAS for crizotinib. Please refer to the confidential appendix for results applying the PAS for both ceritinib and crizotinib. ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CS, company submission; PAS, patient access scheme					

6.3 Additional ERG analyses

6.3.1 Effectiveness and extrapolation

The ERG conducted a series of analyses, exploring alternative assumptions around the modelling of the clinical data (namely, overall survival, progression-free survival and treatment duration for ceritinib and crizotinib). The exploratory analyses included:

- Adjustment of ceritinib clinical data from ASCEND-4 (OS, PFS and treatment duration) to the PROFILE 1014 population;
- Estimating time on treatment for ceritinib using patient-level data from ASCEND-4 and estimating the relative time on treatment for crizotinib using a hazard ratio;
- Alternative survival models to extrapolate overall survival.

All scenarios were applied within the context of the ERG corrected company model.

Proportional hazard of treatment discontinuation

As described in Section 5.2.4.2 the company's approach to modelling time on treatment underestimated the time on treatment for ceritinib patients and was inconsistent with the approach used to model PFS and OS. Table 8 presents the results of this analysis, which the ERG considers more consistent with the approach to modelling PFS and OS and which more accurately estimates duration of treatment on ceritinib. This approach also attempts to account for any differences in the base-line characteristics of crizotinib and ceritinib patients. The steps used to estimate treatment duration for ceritinib and crizotinib are as follows: (1) the KM for time on treatment for ceritinib is adjusted using the MAIC method; (2) median time on treatment is estimated from the adjusted KM curve; (3) the adjusted median for ceritinib and median time on treatment reported in PROFILE 1014 are then used to estimate a hazard ratio for treatment discontinuation for ceritinib versus crizotinib ([redacted]); (4) this hazard ratio is applied to the ceritinib time on treatment curve estimated from ASCEND-4 patient-level time-to-event data, fitted with an exponential curve. Time on treatment for ceritinib is therefore base on the extrapolated patient level data and time on treatment for crizotinib is estimated using the hazard ratio. The mean duration of first-line treatment using this methods for ceritinib was [redacted], and [redacted] for crizotinib (compared with [redacted] and [redacted] in the company base case for ceritinib and crizotinib respectively).

Table 8: Results of ERG analysis of proportional hazard of treatment duration

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
Proportional hazard of treatment duration					
Ceritinib	126,171	3.22	19,383	0.54	36,136
Crizotinib	106,789	2.68	-	-	-

Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CS, company submission; PAS, patient access scheme

As can be seen in Table 8, this alternative approach to estimating time on treatment results in increase in the ICER. This because the mean duration of treatment with ceritinib increases by a greater amount than for crizotinib, which results in an increase in incremental drug acquisition costs.

Population adjustment

Table 85 presents the results of an exploratory analysis where ceritinib clinical data from ASCEND-4 (OS, PFS and treatment duration) were adjusted to reflect outcomes in the PROFILE 1014 population. The ERG considers this a more consistent approach because the hazard ratios for OS and PFS were estimated using ceritinib data adjusted to the PROFILE 1014 population and therefore the sake of consistency the population modelled should be the PROFILE 1014 population.

Weighting the ASCEND-4 data to match PROFILE 1014 patient characteristics caused a slight upward shift in the parametric functions of PFS and OS compared to the base case (Figure 4). The company provided a population-adjusted time on treatment from ASCEND-4 for people on ceritinib adjusted to the PROFILE 1014 population, using a MAIC. This increased the median time on treatment from 15.27 months to [redacted].

Figure 4: Predicted OS and PFS for ceritinib base case and re-weighted curves (based on exponential distribution)

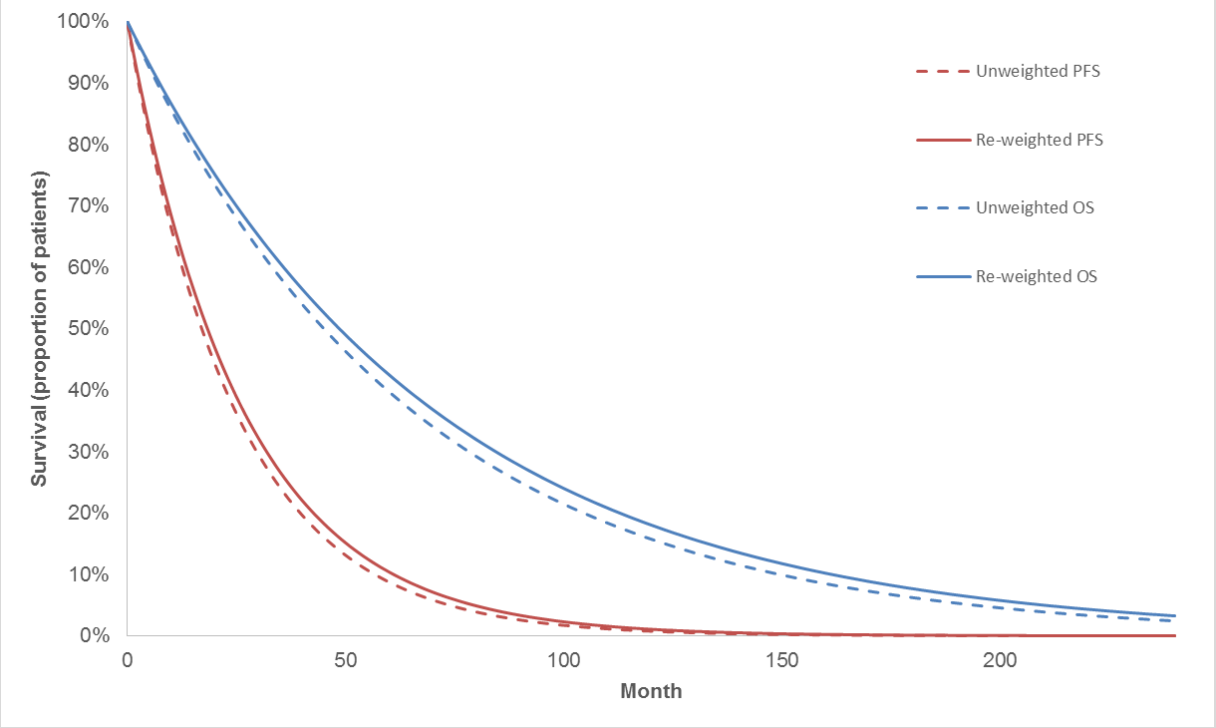


Table 9: Results of ERG analysis of clinical data matched to the PROFILE 1014 population

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
Clinical data matched to the PROFILE 1014 population					
Ceritinib	108,926	3.41	16,328	0.56	29,149
Crizotinib	92,598	2.85	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

This scenario resulted in a small increase to the ICER. The ERG felt that it was important for populations to be consistent and the PROFILE 1014 population was felt to be equally as representative as the ASCEND-4 population, but constraints of the MAIC methodology meant that the trial with only summary data available was the target population of the analysis.

Extrapolation of OS data

Alternative parametric models for overall survival to the exponential model used in the company base case were then explored. Other models explored were Weibull and Gompertz. Results of the scenarios are presented in Table 10.

The company provided a range of OS curves for ceritinib, re-analysed so that estimations were in the PROFILE 1014 population. For consistency, time on treatment was also modelled in the PROFILE 1014 population. Predicted OS with each parametric model are presented in Figure 5.

As with the exponential curve, weighting the ASCEND-4 data to match PROFILE 1014 patient characteristics caused a slight upward shift in the OS parametric functions. The shape of the different parametric functions, and their relative ranking in terms of fit with the observed data, was similar to the base-case parametric functions. The exponential function demonstrated the best fit with the observed data based on AIC/BIC statistics (but implausible results).

Figure 5: Predicted OS for ceritinib using different parametric functions (after applying MAIC weights to match PROFILE 1014 baseline characteristics) (Response B1 from PfC)

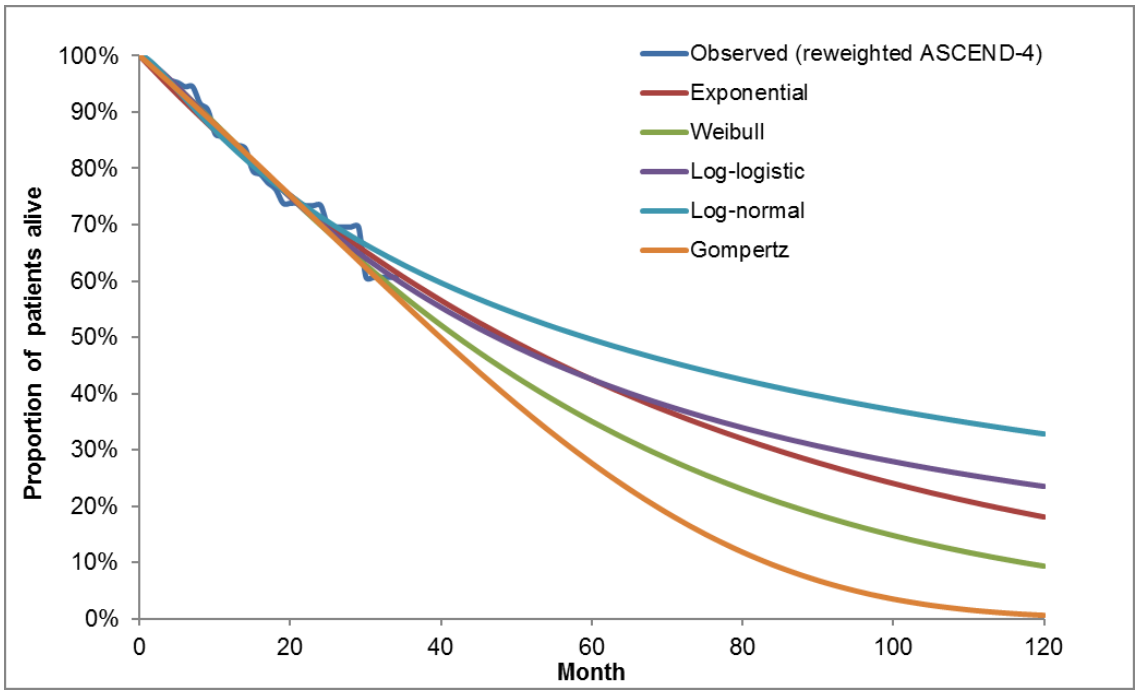


Table 10 Results of ERG exploratory analyses on alternative survival models for OS

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
Weibull curve to model OS and clinical data matched to the PROFILE 1014 population					
Ceritinib	106,706	2.91	15,943	0.47	34,221
Crizotinib	90,763	2.44	-	-	-
Gompertz curve to model OS and clinical data matched to the PROFILE 1014 population					
Ceritinib	104,707	2.47	15,428	0.35	44,602
Crizotinib	89,279	2.12	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied					

Both scenarios results in similar total costs but lower QALYs and an increase in the ICER compared to the ERG-corrected base case scenario. The company appears to make their selection of survival curve for OS on the basis of statistical fit (AIC/BIC), and it does not appear that clinical plausibility

was taken into account. The clinical advisor to the ERG suggested that long-term survival estimates based on the exponential curve were implausibly high. A later cut of data from Pfizer for PROFILE 1014 would help to determine the most appropriate set of assumptions for OS.

6.3.2 Alternative source of clinical data (ALEX trial for crizotinib)

The ERG have noted some concerns about the reliability of the effectiveness estimated derived from the MAIC analysis. The ERG considered that ALEX provided a relevant alternative source of data for the crizotinib patient population to PROFILE 1014.

To explore the impact on the cost-effectiveness analysis of this new MAIC analysis, the ERG requested that the company undertake the following two scenarios:

1. Using the data derived from the MAIC analysis, which used the crizotinib population from ALEX, where the population is adjusted to the ASCEND-4 study as per the company's base-case
2. Using the data derived from the MAIC analysis, which used the crizotinib population from ALEX, model the population to that the data is adjusted to the ALEX trial population.

In order to implement the first scenario, the company provided the ERG with the information presented in Table 11, which was based on the updated MAIC analysis requested.

Table 11: Hazard ratios of PFS and OS and truncated median duration of crizotinib under Scenario B3.i in the PfCs (Company response to PFCs)

Parameter	Parameter value under Scenario B3.i
Hazard ratio of PFS with crizotinib vs. ceritinib	[redacted]
Hazard ratio of OS with crizotinib vs. ceritinib	[redacted]
Truncated median time on treatment for crizotinib	10.7 months
PFS, progression-free survival; OS, overall survival; PfCs, points for clarification	

The effect of using the crizotinib population from the ALEX trial rather than the PROFILE 1014 trial is to increase the ICER of ceritinib vs. crizotinib from £26,354 to £30,212. The use of the ALEX trial data causes the total costs for crizotinib to reduce and the total QALYs to increase the ICER. These results are presented in Table 12.

The second scenario required the analysis undertaken in the first scenario to be further modified, by re-fitting parametric functions of ceritinib PFS and OS, after weighting the ASCEND-4 data to match the base-line characteristics from the ALEX trial. This scenario also required the truncated median

time on treatment to be re-calculated for ceritinib after weighting the ASCEND-4 population to match the ALEX trial population, ([redacted]).

The effect of using the crizotinib population from the ALEX trial rather than the PROFILE 1014 trial, with the ASCEND-4 population being adjusted to match the ALEX trial population is presented in Table 12. Once again, the scenario increases the ICER of ceritinib vs. crizotinib, from £26,354 to £30,189. In this instance, the use of the ALEX trial data causes the total costs crizotinib to reduce, the total costs of ceritinib to increase and the total QALYs for both comparators to increase, compared the ERG's corrected base-case results. As with the previous scenario the ICER for ceritinib vs. crizotinib increases.

Table 12: Results from ERG exploratory analyses using ALEX trial data for crizotinib

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
ALEX for crizotinib effectiveness, ceritinib data in ASCEND-4 population*					
Ceritinib	106,962	3.22	16,127	0.50	32,345
Crizotinib	90,834	2.72	-	-	-
ALEX for crizotinib effectiveness, ceritinib data in ALEX population*					
Ceritinib	107,373	3.27	16,297	0.50	32,411
Crizotinib	91,076	2.77	-	-	-

Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.

*these results differ slightly (taking account of the ERG corrections) from those presented by the company. This was due to the company providing rounded parameter values, rather than formally incorporating these scenario analyses in the submitted, updated model. These rounded parameters resulted in slightly different ICERs being derived in the ERG's analysis, pre ERG correction. The ERG are not concerned with these slight differences.

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

These additional analyses show that the use of PROFILE 1014 within the MAIC analysis appears to be underestimating the ICER for ceritinib vs. crizotinib compared to using ALEX within the MAIC analysis. This scenario shows the inherent uncertainty of using the MAIC to estimate the relative effectiveness of ceritinib and crizotinib, with this adjustment increasing the ICER by approximately

16%. The ERG considers the use of the ALEX trial as source of effectiveness data for crizotinib equally valid to using PROFILE 1014.

6.3.3 Proportion of patients on second-line therapy

The ERG conducted a scenario analysis where the proportion of patients receiving second-line therapy was explored further. In the company base-case analysis, it was assumed that 60% of patients would receive further active therapy following discontinuation from ceritinib or crizotinib, based on clinical advice. This was larger than what was received in the ASCEND-4 and PROFILE 1014 trials, which was 35% and 43% respectively. In this scenario, the ERG explored the impact when the proportion of patients receiving second-line therapy in the model reflected that of the trials.

The results of this scenario are presented in Table 13. Use of the trial-based rates of therapy result in a decrease in total costs: the decrease is greater in the ceritinib arm (consistent with the lower rate of patients receiving second-line therapy), and subsequently incremental costs and the ICER decrease.

Table 13: Results of ERG exploratory analysis for distribution of second-line therapy

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
Trial-based second-line treatment distribution					
Ceritinib	103,778	3.22	14,142	0.54	26,364
Crizotinib	89,636	2.68	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

While the distribution of treatments in this analysis is less reflective of clinical practice, the ERG believe that this adjustment provides estimates that are more consistent with the costs that would be incurred in the trials, and that the company's base-case ICER is overestimating the incremental costs of ceritinib when compared with crizotinib in this respect.

6.3.4 Quality of life

The ERG conducted two scenario analyses around the progressed disease utility: In the first scenario models post-progression utility values were selected to reflect the real world treatment pathway, where patients initiating on crizotinib are expected to receive ceritinib as second-line ceritinib. In the

second scenario models post-progression utility values were selected to better reflect the trial-based treatment pathway, by accounting for the fact that significant proportion of patients receive first-line treatment beyond progression. In each scenario, two amendments were made. Table 14 presents the utility values from Chouaid[41]which were used to estimate post-progression utility in the base case, accompanied by a description of the amendments made to the calculation of the utilities used in the scenario analysis.

Table 14: Utility values used to estimate post-progression utility

Treatment	***n***	***Mean***	**ERG comments**
First-line PD	26	0.67	Corresponds to ALK patients who continue after progression – this is expected to be too low as it is based on patients on chemotherapy agents (not as effective as ALK inhibitors[9]) Remove this from the weighted average PD utility and replace with the sustained utility adjustment Sustained utility estimated as the midpoint of pre-progression utility (0.81) for both crizotinib and ceritinib) and post-progression utility (see below).
Second-line PF	44	0.74	Corresponds to patients within the PF health state (patients who discontinue ALK inhibitors before progression) Remove this from the weighted average PD utility
Second-line PD	17	0.59	Trial scenario: Appropriate for calculations in both arms Real world scenario: Appropriate for calculation for ceritinib arm For crizotinib arm, second-line would be ceritinib – this value is expected to be too low. Alternative utility estimated to be 0.66 from Blackhall et al (value was redacted from the STA for second-line ceritinib, but notes that the values derived from their mapping exercise of ASCEND-2 utilities are consistent with the findings of the Blackhall study)
Third/fourth-line PF	24	0.62	Appropriate for calculation
Third/fourth-line PD	21	0.46	Appropriate for calculation
ALK, anaplastic lymphoma kinase; PD: progressed disease. PF: progression-free; STA, single technology appraisal			

In order to implement these scenarios, in meaningful way it was necessary to use the alternative method of estimating duration of first-line treatment outlined in 6.3.1. This is because in the company's base-case no patients are assumed to receive treatment beyond progression. To apply a sustained utility for patients receiving first-line treatment beyond progression an additional health

state was created, using the difference between the time on treatment curve and the PFS curve. Utility values used in the exploratory analyses undertaken by the ERG are presented in Table 15.

Table 15: Utility values in the ERG scenario analysis

Health state	Scenario 1: Trial scenario	Scenario 2: Real world scenario
Ceritinib		
Progression-free	0.81	0.81
Disease progression	0.56	0.56
Sustained utility on progression	0.68	0.68
Crizotinib		
Progression-free	0.81	0.81
Disease progression	0.56	0.58
Sustained utility	0.68	0.69
ERG, evidence review group		

Results of the scenario analyses are presented in Table 16. In each of the company-presented scenarios, the total number of QALYs accumulated in each arm were reduced when the alternative set of utility values were used. In the trial scenario, the same utility values were applied in each arm and this resulted in this scenario having a very similar number of incremental QALYs to the base-line scenario (the amended base case), and subsequently a smaller increase in the ICER. The real world scenario, however, resulted in a greater number of QALYs in the crizotinib arm compared with the trial scenario, reflecting that this scenario accounted for the improved quality of patients in the PD health state in this arm due to second-line ceritinib therapy. Therefore, this scenario had lower incremental QALYs and a higher ICER than the trial scenario. The ERG felt that the trial scenario was more defendable in this analysis despite the fact that it was considered to be less reflective of quality of life we might expect in clinical practice. This is because the OS benefits associated with second-line ceritinib were not mirrored in the clinical trial data, where only a small proportion of patients receive this treatment.

Table 16: Results of ERG exploratory analysis with alternative utility values for post-progression

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
Base line scenario (base case utility values alternative method of estimating time on treatment)					
Ceritinib	126,171	3.22	19,383	0.54	36,136
Crizotinib	106,789	2.68	-	-	-
Scenario 1: Trial scenario					
Ceritinib	126,171	3.03	19,383	0.53	36,618
Crizotinib	106,789	2.50	-	-	-
Scenario 2: "Real world" scenario					
Ceritinib	126,171	3.03	19,383	0.48	40,192
Crizotinib	106,789	2.55	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

6.3.5 Resource use and costs

The ERG conducted two scenario analyses to take account of the relative dose intensity assumptions applied to drug costs within the model, and to allow for some drug wastage to occur.

As discussed in Section 5.2.9, the ERG accept the relative dose intensity assumptions included in the CS model. However, in line with previous ERG submissions (TA406) the ERG consider it unreasonable to also include half cycle corrections for drug costs. Removing this correction allows for drugs prescribed at the beginning of the cycle to be wasted should a patient discontinue treatment within that cycle. This adjustment still allows for drug wastage as a result of discontinuation of treatment to effectively be treated as a cost-saving within the model. The impact of this adjustment is presented in Table 17. When compared to the ERG corrected base case, the ICER for ceritinib vs. crizotinib is reduced when the half-cycle correction is removed. This is because this scenario increases the total costs for both ceritinib and crizotinib.

The second scenario analysis relates to administration costs for the oral chemotherapies (ceritinib and crizotinib) in both first-line treatment and in subsequent treatment following progression. In Section 5.2.9, it was discussed that including a pharmacist's time for dispensing prescriptions is likely to be underestimating the treatment administration costs for the oral chemotherapies. The ERG also believe

that pharmacist's time cost does not take account of the administration costs required to implement the relative dose intensity assumptions included in the company's model. An outpatient administration cost, SB11Z, which is labelled as "Deliver oral exclusively oral chemotherapy" was included in the economic model. This cost was derived from NHS reference costs, 2015-2016 and is in line with the additional administration cost included in the previous appraisal of crizotinib (TA406). The monthly unit cost for this additional administration cost is £181. The results, when this cost is included, are presented in Table 17. In this instance, the total costs for ceritinib are increased to a larger degree compared with crizotinib and the resulting ICER increases to £29,773.

Table 17: Results of ERG exploratory analysis for drug and drug administration costs

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case scenario (ERG-corrected)					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
Scenario 1 – remove half-cycle correction for drug cost					
Ceritinib	112,593	3.22	14,311	0.54	26,681
Crizotinib	98,281	2.68	-	-	-
Scenario 2 – additional administration cost included					
Ceritinib	110,914	3.22	15,970	0.54	29,773
Crizotinib	94,944	2.68	-	-	-
Scenario 3 – both scenarios incorporated					
Ceritinib	116,635	3.22	15,297	0.54	28,518
Crizotinib	101,338	2.68	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

Table 17 also presents the results when both of the scenarios relating to drug and drug administration costs are incorporated. The resulting ICER for ceritinib compared with crizotinib is £28,518. The ERG believe that these adjustments better reflect the costs that would be incurred in clinical practice and that the company's base-case ICER is underestimating the incremental costs of ceritinib when compared with crizotinib.

6.4 ERG preferred base-case analysis

Table 18 presents the ERG's preferred range of scenarios to estimate the cost-effectiveness of ceritinib compared with crizotinib. Based on the assessment of the company analysis and the exploratory analyses conducted in Section 6.3, the ERG considers that there is considerable uncertainty associated with the survival data that is not parameterisable.

The ERG presents two scenarios, and within each scenario an optimistic estimate and a conservative estimate of cost-effectiveness based on different methods to estimate long-term survival. Given the data immaturity from both trials and lack of long-term observational data in these patients to facilitate curve selection, the ERG does not think it is reasonable that one model can be selected confidently over any others.

The scenario is based on the following sets of assumptions:

- ERG resource use and costs (Section 6.3.5)
- Proportion of patients on second-line therapy based on the rates from the ASCEND-4 and PROFILE 1014 trials (Section 6.3.3)
- ERG utilities for post-progression patients, based on the "trial scenario" (Section 6.3.4)
- All clinical data in PROFILE 1014 population (Section 6.3.1)
- Gompertz survival curves for OS (Section 6.3.1).

The ERG considers the alternative scenario presented here to be at least as reasonable as the company base case analysis. Combining these modifications to the company model leads to a considerable increase in the ICER.

Table 18: Results of ERG preferred scenario analyses

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
ERG-corrected company base case					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
ERG preferred base case					
Ceritinib	139,573	2.40	19,887	0.37	58,808
Crizotinib	119,687	2.03	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied. Note that when adjusted for population differences and modelled with a hazard ratio, the mean treatment duration of ceritinib was [redacted], and [redacted] for crizotinib					

The ERG notes that these results should be interpreted with caution. Without access to patient-level data for crizotinib treatment duration, there is no way to accurately model crizotinib time on treatment since the truncated median approach underestimates duration. Treatment duration is a key driver of the model (as demonstrated by the results in Section 6.3.1). It is also difficult to validate the outcome of the hazard ratio approach without access to patient-level data.

6.5 Exploration of proportional hazards assumption

The analysis of the clinical data used in both the company's and ERG base-case analysis both make the assumption that the proportional hazards assumption holds i.e. that the hazard remain constant over the model time. In this section, the ERG explores the impact of relaxing the assumption that the hazards of disease progression, death and treatment discontinuation are not constant. To do this, separate parametric models were fitted to the PFS and OS curves. Time on treatment is estimated as per the company base-case suing the truncated median time on treatment. ASCEND-4 ceritinib survival data was re-weighted to match PROFILE 1014 patient characteristics as it is not possible to fit independent parametric curves while modelling the ASCEND-4 population.

Exponential survival functions for PFS and OS

Firstly, the ERG explored the use of the exponential curve when fit to the Kaplan Meier PFS and OS curves for ceritinib and crizotinib independently (B1b of PFC), to provide a comparison analogous to the company base-case.

Predicted PFS and OS used in this analysis are presented in Figure 6 and Figure 7 respectively (with the curve for crizotinib estimated with hazard ratio for comparison). With the exponential function, the two methods used to estimate PFS and OS for crizotinib were very similar, with the curve fit using the hazard ratio producing slightly lower survival estimates.

Figure 6: Predicted PFS for ceritinib and crizotinib using exponential parametric function

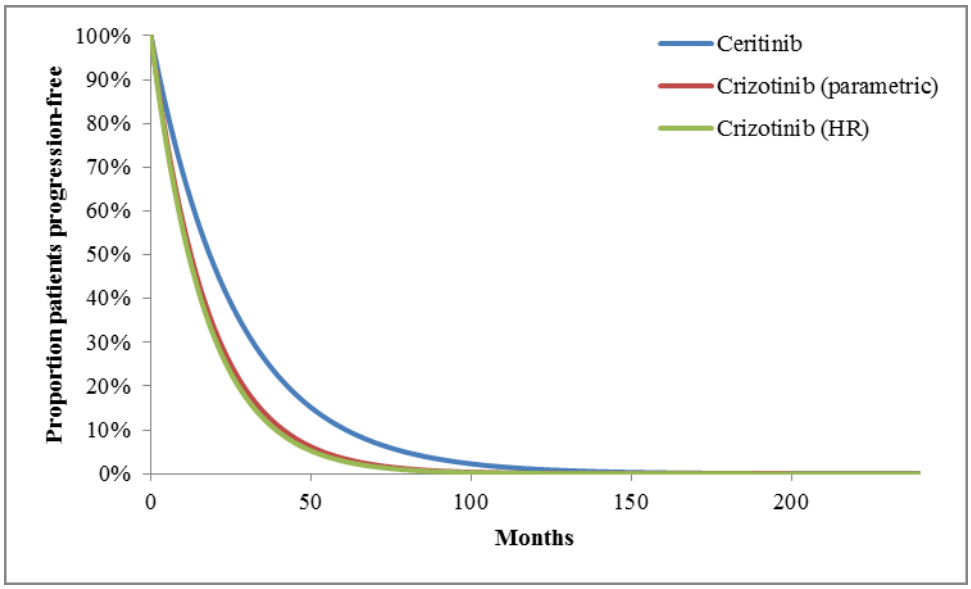
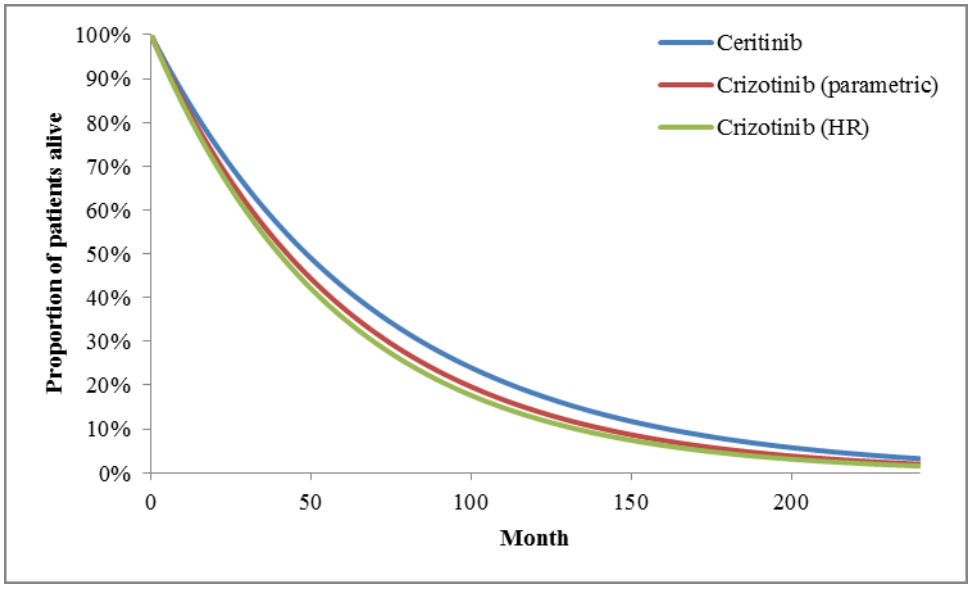


Figure 7: Predicted OS for ceritinib and crizotinib using exponential parametric function



Alternative parametric models for OS

The ERG then explored alternative parametric models for OS. Other models explored were Weibull and Gompertz. The same parametric curve was fitted to both ceritinib and crizotinib KM data , as the

ERG did not consider there sufficient justification for fitting curves of different types (e.g. exponential to the ceritinib arm and Weibull to the crizotinib arm). PFS continued to be modelled with the exponential function as the ERG accepted that this was the most appropriate distribution for this variable.

Predicted overall survival for ceritinib and crizotinib using different survival functions are presented in Figure 8 and Figure 9.**Error! Reference source not found.** According to AIC/BIC statistics, the exponential curve has the best statistical fit for both ceritinib and crizotinib. However, the ERG feels that the exponential curve is likely to overestimate survival for both ceritinib and crizotinib. Given current expectations regarding the long-term survival of patients on ALK inhibitors, the ERG considers the Weibull curve to be the most clinically plausible. Selecting this curve predicts that 35% of patients receiving crizotinib are alive at 5 years. This most closely matches the data available from the Davis study[29], which predicted that a similar proportion of patients would be alive after 3 years. The Weibull curve was also considered by the company in TA406 (first-line crizotinib)[9] to be the most plausible distribution.

Figure 8: Predicted OS for ceritinib using different parametric functions (after applying MAIC weights to match PROFILE 1014 baseline characteristics) (Company response to PFCs)

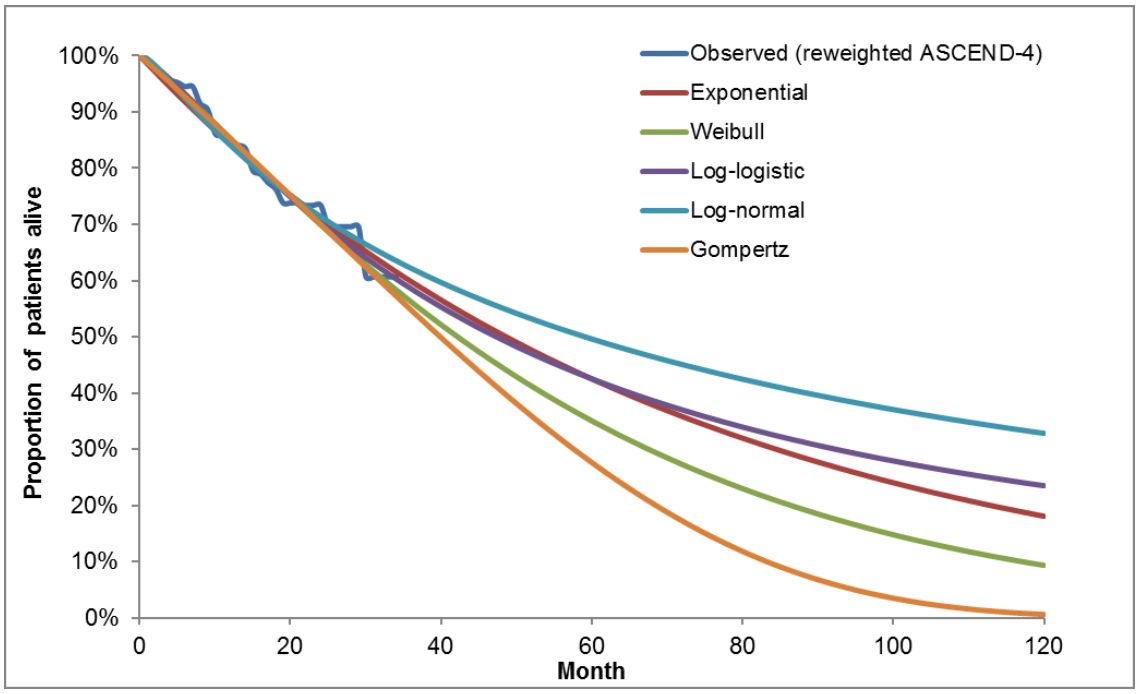
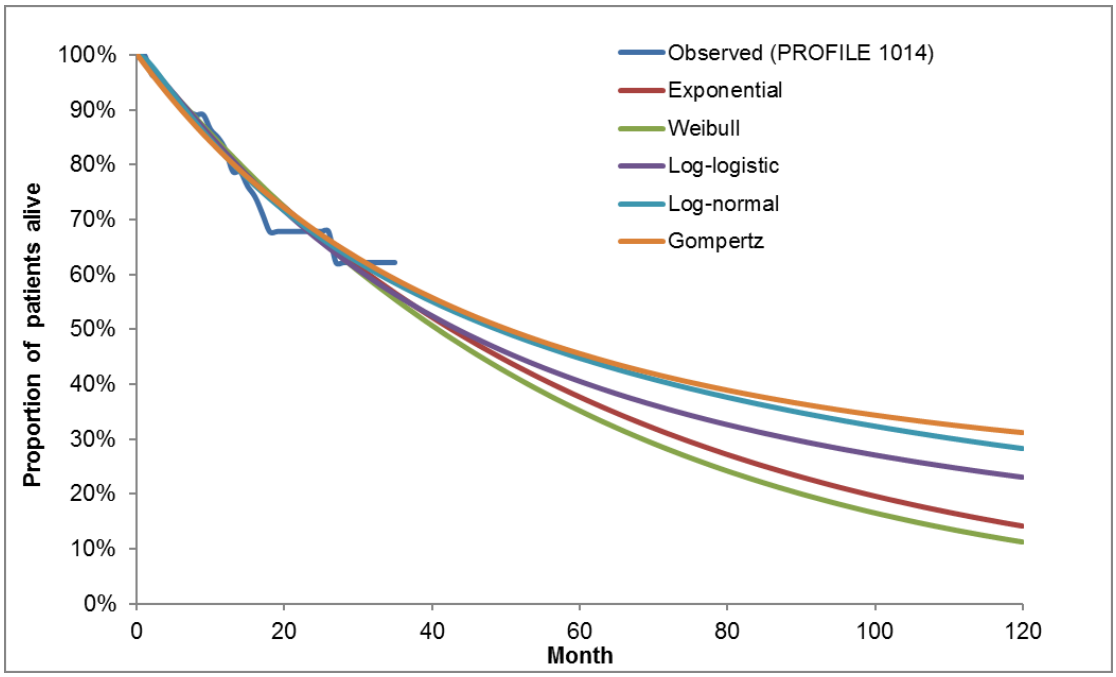


Figure 9: Predicted OS for crizotinib using different parametric functions (separately estimated based on published Kaplan-Meier curves from PROFILE 1014) (Company response to PFCs)



Results of the exploratory analyses

Results of the analyses using the exponential curve and Weibull curve are presented in Table 19. The use of the Weibull curve resulted in very similar estimates of long-term survival between the ceritinib and crizotinib arm, implying that the benefit of ceritinib over crizotinib is to delay progression rather than to extend overall survival. Given the uncertainty in overall survival for both comparators, this scenario could be considered a conservative approach.

Table 19: Results of ERG exploratory analyses of non-proportional hazards

Comparator / scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
ERG-corrected base case					
Ceritinib	106,962	3.22	14,985	0.54	27,936
Crizotinib	91,977	2.68	-	-	-
Exponential survival functions for PFS and OS					
Ceritinib	108,926	3.41	15,783	0.41	38,535
Crizotinib	93,143	3.00	-	-	-
Weibull survival function for OS					
Ceritinib	106,706	2.91	14,307	0.07	191,628
Crizotinib	92,399	2.84	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.					

Comparing the results of the analogous scenarios in Section 6.3.1, the results are similar in the analysis when exponential curves were used, implying that the assumption of proportional hazards is relatively plausible in this instance. However, the results are very different when the Weibull and curves is used, which may suggest that the assumptions of proportional hazards is inappropriate. The ERG is however, notes that he immaturity of the OS data means fitting independent parametric curves is subject to significant uncertainty. The ERG particularly highlights that predicted survival for patients receiving crizotinib is very high (regardless of curve selected) and substantially higher than reported in the Davis cohort study[29]. The apparent inconsistency in results when fitting independent parametric curves may therefore be the result of poor extrapolation rather the lack of any difference in OS.

The ERG also note there are some limitations to the implementation of independent survival curves (relaxing the proportional hazards assumption) as it means that alternative method of estimating duration of treatment used in 6.3.1 cannot be implemented as this relies on the proportional hazard assumption. Relaxing the proportional hazards assumption also prevents the ERG from implementing their alternative set of utility values (which rely in the creation of a post-progression on-treatment health state within the model).

6.6 Conclusions from ERG analyses

The ERG has presented a number of additional analyses. These analyses were carried out in a number of stages. The first stage addressed a number of minor calculation errors in the company's revised model (Section 6.2). The impact of these changes had a very small impact on total costs and did not impact the ICER of £27,936 per QALY without ceritinib PAS applied. When the PAS for ceritinib was applied, ceritinib remained the dominant treatment option.

Using the corrected model, the ERG then presented a number of analyses considering a range of issues raised in Section 5 (Section 6.3). These scenario analyses addressed the following issues:

- Assumptions around how clinical data is modelled:
  - ERG method of estimating treatment duration;
  - The population in which effectiveness is estimated;
  - The extrapolation of OS data.
- Estimating the proportion of patients on second-line therapy from the ASCEND-4 and PROFILE 1014 trials;
- Alternative assumptions around how resource use and unit costs were incorporated, specifically around drug wastage and administration costs;
- How quality of life is modelled in post-progression patients: the use of alternative data sources to estimate health state utilities and alternative patient health states to predict quality of life.

The ERG also identified an additional source of data to model survival of patients receiving crizotinib (Section 6.3.2). The results of the analysis when using data from ALEX instead of PROFILE 1014 are broadly similar; the ICER increases from £27,936 per QALY to around £32,000 per QALY.

The most of important these scenarios related to changes made by the ERG to the clinical data. These analyses explored two distinct issues with the assumptions made in the company's analysis; firstly the selection of survival curve to extrapolate overall survival, and secondly the method used to estimate time on first-line treatment. The results of this analysis demonstrated that these issues have a significant impact on the ICER, which is due in part to the immaturity of the OS data which leads to considerable uncertainty around the extrapolation. This exploration of alternative modelling assumptions was concluded with the ERG presenting a preferred set of assumptions.

The ERG presents a range of plausible ICERS to aid the Committee in determining whether ceritinib is cost-effective compared with crizotinib. The ERG's analyses suggests that the ICER for ceritinib compared with crizotinib may be £53,808 per QALY. These scenarios are 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 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 from ASCEND-4 and PROFILE 1014, which leads to considerable uncertainty around the extrapolation. Using the same parametric functions fitted in the company's base where proportional hazards is assumed and that provided the best statistical fit, this analysis resulted in an ICER of £38,535 per QALY. When using the Weibull parametric function which had the most conservative estimate of long-term survival for crizotinib the ICER increased to £191,628 per QALY.

Based on the ERG's base-case analysis, there is considerable uncertainty around whether ceritinib is likely to represent good value to the NHS considering typical willingness to pay thresholds.

8 Overall conclusions

The section should focus on any difference(s) of opinion between the company and the ERG that might influence the size of the ICER. Priority should be focussed on discussing information that will be useful to the Appraisal Committee including strengths, weaknesses and remaining uncertainties. Further summary of evidence is not required in this section.

There is reliable evidence that ceritinib has a beneficial effect on PFS when compared with and cisplatin or carboplatin plus pemetrexed maintenance therapy. There is no direct comparative evidence for ceritinib versus the current standard of care, crizotinib.

The presented comparison of ceritinib with crizotinib is based on a MAIC analysis, an observational comparison. The size of the PFS treatment difference generated by this analysis is uncertain.

The OS data from the RCT is immature; follow-up was too short for a definitive assessment of OS. The MAIC results for the OS treatment effect difference between ceritinib and crizotinib are highly uncertain, being the result of an observational comparison of immature data.

The economic evidence presented by the company primarily consisted of a *de novo* model. The company's model used a partition survival model approach which utilised parameterised data from the ASCEND-4 trial to determine the distribution of patients between the health states over time. The company found ceritinib to be more costly (cost difference of £14,985, without any PAS discounts applied) and more effective (0.54 QALY gain) compared with crizotinib. The deterministic base-case ICER (without any PAS discounts applied) was £27,936 per QALY, and the mean probabilistic ICER (without PAS) was £29,239 per QALY.

The ERG considers the company's assessment of cost-effectiveness of ceritinib to be uncertain with respect to a number of assumptions used in the model. These concerned the reliability of clinical inputs based on the MAIC comparison of ceritinib and crizotinib; the selection of survival model to parameterise and extrapolate overall survival; the method used to estimate duration of first-line treatment; the distribution and proportion of patients receiving second-line therapy; and, the inclusion of additional drug administration costs.

The ERG attempted to address some of the key issues and uncertainties by conducting a series of explanatory analyses exploring alternative assumptions and addressing the uncertainties identified in the company's model. The ERG base-case analysis estimated ceritinib to be more costly (cost difference £19,887, without PAS applied) and more effective (0.37 QALY gain) compared with

crizotinib. This suggests that the ICER for ceritinib compared with crizotinib, without any PAS applied, is £53,808 per QALY.

The ERG also carried out further exploratory analysis around the assumption of proportional 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. Using the same parametric functions fitted in the company's base and that provided the best statistical fit, the ICER was £38,535 per QALY (without PAS). When using the function in which best aligned with real world data on the benefits of ALK inhibitors, the ICER increased to £191,628 (without PAS).

8.1 Implications for research

Mature OS data for ceritinib and crizotinib are needed.

A RCT directly comparing ceritinib and crizotinib in untreated advanced ALK+ NSCLC is required to reliably evaluate the true difference in effect between these two treatments.

ADDENDUM
Evidence Review Group's Report
Ceritinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer

Results of additional scenario analyses

1 Impact of additional clinical and economic analyses undertaken by the ERG (with confidential PAS for ceritinib and crizotinib).

This confidential appendix presents additional results of the exploratory analyses conducted by the ERG (Section 6 of the main ERG report). The results in this section reflect the outcome of analyses when the confidential PAS discounts for ceritinib and crizotinib are not applied.

The sections of this addendum are as follows:

- Section 1.1 Disaggregated results of the ERG base-case analysis;
- Section 1.2 ERG base-case model: scenario analyses;
- Section 1.3 ERG base-case model: scenario analyses with exponential function to model overall survival;
- Section 1.4 ERG base-case model: scenario analysis with non-proportional hazards.

1.1 Disaggregated results of the ERG base-case analysis

Addendum Table 1 presents the summary cost-effectiveness results of the ERG base-case model, and Addendum Table 2 and Appendix Table 3 present the disaggregated results of the ERG base-case model (costs and QALYs respectively).

Table 1 Results of the ERG base-case model

	Mean Costs	Mean QALYs	Incremental Costs	Incremental QALYs	ICER
Ceritinib	139,573	2.40	19,887	0.37	53,808
Crizotinib	119,687	2.03	-	-	-
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied. ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme					

Table 2 ERG base-case model - disaggregated costs

Cost	Ceritinib	Crizotinib	Incremental Costs
Drug and drug administration costs, initial treatment	119,684	98,764	20,920
Drug and drug administration costs, post-progression treatment	4,471	6,000	-1,529
Treatment-associated adverse event costs	340	218	122
Medical costs	15,078	14,704	374
Pre-progression costs	4,510	2,986	1,524
Post-progression costs	4,083	5,143	-1,060
Terminal care costs	6,485	6,575	-90
Total costs	**139,573**	**119,687**	**19,887**
Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied. ERG, Evidence Review Group; PAS, patient access scheme			

Table 3 ERG base-case model - disaggregated QALYs

QALYs	Ceritinib	Crizotinib	Incremental QALYs
QALYs: Stable	1.65	1.09	0.56
QALYs: Progressive	0.75	0.94	-0.19
Total QALYs	**2.40**	**2.03**	**0.37**
ERG, Evidence Review Group; QALYs, quality-adjusted life year			

1.2 ERG base-case model: scenario analyses

Addendum Table 4 presents the results of scenario analyses undertaken within the ERG base-case model.

The scenarios undertaken are as follows:

- Weibull curve to model overall survival (corresponding to Scenario 3 in Table 1 of the main ERG report);
- Data from the ALEX trial to model crizotinib, with ceritinib unadjusted data from the ASCEND-4 trial (corresponding to Scenario 5 in Table 1 of the main ERG report);
- Data from the ALEX trial to model crizotinib, with ceritinib data from ASCEND-4 adjusted to the ALEX trial population (corresponding to Scenario 6 in Table 1 of the main ERG report);
- Alternative post-progression utilities (real world scenario) (corresponding to Scenario 9 in Table 1 of the main ERG report).

Table 4 Results of the scenario analyses within the ERG base-case model

	Mean Costs	Mean QALYs	Incremental Costs	Incremental QALYs	ICER
ERG base-case					
Ceritinib	139,573	2.40	19,887	0.37	53,808
Crizotinib	119,687	2.03	-	-	-
Scenario: Weibull curve to model OS					
Ceritinib	141,572	2.78	20,402	0.47	43,073
Crizotinib	121,170	2.31	-	-	-
Scenario: ALEX data to model crizotinib (unadjusted ceritinib)					
Ceritinib	139,573	2.40	19,925	0.35	57,478
Crizotinib	119,648	2.05	-	-	-
Scenario: ALEX data to model crizotinib (adjusted ceritinib)					
Ceritinib	138,876	2.22	19,852	0.32	62,560
Crizotinib	119,023	1.90	-	-	-
Scenario: Alternative post-progression utilities (real world scenario)					
Ceritinib	139,573	2.40	19,887	0.34	58,149
Crizotinib	119,687	2.06	-	-	-

Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.
ERG, Evidence Review Group; HRQL, health-related quality of life; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme

1.3 ERG base-case model: scenario analyses with exponential function to model OS

Addendum **Error! Reference source not found.**Table 4 presents the results of scenario analyses undertaken within the ERG base-case model when the exponential curve was used to model overall survival.

The scenarios undertaken reflect those presented in Addendum Section 1.2 (with the exception of the scenario with the Weibull curve for overall survival).

Table 5 Results of the scenario analyses within the ERG base-case model using exponential function to model OS

	Mean Costs	Mean QALYs	Incremental Costs	Incremental QALYs	ICER
Scenario: Exponential curve to model OS					
Ceritinib	143,792	3.22	20,787	0.56	£37,410
Crizotinib	123,005	2.67	-	-	-
Scenario: ALEX data to model crizotinib (unadjusted ceritinib)					
Ceritinib	143,792	3.22	20,777	0.52	39,724
Crizotinib	123,015	2.70	-	-	-
Scenario: ALEX data to model crizotinib (adjusted ceritinib)					
Ceritinib	143,417	3.10	20,780	0.51	40,851
Crizotinib	122,637	2.59	-	-	-
Scenario: Alternative post-progression utilities (real world scenario)					
Ceritinib	143,792	3.22	20,787	0.51	41,070
Crizotinib	123,005	2.72	-	-	-

Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.
ERG, Evidence Review Group; OS, overall survival; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

1.4 ERG base-case model: scenario analysis with non-proportional hazards

Addendum Table 6Table 4 presents the results of additional scenario analyses undertaken within the ERG base-case model.

Table 6 Results of the scenario analyses within the ERG base-case model (non-proportional hazards)

	Mean Costs	Mean QALYs	Incremental Costs	Incremental QALYs	ICER
ERG base-case					
Ceritinib	139,573	2.40	19,887	0.37	53,808
Crizotinib	119,687	2.03	-	-	-
Scenario: non-proportional hazard of treatment effectiveness, exponential survival function for all clinical data					
Ceritinib	115,400	3.41	15,305	0.41	37,368
Crizotinib	100,095	3.00	-	-	-
Scenario: non-proportional hazard of treatment effectiveness, Weibull survival function for OS and exponential survival function for PFS and treatment duration					
Ceritinib	113,180	2.91	13,829	0.07	185,225
Crizotinib	99,352	2.84	-	-	-

Please note that these results do not incorporate the PAS for ceritinib or for crizotinib. Please refer to the confidential appendix for results with both of these PAS applied.

ERG, Evidence Review Group; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PAS, patient access scheme