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 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 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 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 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 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 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 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

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

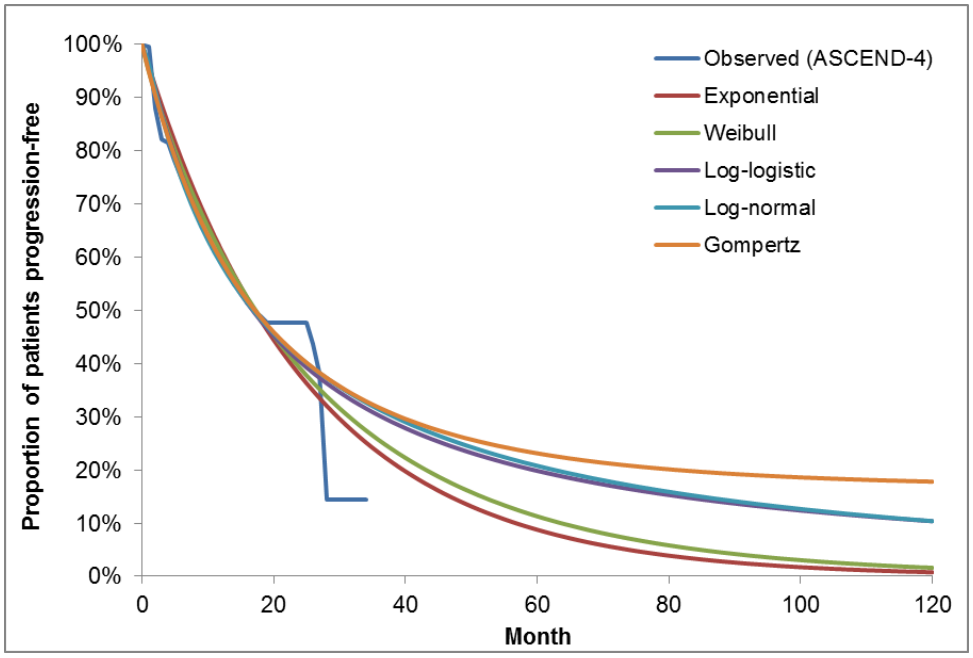
As stated above, the CS suggests that the distribution of second-line therapies received in the ASCEND-4 and PROFILE 1014 trials was not reflective of clinical practice in the UK and that it was expected that patients initiating on ceritinib would receive platinum doublet chemotherapy and best supportive 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 .

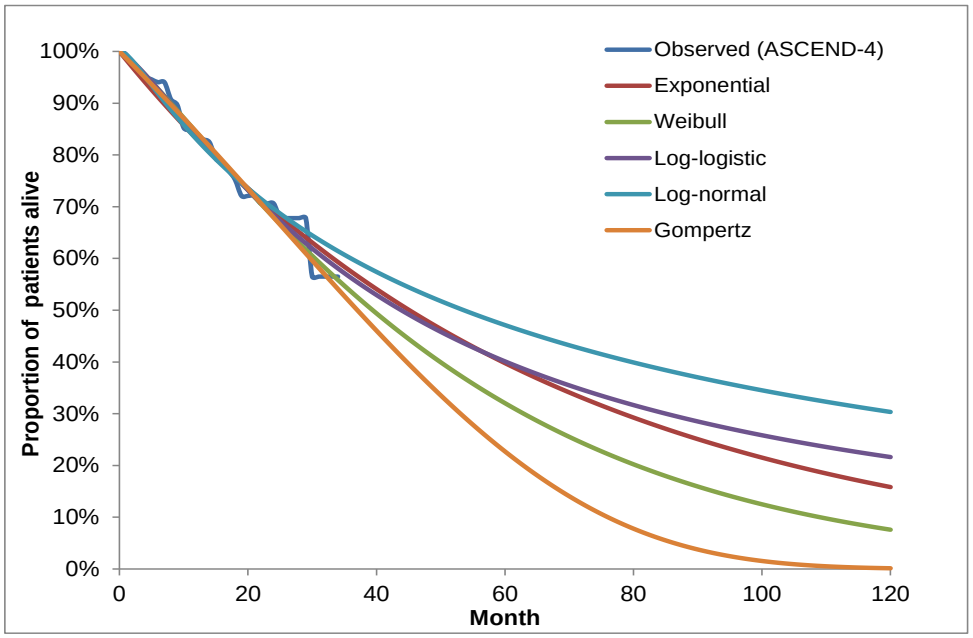
Figure 2: Observed and predicted PFS for ceritinib patients (CS, Figure 17, p 89)



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 5.2.10 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 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.

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]. 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. 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 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

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 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 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, 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 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.

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 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 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 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 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 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 45 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 14). 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)

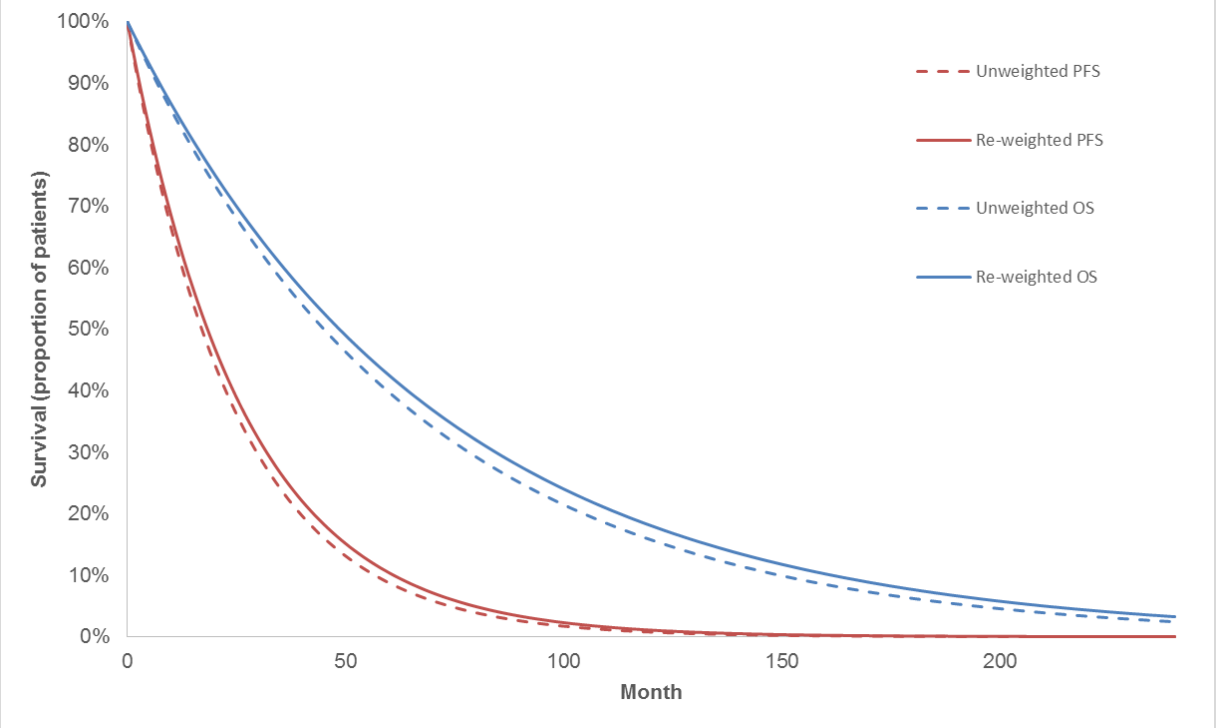


Table 9: Results of ERG analysis of clinical data matched to the PROFILE 1014 population

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 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 15.

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)

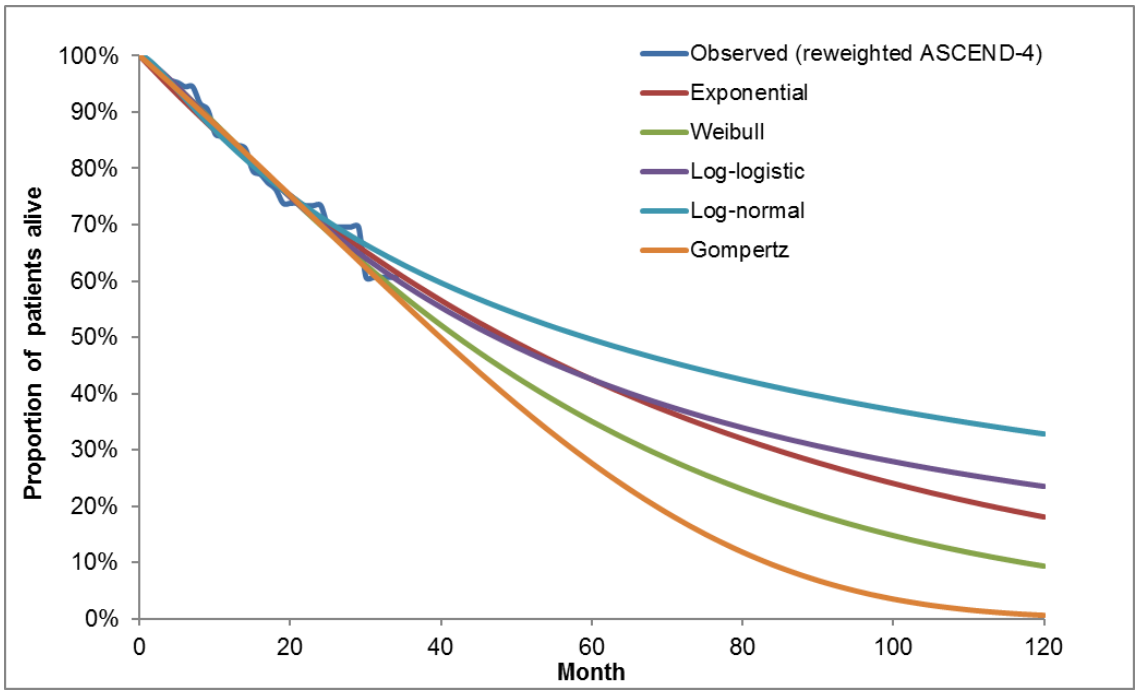


Table 10 Results of ERG exploratory analyses on alternative survival models for OS

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 47, 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 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 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 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 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 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 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 51.

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 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 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 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 £29,773.

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 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 £28,518. 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 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 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 16 and Figure 17 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

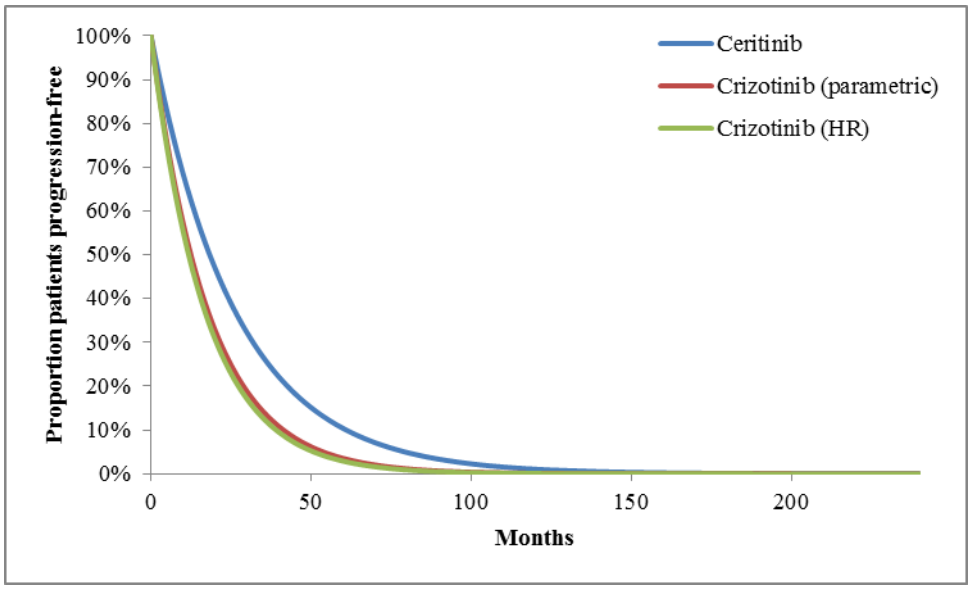
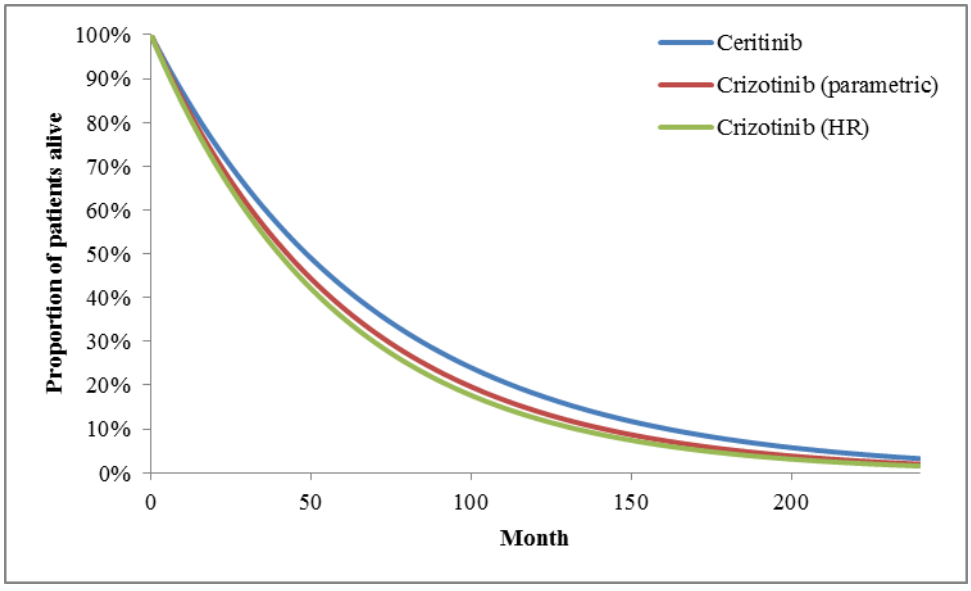


Figure 7: Predicted OS for ceritinib and crizotinib using exponential parametric function



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 18 and Figure 19. 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)

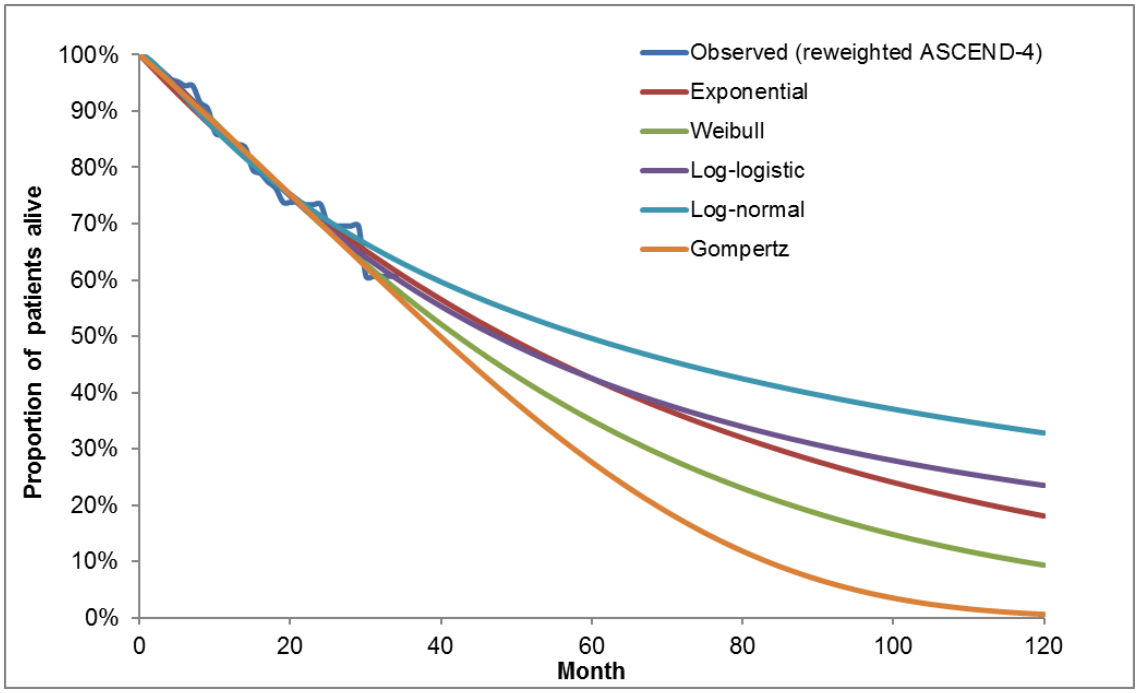
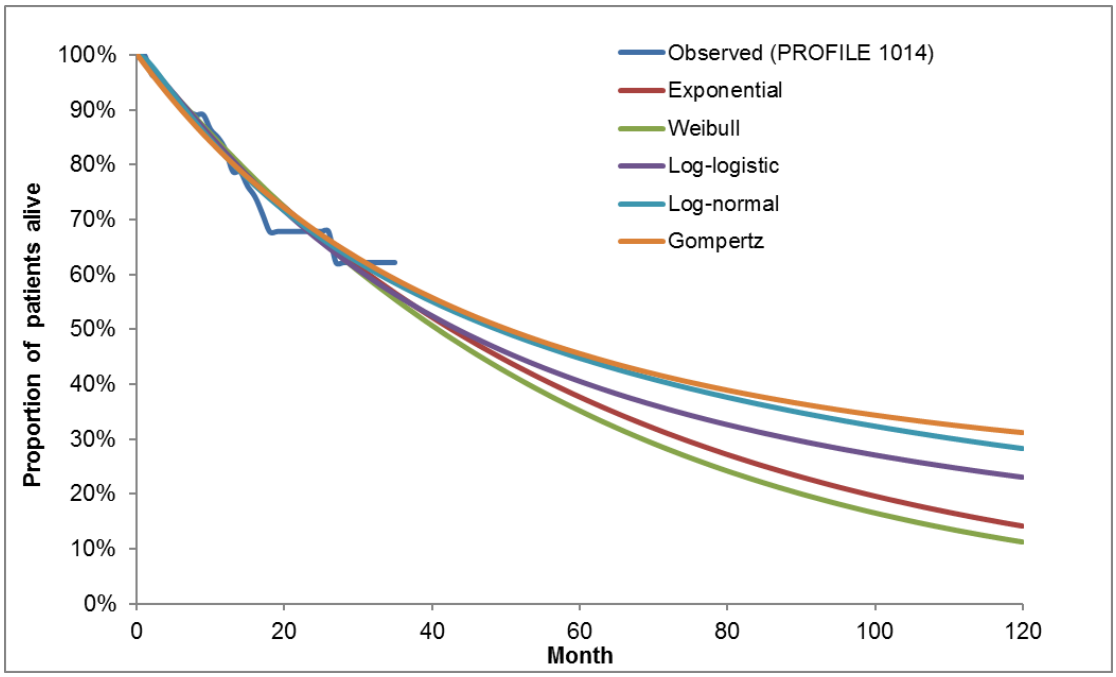


Figure 9: Predicted OS for crizotinib using different parametric functions (separately estimated based on published Kaplan-Meier curves from PROFILE 1014) (Company response to PFCs)



Results of the exploratory analyses

Results of the analyses using the exponential curve and Weibull curve are presented in Table 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 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.