Title: Lung cancer (non-small-cell, anaplastic lymphoma kinase positive, previously treated) – ceritinib

Produced by ERG: Warwick Evidence

Authors: Joshua Pink, Assistant Professor in Health Economics, Warwick Evidence University of Warwick
Emma Loveman, Partner/Senior Researcher, Effective Evidence LLP
Frances Taggart, Research Fellow, Warwick Evidence, University of Warwick
Andy Clegg, Partner/Senior Researcher, Effective Evidence LLP
Rachel Court, Information Specialist, Warwick Evidence, University of Warwick
Aileen Clarke, Professor of Public Health Research, Warwick Evidence, University of Warwick
Alastair Greystoke, Clinical Fellow, Northern Institute for Cancer Research, Newcastle University
Paul Sutcliffe, Associate Professor, Warwick Evidence, University of Warwick

Correspondence to: Paul Sutcliffe
Deputy Director for Warwick Evidence
Head of Populations, Evidence and Technologies
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry
CV4 7AL
02476 574505

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Please note that: Sections highlighted in yellow and underlined are 'academic in confidence'. Sections highlighted in aqua and underlined are 'commercial in confidence'.

1. SUMMARY

1.1 Critique of the decision problem in the Company Submission

The CS decision problem matches the population, interventions, comparators and outcomes described in the final NICE scope, as seen in Box 1.

Box 1: NICE final scope

Intervention	**Ceritinib**
Population	People with anaplastic lymphoma kinase-positive (ALK+) advanced non-small-cell lung cancer previously treated with crizotinib.
Comparators	Best supportive care (BSC)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • overall response rate • adverse effects of treatment • health-related quality of life.

The intervention, ceritinib, is indicated for the treatment of ALK+ metastatic NSCLC in those who have progressed on, or are intolerant to, treatment with crizotinib. The Company received conditional marketing authorisation for ceritinib from the European Medicines Authority (EMA) in May 2015. The Company refers to the Summary of Product Characteristics (SPC) for recommendations for dose interruption, reduction or discontinuation but does not specify reasons for these.

The comparator appropriate to the NICE scope is BSC. There is no direct evidence of ceritinib versus BSC and the CS use evidence from a small subgroup of a retrospective study of patients who have progressed following treatment with crizotinib.

1.2 Summary of clinical effectiveness evidence submitted by the Company

The CS undertook a systematic review to search for evidence to meet the decision problem, which the ERG considered of reasonable quality. The CS includes evidence from two ongoing studies of ceritinib (one a subgroup), providing evidence that is from the most recent data cut. These were the group of participants in the ASCEND-1 study who had previously been treated with crizotinib, and the full population in the ASCEND-2 study. The ERG considers that both of these studies are relevant to the decision problem. A further study, which is a retrospective review of participants who were included in one centre of the ASCEND-1 study was also identified in the CS. The CS presents a summary of these data and the ERG agrees with the CS that as only two participants in this

with respect to the nature of the data being interim rather than based on the final analysis set. Overall, the ERG advise caution because of the nature of these studies as uncontrolled, where confounding factors which would normally be controlled for by the randomisation process in an RCT may be exerting an influence on outcomes.

4.1.5 Evidence synthesis

See Section 4.4 Critique of the indirect comparison and/or multiple treatment comparison.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Six studies were ultimately identified as eligible in the CS (Table 8, page 44). Four of these are directly relevant to the decision problem. Three studies of relevance include a phase 1 uncontrolled study (ASCEND-1), a phase 2 uncontrolled study (ASCEND-2) and a retrospective analysis (Gainor et al., 2015)[11] from which the majority of participants had been enrolled in the ASCEND-1 study. The ASCEND-1 and ASCEND-2 studies are reported to be ongoing and results presented are from a recent data-cut. An earlier data-analysis from the ASCEND-1 study has been published.[14] The fourth study of relevance to the decision problem is an ongoing RCT (ASCEND-5) of ceritinib versus chemotherapy in those with ALK+ advanced NSCLC previously treated with crizotinib. No details of this study have been provided in the CS (see Section 4.5 for results of ERG search for ongoing studies). The remaining two studies (ASCEND-3 and ASCEND-4) are in crizotinib naïve and previously untreated populations and are therefore not relevant to the decision problem. However, efficacy and safety data from ASCEND-3 is presented in Appendix 5 and the ERG considers the data for adverse events as relevant (see Section 4.4 below). No data is available for ASCEND-4.

No RCT evidence relating to ceritinib in the population specified was identified.

Only ASCEND-1 has published data[14] but this publication related to data at a cut off in 2012. More recent data (April 2014) from ASCEND-1 are presented in the CS and the clinical study report (CSR) for ASCEND-1 has been provided to the ERG. ASCEND-2 has not previously been published and data from August 2013 are presented in the CS and the CSR has been provided to the ERG.

All relevant included studies were sponsored by the Company. The Gainor et al. (2015)[11] study was supported by a non-commercial grant.

The inclusion criteria of the two ASCEND studies were as follows:

ASCEND-1:

Eligibility to the ASCEND-1 study included locally advanced or metastatic malignancies characterised by ALK+ that had progressed despite standard therapy. This included NSCLC. Patients aged at least 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less and a life expectancy of at least 12 weeks were eligible. Inclusion criteria for the subset of ASCEND-1 which is of relevance to the decision problem includes prior treatment with a prior ALK inhibitor, and the first dose of ceritinib expected to be within 60 days since the last dose of the prior ALK inhibitor. Those with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within two weeks prior to study start to control their CNS disease were excluded.

ASCEND-2:

Patients were ≥ 18 years with histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC carrying an ALK rearrangement. They were previously treated with cytotoxic chemotherapy (one to three prior lines, of which one must have been a platinum doublet) and had to have recovered from all toxicities related to prior anticancer therapies to grade ≤ 2. At study entry NSCLC should have progressed during therapy with crizotinib or within 30 days of the last dose. Those with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within two weeks prior to study start to control their CNS disease were excluded.

Table 3 summarises the key baseline characteristics for the ASCEND-1 and ASCEND-2 study populations of relevance to the decision problem.

The ERG requested information from the Company about the number of prior treatment regimens in the ASCEND-1 and ASCEND-2 studies. In response to the clarification request the Company provided details as follows:

In ASCEND-1 "[redacted] Table 14.1-3.8b (Page 16 of 18) provided by the Company in request to the clarification

request also shows that [redacted] The ERG notes that it is unclear which regimens were given at each line of therapy as detailed in Table 3, and that 56.5% of participants had received 3rd line therapy or beyond.

In ASCEND-2
"[redacted]" Other treatments were reported in a detailed table in the clarification response (CS Table 14.1 - 3.5), these included [redacted] [redacted] and [redacted], and [redacted] of participants had received an [redacted]. The ERG notes that it is unclear which regimens were given at each line of therapy as detailed in Table 3, and that [redacted].

Clinical advice to the ERG suggested that in the UK all patients eligible for ceritinib should have received either carboplatin and/or cisplatin; most will have received pemetrexed and a small proportion may have received gemcitabine or vinorelbine. Gefitinib would not be used in this context in the UK.

The CS presents details of the flow of participants from the two ASCEND studies on pages 66 and 68. For the ASCEND-2 89 participants withdrew after receiving treatment. 56 of these withdrew because of disease progression, 11 withdrew because of the participant's or guardian's decision, 10 had adverse events. For six patients the clinician decided to end the treatment, one was lost to follow up and five died. For ASCEND-1 the participants withdrawing totalled 111. Of these 74 withdrew because of disease progression, 17 because of adverse events, 15 withdrew consent, four died and one was lost to follow up. The ERG requested further details on when withdrawals occurred from these 2 studies. From the information provided, the ERG notes that for ASCEND-2 [redacted] For ASCEND-1 [redacted]

The Company also stated in their response to clarifications that [redacted].

Table 3: Baseline characteristics of the ceritinib studies

Name of study, Sample N	Mean Age (SD), range	Sex N (%)	Ethnic group** N (%)	Disease burden (Sum of Diameters) at baseline for Target lesions based on BIRC assessment) (cm)	ECOG – Performance status grade at baseline, N (%)	Time from initial diagnosis of primary site (months)	Number of prior regimens (for advanced / metastatic disease), N (%)
ALK+ NSCLC previously treated with ALK inhibitor, treated with ceritinib 750mg							
ASCEND-1 163*	51.5 (11.63) min 24 max 80	Male 75 (46) Female 88 (54)	Caucasian 108 (66.3) Asian 47 (28.8) Other 8 (4.9)	[redacted]	0 =38 (23.3) 1 = 104 (63.8) 2+ = 21 (12.9)	to first dose of ceritinib: [redacted] Median =21.2 Min =2.4 Max =174.2	1=26 (16) 2=45 (27.6) 3=35 (21.5) >3=57 (35.0)
ASCEND-2 140	51.2 (11.62) min 29 max 80	Male 70 (50) Female 70(50)	Caucasian 84 (60) Asian 53 (37.9) Other 3 (2.1)	[redacted]	0 = 42 (30.0) 1 = 78 (55.7) 2+ = 20 (14.3)	[redacted]	1=0 2 =61 (43.6) 3 =50 (35.7) >3=29 (20.7)

Table 5: Quality assessment of Ou et al. (2014)[1]

Quality criteria for the assessment of uncontrolled studies in the CS	Response
Are the characteristics of the patients included in the study clearly described?	Yes[a]
Are the interventions of interest clearly described?	No
Are the main findings of the study clearly described?	Yes
Have the characteristics of patients lost to follow-up been described?	n/a
Were the subjects in the study representative of the entire population from which they were recruited?	?
Where applicable, were patients in different intervention groups recruited from the same population?	Yes
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	?
Do the analyses adjust for different lengths of follow-up of patients?	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes
Were losses of patients to follow-up taken into account?	Yes

n/a: not applicable; ?: uncertain

[a]Not for the BSC group which is the most relevant group to the NICE scope and decision problem.

4.3.1 Generalisability of the study populations to the UK population

The ERG considers that there are some potential differences between the participants in the included studies and those who will be eligible for treatment with ceritinib in the UK. In ASCEND-1 the number of participants from the UK was [redacted], in ASCEND-2 this was [redacted] participants (provided in response to a clarification request). The participants in the studies may be of younger age and the ethnic mix of the participants in the studies is different from the population in the UK. Clinical advice to the ERG is that the time from initial diagnosis in the ASCEND study populations is likely to be substantially longer than it would be for these people in UK practice.

The median age in the ASCEND studies was in the region of 52 years. This may be lower than the age of people eligible for ceritinib in the UK population; the ERG clinical experts suggest this is more likely to be approximately 60 years. A recent epidemiological study of patients in routine clinical settings in the 25 practices in the USA found the median age on diagnosis of NSCLC was 67 years.[17]

Although the ERG is not aware of any evidence that any particular patients characteristics affect response to these treatments there is evidence that reaction to other drugs used in the treatment of

has subsequently provided clarification. Data on PFS and OS from the ASCEND-1 and ASCEND-2 study were extracted from the CSR as individual patient data, possible as ASCEND-1 reported data per patient and data for ASCEND-2 could be digitized to provide pseudo-IPD. An unadjusted method for pooling individual data on time (months) from randomisation to either progression, death or censoring was used to calculate PFS (time from randomisation to progression or death) and OS (time from randomisation to death). No meta-analyses were undertaken of the other reported outcomes in the CS.

Uncertainties regarding the comparability of the patients in the ASCEND-1 and -2 studies and the BSC subgroup from Ou et al. (2014),[1] principally due to the limited information provided about their characteristics and the small patient sample, are acknowledged in the CS. As noted above, differences are evident in the ECOG performance status and prior therapy between the participants, which may affect the outcomes. These should be considered when assessing the outcomes.

The lack of data meant it was not possible to undertake sensitivity analyses or sub-group analyses.

The narrative synthesis accurately presents the outcomes of ORR, DCR, TTR, DOR, measures of survival (PFS and OS) and adverse events reported in the CS. No evidence is reported regarding HRQoL. The outcomes reported in the narrative synthesis in the CS are from the BIRC assessment, except for OS where only the investigator assessment is reported. It is evident that the BIRC assessment is more favourable for PFS (for ASCEND-2) and DOR (for ASCEND-1), less favourable for ORR (for ASCEND-1 and -2) and DCR (for ASCEND-2) and [redacted] for TTR (for ASCEND-2). For the outcomes of DCR and TTR data is not reported in the ASCEND-1 study. It should be noted that the BIRC assessments for ORR, DOR, and PFS in ASCEND-1 and TTR in ASCEND-2 are identified as CIC.

In the only comparison of ceritinib with BSC, and BSC and systemic chemotherapy combined, the pooled median OS was estimated to be [redacted] for ceritinib from the ASCEND-1 and -2 studies from the investigator assessment and 2.2 months (95% CI: 1.1, 3.8) and 3.9 months (95% CI: 2.7, 5.1) for the BSC and BSC and chemotherapy combined groups respectively. No data on OS from the BIRC was made available for the assessment in ASCEND-1 and -2 studies.

Although the CS does not compare the other reported outcomes with BSC or another comparator, they are presented for ceritinib. Estimates for both the investigator and BIRC reported outcomes of ORR, DOR and PFS were made available. The pooled estimate for PFS from the ASCEND-1 and -2 studies used the outcomes from the BIRC finding a pooled median survival of [redacted], longer

assessment of the ASCEND-2 study. This is slightly higher than the investigator assessed outcome for median PFS in the August 2014 results (5.7 [95% CI 5.4, 7.6]). The median PFS reported in the CSR for the primary analysis on 26th February 2014 was [redacted].

For ASCEND-1 the BIRC assessment outcome for median PFS was 6.97 (95% CI 5.65, 8.67) this was similar to the investigator assessed outcome of 6.93 (95% CI: 5.55, 8.67).

Table 8: PFS in the ASCEND-1 and ASCEND-2 studies and the pooled estimate

	ASCEND-2 Ceritinib 750mg (BIRC assessment data cut 13th August 2014)	**ASCEND-1 Ceritinib 750mg (BIRC assessment data cut 14th April 2014)**	**Pooled ASCEND-1 and ASCEND-2 results (BIRC assessment)**
Numbers	140	163	303
No. of events, n (%)	93 [redacted]	[redacted]	-
No. patients censored, n (%)	[redacted]	[redacted]	-
Median PFS, months (95% CI)	7.2 (5.4, 9.0)	[redacted]	[redacted]
12-month PFS, % (95% CI)	[redacted]	[redacted]	-

Data checked with CSRs and posters by Mok et al. (2015)[20] and Felip et al. (2014)[21]

No data on PFS for the comparator of BSC was presented in Ou et al. (2014)[1]

1.1.1. Overall response rate (ORR) estimates

The definition of ORR is the percentage of patients with CR or PR to treatment as defined by RECIST in the investigator assessment and also BIRC assessment. CR is the disappearance of all known lesions, confirmed at 4 weeks; PR is at least 30% decrease in lesions, confirmed at 4 weeks.

The ASCEND-1 and -2 studies adopted different versions of the RECIST criteria (ASCEND-1 RECIST v1.0 and ASCEND-2 RECIST v1.1). The Company clarified that the difference in the RECIST criteria has the potential to affect comparisons of efficacy, particularly as it does not facilitate comparison of ORRs. This is due to RECIST v1.0 allowing up to 10 target lesions with up to 5 each per individual organ compared to RECIST v1.1 with up to 5 target lesions and up to 2 each per individual organ. RECIST V1.0 and v1.1 differ in their definition of a new lesion (v1.0 not clearly defined; v1.1 clearly defined) and the minimum measurable lesion size (v1.0 ≥10mm spiral computed tomography, ≥20mm other techniques; v1.1 ≥10mm CT scan and ≥20mm chest x-ray). The Company

adverse events (including suspected to be drug related), adverse events leading to discontinuation and events leading to dose adjustments (CS Table 32). A more detailed breakdown of the all grade adverse events (reported in at least 10%) and grade 3/4 adverse events (reported in at least 2%) is provided in CS Table 34, and a summary of grade 3/4 adverse events suspected to be drug related is presented in CS Table 35. Similar tables are presented for ASCEND-1 (CS Tables 36-39) and the CS presents data from the ASCEND-3 study (CS Appendix 5) and the treatment naïve subgroup of ASCEND-1 in Appendix 6. Much of these data are marked CIC. The ERG has not reproduced all of these data tables as the Company provided pooled data in their clarification response (see below).

A high proportion of participants experienced drug related adverse events in these studies. On page 26 of the CS it states that approximately 54% of participants required at least one dose adjustment due to adverse reactions, with a median time to first dose reduction approximately 7 weeks. Data presented in CS Tables 32 and 36 (reproduced in Table 13 here) suggest that the proportion of participants with any grade adverse event that led to dose adjustment or interruption was [redacted] for both studies (see Table 13).

Table 13: Overall summary of adverse events in ASCEND-1 and ASCEND-2

	All Grades n (%)		**Grade 3/4 n (%)**	
Adverse events	**ASCEND-2 Ceritinib 750 mg (n=140)**	**ASCEND-1 Ceritinib 750 mg (n=163)**	**ASCEND-2 Ceritinib 750 mg (n=140)**	**ASCEND-1 Ceritinib 750 mg (n=163)**
All Deaths[a]	[redacted]	63 (38.7)	[redacted]	[redacted]
On-treatment Deaths[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events Suspected to be Drug Related	140 (100.0) [redacted]	163 (100.0) [redacted]	[redacted]	[redacted]
Serious Adverse Events Suspected to be Drug Related	57 (40.7) 24 (17.1)	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
AEs Leading to Discontinuation	11 (7.9)	[redacted]	[redacted]	[redacted]
AEs Requiring Dose Adjustment or Interruption	[redacted]	[redacted]	[redacted]	[redacted]

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than 1 category are counted once in each of those categories.
[a] All deaths including those >30 days (ASCEND-2) or >28 days (ASCEND-1) after the last dose of study drug.
[b] Deaths occurring more than 30 days (ASCEND-2) or 28 days (ASCEND-1) after the last dose of study drug are not included.
AEs occurring more than 30 days after the last dose of study drug are not summarized.

differences in patients' response to the drug cannot be evaluated with evidence currently available. However, it does not appear to the ERG that there is a higher rate of adverse events in Asian populations in these studies.

4.5.2 Brain metastases and treatment with ceritinib and crizotinib

In the ASCEND-2 study 71.4% (n=100) had brain metastases at baseline. Mok et al. (2015)[20] suggests that the whole-body responses by BIRC (and investigator review) were similar in the 100 patients with brain metastases at study entry to that of the overall study population (n=140). This appears to be based on observation of the data, and it is unclear if this is an *a priori* analysis, however, these data do suggest there is little difference in response rates to ceritinib in those with and those without brain metastases at baseline. Table 16 below shows these data, which also has data for the 40 participants without brain metastases, and was taken from the published abstract[22] rather than the poster presentation. In addition, the publication also presents data for those considered to have active brain lesions (rather than those who have been treated with radiotherapy and are stable) by BIRC and investigator review. The overall intracranial response rates (OIRR) and intracranial disease control rates (IDCR) following ceritinib are presented. Of the patients with brain metastases at study entry, 33 were considered through BIRC assessment to have confirmed target lesions at baseline. Clinical advice to the ERG is that the numbers may be small because brain disease can be difficult to define using RECIST criteria because brain disease (particularly if asymptomatic) is often small and difficult to measure. Of these, 13 patients had an overall intracranial response, giving an OIRR of 39.4% (95% CI: 22.9, 57.9). Some 28 patients had their intracranial disease controlled, resulting in an IDCR of 84.8% (95% CI: 68.1, 94.9).

Table 16: Whole body response rates for those with and those without brain metastases, and the total ASCEND-2 population

	Brain metastases	**No Brain metastases**	**All**
	N=100	N=40	N=140
WB ORR (CR+PR) - n (%) [95% CI]	33 (33)[23.9, 43.1]	21 (52.5)[36.1, 68.5]	54 (38.6)[30.5, 47.2]
WB DCR (CR+PR+StD) - n (%) [95% CI]	74 (74.0) [64.3, 82.3]	34 (85.0) [70.2, 94.3]	108 (77.1) [69.3, 83.8]
Median Duration of Response - months [95% CI]	9.2 [5.5, 11.1]	10.3[7.4, 16.6]	9.7 [7.1, 11.1]

[95% CI]			

Investigator assessed outcomes; WB – whole body; ORR – Overall Response Rate; CR = Complete Response, PR – Partial Response, StD – Stable Disease; CI = Confidence Interval

In ASCEND-1, a published conference presentation and abstract summarises data for 98 (60%) patients in the ALK-inhibitor treated group (N=163) who had brain metastases at baseline.[22] The median ORR was 51% (95% CI: 40.7, 61.3) for the ALK inhibitor-treated cohort with brain metastases, and DOR was 6.9 months (95% CI 5.4, 8.3). Although not compared in the presentation the ERG notes that these rates are [redacted] than those reported for the total sample (N=163, [redacted]) as per BIRC assessment for the ORR, see Table 9 and [redacted] than those reported for the total sample (by BIRC assessment) for DOR (N=75, [redacted], see ERG Table 12. The conference presentation also reports intracranial responses but these results did not account for the effect of prior radiotherapy.

There are no subgroup analyses of the survival outcomes for those with and those without brain metastases in these two studies. However, on measures of response, the results suggest that ceritinib has a similar response in those with brain metastases to those without brain metastases, and that active brain lesions may also respond to ceritinib.

The effects of treatment with crizotinib on brain metastases is less certain. An analysis of the patients with brain metastases in the PROFILE 1005 and 1007[23] studies with crizotinib showed an overall intercranial response rate of 18% in those who were asymptomatic and 33% in those who had received previous treatment for their brain metastases. The intercranial DCR for the two groups was 56% and 62% respectively. As noted above, the inclusion criteria in the PROFILE 1001 and PROFILE 1005 studies (population in Ou et al., 2014[1]) dictated that patients were excluded if they had symptomatic brain lesions. The population in the Ou et al. (2014),[1] used for the BSC comparator in the CS, may therefore be different to the populations in the ASCEND studies for ceritinib. The population in Ou et al. (2014)[1] may also differ from the UK population because in the NHS those with active brain metastases may be given crizotinib. The effects of crizotinib on these populations may be different than in those with asymptomatic brain metastases.

4.5.3 Ongoing studies

The CS lists three other ongoing studies from the ceritinib clinical trial programme in CS Table 8. One of these studies is of relevance to the decision problem. The ASCEND-5 trial (NCT01828112) is an RCT of oral ceritinib versus chemotherapy (permetrexed or docetaxel) in those with ALK+ NSCLC who have been previously treated with chemotherapy and crizotinib. Study results are anticipated in the first half of 2016 (CS page 91); 236 participants have been recruited.

ERG summary:

- Whilst the model used is a very simple one, consisting of just three states, it is consistent with other models built in metastatic and other cancer (including many of those submitted to and accepted by NICE in previous evaluations), and does capture the two important clinical endpoints of OS and PFS. The cycle length (1 month) should be sufficiently short to capture changes over a relevant time interval.

5.2.3 Population

The population modelled in this submission, ALK+ advanced NSCLC patients previously treated with crizotinib, matches the whole population of the ASCEND-2 study, and a subset of the population from the ASCEND-1 study. These study populations are assumed to be sufficiently similar to the UK treatment population as to provide a valid comparison, without the need for any adjustments for differing patient characteristics. Individuals in the modelled cohort have an initial age of 52 years.

ERG summary:

- All the results presented by the Company are based on modelling a population based on ASCEND-2 and a subset of ASCEND-1, with no adjustments made for possible differences between this and the UK clinical population. Therefore, differences between the modelled and real populations, and the impact this may have on treatment efficacy and thus cost-effectiveness, should be borne it mind when interpreting any of the results in this report.

5.2.4 Interventions and comparators

In the Company's base-case analysis, ceritinib is compared to BSC. Ceritinib treatment is assumed to continue until disease progression, with treatment terminated on disease progression. A sensitivity analysis assesses the impact of continuing ceritinib treatment for a median duration of 1.6 months after progression, based on data from ASCEND-2.

Some patients, following disease progression on crizotinib, may be treated with systemic chemotherapy rather than BSC. A scenario analysis was undertaken, in which 70% of patients in the comparator arm are assumed to receive BSC, and 30% receive 4 cycles of docetaxel, followed by BSC. The percentages of people receiving alternative treatments, and the number of cycles they would receive, are both based on expert clinical opinion.

"The clinical expert consulted [redacted] for this submission by Novartis confirmed that the clinical-pathological characteristics of ALK +ve NSCLC patients are very similar to those of NSCLC patients with EGFR mutations. In fact, EGFR mutations tend to occur predominately in patients with adenocarcinoma, who are light smokers or who have never smoked; and in patients who are relatively young (mean age ~ 50-years-old).

In a study by Shaw et al. (2009),[26] looking at the clinical features of ALK +ve patients the authors concluded that in patients with NSCLC who have clinical characteristics associated with EGFR mutation but who have negative EGFR testing, as many as one in three patients may harbor EML4-ALK. This would imply that the prevalence of ALK +ve is around 33% when we select patients who have the EGFR mutation characteristics.

Because of these baseline characteristics similarities, data from the EGFR TKIs trial by Shepherd et al, 2005[2] was deemed suitable to inform the comparator arm of the model, with respect to PFS data."

In the absence of PFS data for BSC in ALK+ NSCLC, the ERG sought clinical advice as to whether the EGFR+ population represented, in terms of prognosis, the most similar and thus relevant alternative source of data, and it was confirmed this is indeed the case. However, it is important to be clear that the use of this data source introduces a number of additional sources of uncertainty, both from the naïve comparison of single-arm studies without adjustment for different baseline characteristics, and from the assumption of equivalent PFS rates for ALK+ and EGFR+ NSCLC.

As with OS, the proportional hazards assumption was not met, and the AICs and BICs for the fitted distributions are shown in Table 21.

Table 21: AIC and BIC criteria for progression-free survival models

Parametric model	**PFS for ceritinib**		**PFS for BSC**	
	AIC	BIC	AIC	BIC
Exponential	757.66	761.38	605.60	609.08
Weibull	751.57	759.02	585.21	592.17
Gompertz	758.46	765.91	607.35	614.31
Log-logistic	743.96	751.42	530.50	537.46
Log-normal	749.78	757.23	551.92	558.88

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

that treatment benefit will continue post treatment discontinuation and after the time horizon of the study. This is a less important assumption than [redacted] 64 [redacted]S, as a considerably lower proportion of patients remain in the PFS state at the conclusion of the study. Kaplan-Meier PFS data, together with the chosen parametric curves, are shown in Figure 4.

Figure 4: Kaplan-Meier curves and fitted parametric functions for progression-free survival, base case

5.2.6.4. Ceritinib versus docetaxel

For the sensitivity analysis where a percentage of people in the control arm are assumed to receive docetaxel rather than BSC, OS with docetaxel is extrapolated from Kaplan-Meier data from the systemic chemotherapy arm of the Ou et al. (2014),[1] following the same methodology as above. No studies were found with data on PFS for patients receiving systemic chemotherapy, so data from the Shepherd et al. (2005)[2] was used once again, with the assumption that progression rates would be the same for people treated with docetaxel and BSC. OS and PFS for the whole group (70% BSC, 30% docetaxel followed by BSC) was then calculated as a weighted average of the two survival curves produced for the separate groups (see section 4.4). The same caveats apply to this analysis as to the comparison of ceritinib with BSC, namely that data are taken from single arm, non-randomised studies and compared without any adjustment for differences in patient population or study design.

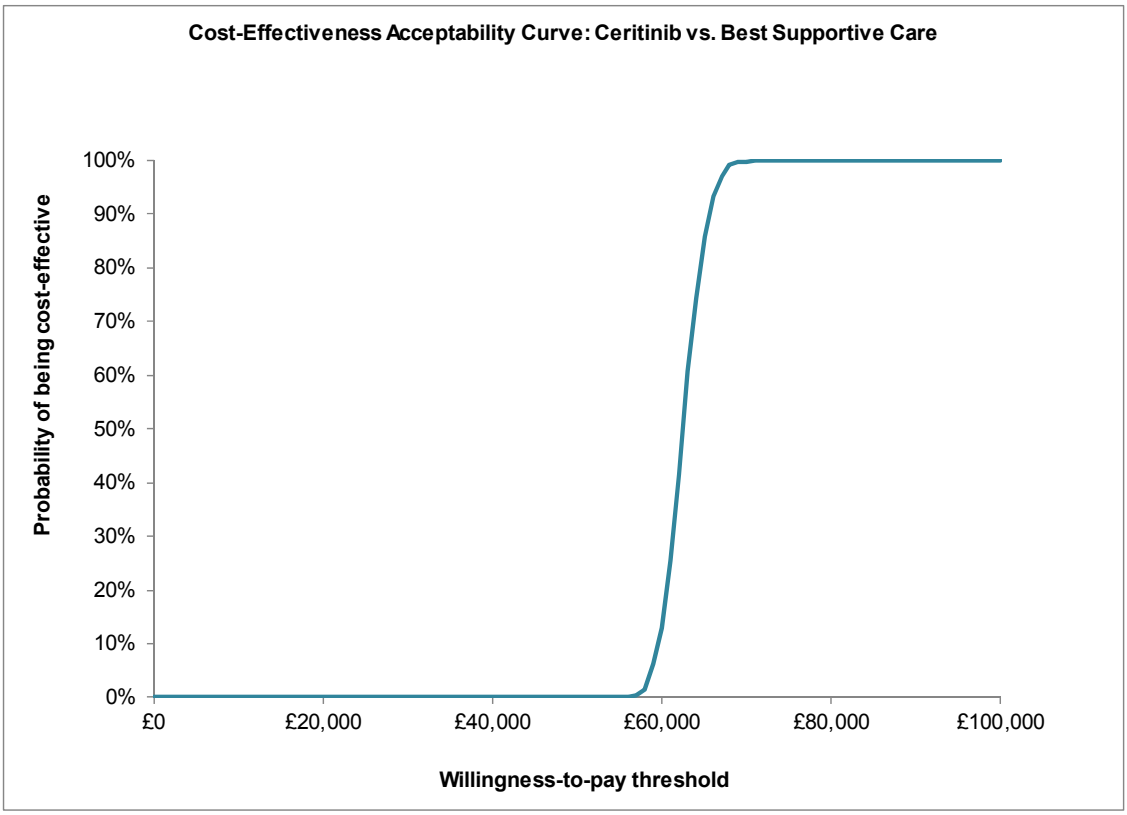

Figure 6: Cost-effectiveness acceptability curve for ceritinib vs. BSC

Table 34 and Table 35 show the QALYs and costs accumulated in each health state, for the two treatment strategies. 68% of incremental QALYs for ceritinib versus BSC are in the PFS state, as are 96% of the incremental costs. Terminal care is the only state where costs for BSC are higher than those for ceritinib.

Table 34: Summary of QALY gain by health state

Health state	QALY ceritinib	QALY BSC (no active treatment)	Increment	Absolute increment	% absolute increment
Progression-free survival	0.72	0.16	0.56	0.56	67.6%
Post-progression survival	0.36	0.09	0.27	0.27	32.4%
Total	1.08	0.25	0.83	0.83	100.0%