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'.

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List of Abbreviations

AIC	Akaike Information Criterion
ALK+	Anaplastic Lymphoma Kinase Positive
ALT	Alanine Amino Transferase
AST	Aspartate Aminotransferase
BIC	Bayesian Information Criterion
BIRC	Blinded Independent Review Committee
BSC	Best Supportive Care
CDF	Cancer Drugs Fund
CI	Confidence Interval
CR	Complete Response
CS	Company Submission
DCR	Disease Control Rate
DOR	Duration Of Response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
FDA	Food and Drug Administration
GI	Gastrointestinal
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
MedDRA	Medical Dictionary for Regulatory Activities
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OR	Odds Ratio
OS	Overall Survival
PFS	Progression-Free Survival
PICO	Population, Intervention, Comparator, Outcome
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-

	Analyses
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Relative Risk
SD	Standard Deviation
SPC	Summary of Product Characteristics
STA	Single Technology Assessment
TTF	Time to Treatment Failure
TTP	Time To Progression
UK	United Kingdom
WTP	Willingness To Pay

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 and -2 studies 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

study were not included in the analysis of the ASCEND-1 study, these data are of limited importance to the decision problem.

The CS presents outcomes of response rates and measures of survival (progression free survival and overall survival) and adverse events. The outcomes reported in the CS are from both an investigator assessment and from a blinded independent review committee (BIRC). It is evident that the BIRC assessments differ for a number of outcomes from the investigator assessments. The ERG considers the BIRC assessments likely to be less biased, and has therefore focused on the BIRC assessed outcomes in their critique of the data.

- In the only comparison of ceritinib with BSC the pooled median overall survival was estimated to be [redacted] for ceritinib from the ASCEND-1 and -2 studies and 2.2 months (95% CI: 1.1, 3.8) for the BSC comparator.
- The pooled estimate for progression free survival from the ASCEND-1 and -2 studies used the outcomes from the BIRC; finding a pooled median survival of [redacted].
- The overall response rate for patients receiving ceritinib was 35.7% (95% CI 27.8, 44.2) from the BIRC in ASCEND-2 and 46.0% (95% CI 38.2, 54.0) from the BIRC in ASCEND-1. These data were not pooled.
- The duration of response (DOR) was 9.7 (95% CI 5.6, 12.9) from the BIRC in ASCEND-2 and 8.77 months (95% CI 5.98, 13.11) from the BIRC in ASCEND-1. These data were not pooled.
- A high proportion of patients experienced adverse events, the most frequently reported were abnormal liver function tests, diarrhoea, nausea, fatigue and hyperglycaemia.

1.3. Summary of the ERG's critique of clinical effectiveness evidence submitted

The key issue of concern to the ERG is the uncontrolled nature of the included studies, where no comparative data is available to meet the decision problem.

As no comparative studies were identified, the CS use data from a retrospective non randomised study of participants who have progressed while on treatment with crizotinib as the comparator evidence for BSC. The participants in this study had received crizotinib as second or subsequent line of therapy and had experienced progressive disease following either complete response, partial response or stable disease. The main subgroup of relevance is the subgroup who did not continue crizotinib therapy beyond progressive disease but received BSC. Although results for this subgroup were reported in the study, no baseline characteristics for this subgroup are presented; those from a combined group which

included those who received chemotherapy were presented. It is therefore unclear how similar these participants are to those in the ceritinib studies.

The CS presents an unadjusted pooling of individual data to calculate progression free survival and overall survival from the interim data cuts of the ASCEND-1 and -2 studies. No pooling of the other reported outcomes in the CS was undertaken.

The CS presents data for a naïve indirect comparison between pooled estimates from the ASCEND-1 and -2 studies and the BSC subgroup from the retrospective study for the key outcome of relevance to the economic evaluation, overall survival. The ERG notes that this naïve indirect comparison has a number of limitations, particularly around uncertainties in the comparability of the studies and the indirect comparison being based on observation of the data only.

A number of participants in the ASCEND-1 and ASCEND-2 studies had subsequent treatment post progression with ceritinib, and this may have influenced the key outcomes in the CS.

Despite the limitations with these data, and the limitations in the approach used in the CS, the ERG has not been able to identify any better quality data and the ERG clinical advisor has confirmed that these are the most relevant data.

In the two ASCEND studies a proportion of participants had received more than 2 regimens of therapy before inclusion in the studies. Some details of these prior regimens is provided, however; the ERG notes that a proportion of participants in these studies are likely to be different to the population under the current marketing authorisation.

The ERG discuss other potential issues around the generalisability of the participants in these studies to the patient group in the NHS setting, including the age, ethnicity and the nature of brain metastases compared with those likely to be suitable for treatment in the UK.

1.4. Summary of cost effectiveness submitted evidence by the Company

The company submitted a de novo Markov model with a one month cycle length and a 10 year time horizon. The model defined states of progression-free survival, post progression and death for ALK+ NSCLC patients who have previously been treated with crizotinib, with all patients entering the model in the pre-progression state.

The initial patient cohort in the model represents the population from the ASCEND-2 study, and the relevant subset of the population from ASCEND-1. Overall survival and progression-free survival for ceritinib are both derived from parametric survival curves fitted to pooled data, without adjustment for baseline characteristics, from the two studies. Overall survival with BSC is taken from a separate single-arm, retrospective study in ALK+ NSCLC,[1] whilst data on progression-free survival come from another single arm study, this time in epidermal growth factor receptor positive (EGFR+) patients.[2] Naive indirect comparisons are performed between these different studies, meaning there are no adjustments made for differences in patient or study characteristics. The benefits of treatment with ceritinib are assumed to persist both after the time horizon of the trial, and after treatment discontinuation.

A sensitivity analysis is also conducted, assuming that 30% of patients would be switched to active therapy (4 cycles of docetaxel, followed by BSC) rather than BSC in the control arm. Overall survival rates are taken from the same study as for BSC (this time the systemic chemotherapy arm of the study),[1] and docetaxel is assumed to give the same progression-free survival times as BSC.[2]

Quality of life values for the pre-progression state are calculated by mapping data from the EORTC-QLQ-C30 questionnaire to the EQ-5D, using a published mapping algorithm. The Company submission states that patients in the progression-free survival state on BSC/docetaxel were assumed to have the same utility as those on ceritinib. The EQ-5D was only administered to patients who were in the pre-progression state (or immediately post-progression), so utility values for the post-progression state were taken from Chouaid et al. (2013).[3] No quality of life losses associated with treatment related adverse events were included in the base case.

Costs of treatment with ceritinib/docetaxel were combined by multiplying reference prices for the drugs with dose intensities (percentage of prescribed doses actually taken) from the relevant clinical studies. All patients were assumed to continue taking ceritinib in the progression-free survival state, and to discontinue immediately post progression. BSC was assumed to have a treatment cost of zero. Costs of managing adverse events (included in the model if a grade 3/4 adverse event affecting ≥5% of patients) were calculated by multiplying trial data on events with NHS reference costs for the treatment of those events.

Disease management costs were stratified into pre progression, post progression and terminal care costs. Resource use frequencies in the pre- and post-progression states were based on expert panel estimations from previous NICE appraisals, which are then combined with unit costs for that resource use, taken primarily from NHS reference or PSSRU costs.

1.4.1. Base case results

The company base case results indicate that ceritinib will provide an additional 0.83 QALYs versus BSC and costs and additional £51,952, with an ICER of £62,456 per QALY. The parameters included in sensitivity analyses to which this estimate is most sensitive are the costs of ceritinib, whether ceritinib treatment is assumed to continue for a period post-progression, and the survival functions used to extrapolate both progression-free and overall survival.

In the sensitivity analysis where 30% of patients receive docetaxel rather than BSC, the ICER for ceritinib versus this composite comparator is £63,920 per QALY.

1.5. Summary of the ERG's critique of cost effectiveness evidence submitted

1.5.1. Strengths

The decision problem presented in the CS is in line with the NICE scope.

The CS presents a systematic review of the clinical effectiveness of ceritinib that the ERG consider to be of reasonable quality. A systematic search for evidence was undertaken and the CS applied an appropriate inclusion criteria to identify studies of relevance.

Two single-arm cohort studies of reasonable quality have been included. The summarised evidence of clinical effectiveness and adverse events has been accurately presented.

The model constructed by the Company is clearly explained and logical. The model developed appears to capture important features of the disease (progression-free survival and overall survival), and the cycle length (1 month) is sufficiently short to allow accurate modelling of changes over short time periods.

The perspective, time horizon and discount rates chosen by the company all follow NICE recommendations, and are appropriate to the decision problem.

Other than two easily fixed issues (utility values for the pre-progression state and Kaplan-Meier/survival curve plots presented in the submission, section 5.2.13), there were no discrepancies found between the models reported in the company submission and the copy of the model given to the ERG, nor were there any additional discrepancies between the results obtained by re-running analyses from the submitted model and those reported in the manuscript. Changes made by the ERG to the company's base case assumptions increased the ICER for ceritinib versus both BSC and docetaxel.

1.5.2. Weaknesses and areas of uncertainty

There are no comparative studies of ceritinib versus BSC. Therefore the assessment of the treatment effects of ceritinib are based on a naïve indirect comparison using a pooled analysis of two single-cohort studies in ceritinib compared with a small subgroup of people having BSC from a retrospective study. There are a number of areas of uncertainty:

- The two single arm cohort studies are ongoing and data presented is interim data that has not been peer reviewed
- Data on progression-free and overall survival for ceritinib are both based on pooling data from ASCEND-1 and ASCEND-2, without any adjustment for baseline characteristics. The pooled analysis is from individual patient data and although the methods appear appropriate, the ERG are unable to fully verify the accuracy of the presented result
- The retrospective nature of the study used for the BSC arm means there is a high risk of bias but the ERG agrees there does not appear to be any other data to use at present
- There is limited information in the BSC study regarding potential confounding factors that can be compared with the studies used to assess the effectiveness of ceritinib
- There is no statistical indirect comparison of data from the intervention studies and the comparator study. Data are compared through observation only
- No adjustment is made for baseline differences between the various studies. Additionally, data on progression-free survival with BSC are based not on ALK+ NSCLC, but rather on EGFR+ NSCLC.

Patients in the Ou et al. (2014)[1] study from which BSC overall survival data are taken were not randomly assigned to different treatments, but allocated according to clinical judgement. Therefore, those assigned to the BSC arm may be sicker patients who it is assumed will not benefit from further active treatment, hence underestimating the overall survival for the whole population.

It is assumed that the benefits of treatment with ceritinib (gains both in overall survival and progression-free survival) persist both after the time horizon of the trial, and after treatment discontinuation. No convincing justification was given to support this optimistic assumption.

Patients are assumed to discontinue ceritinib treatment immediately post-progression, even though data from the ASCEND studies imply patients will continue to be treatment for an average of 1.6 months post-progression.

Data on resource use in both the pre- and post-progression states are based not on trial data, but on expert opinion. Additionally, these assumptions are based on the whole NSCLC population, not specifically the ALK+ subpopulation.

The same utilities are applied to the ceritinib and BSC pre-progression health states, even though this value includes the impact of ceritinib treatment-related adverse events, which would not be relevant for the BSC arm.

1.6. Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of modifications to the model assumptions made by the company. Specifically:

- The log-normal model was used for extrapolating overall survival for BSC, rather than the Weibull model in the original submission
- Patients are assumed to receive ceritinib for an average of 1.6 months post progression, in line with data from the ASCEND studies, in contrast to the company base case where ceritinib treatment was considered to be discontinued at the moment of disease progression
- The full list of grade 3/4 drug-related adverse events is included in the ceritinib arm of the model, not just those which occur in ≥ 5% of patients
- Costs, equivalent to two additional blood tests and two additional outpatient visits, were included for managing lab abnormalities, as opposed to the cost of £0 in the original model
- Utilities for the progression-free state are set to be the same in the ceritinib and BSC arms of the model (in line with the approach reported in the CS), and utilities for the BSC progression-free state are then adjusted to account for the lower rates of adverse events with BSC compared to ceritinib.

In the ERG's base case, ceritinib provides an additional 0.80 QALYs versus BSC and costs and additional £63,281, with an ICER of **£79,528** per QALY.

Additionally, in both the Company's and ERG's base case models, the benefits of ceritinib treatment on overall survival and progression-free survival were assumed to last for the entire time horizon of the model (10 years). Any reduction in the length of treatment benefit will reduce the cost-effectiveness of ceritinib (table 42).

2. BACKGROUND

2.1. Critique of Company's description of underlying health problem.

The Company describes non-small cell lung cancer (NSCLC) and the anaplastic lymphoma kinase positive (ALK+) subtype[4, 5] on CS pages 32-4 and the ERG clinical advisor agrees that this is a clear and accurate overview of the condition of relevance to the decision problem. Approximately 5% of advanced (stage IIIb/IV) NSCLC are ALK+. Those with ALK+ are generally younger and have little to no smoking history compared with those with NSCLC who are ALK negative. Most cases are adenocarcinomas.[4] The ERG notes that there are not any particular patient characteristics that are known to affect response to treatments in this population, for example, patient ethnicity or gender.[4]

The CS states on page 34 that ALK+ patients have prognoses similar to, or possibly worse than, those with ALK negative NSCLC. This is based on evidence from 300 adenocarcinoma NSCLC cases diagnosed between 1997 and 2008 and selected from the Mayo Clinic Lung Cancer Cohort, an observational follow-up study.[6] No patients had been treated with crizotinib. Cases of ALK+ and ALK- were matched and the authors attempted to consider potential confounding variables in their analyses. The authors, however, point out potential limitations in these data including the retrospective nature of the study, the small sample size and the broad category of treatment modality used. The ERG agrees with the CS interpretation that the prognoses for those with ALK+ may be similar, but could be worse, than those with ALK negative NSCLC.

In CS Section 3.1.3 (page 33) the Company provide estimates that 66 patients would be eligible for ceritinib treatment in England and Wales. This is based on the number of patients notified to the Cancer Drug Fund for crizotinib in 2014 (n=111) for England and an assumption that two patients in Wales are currently receiving crizotinib. The CS than takes the probability of 84% survival taken from a Randomised Controlled Trial (RCT) of crizotinib (PROFILE 1007) together with an estimate that 70% of these patients might be eligible for ceritinib (based on advice from their clinical experts), to estimate the number eligible as 66. The ERG clinical advisor agrees that approximately 70% of people with progression post treatment with crizotinib would be eligible for treatment with ceritinib. The CS presents an alternative estimate, using a similar approach to that used in TA296 (crizotinib). The key difference is in the estimate of the number of ALK+ patients who would be treated with crizotinib, n=167. This is based on an assumption that 70% of ALK+ patients treated with first line therapy would be eligible for second-line treatment with crizotinib, taken from a 6-month survival probability for advanced NSCLC. Using this estimate, and the same probability of survival from crizotinib and subsequent eligibility for treatment with ceritinib, the CS suggests that 98 patients would be eligible (CS Appendix 2).

The CS also cites evidence that approximately one third of patients with ALK+ will fail to respond to crizotinib.[7, 8] The ERG is unclear if these are accounted for in the above estimates.

2.2. Critique of Company's overview of current service provision

The CS presents a treatment pathway for ALK+ NSCLC on pages 35-6. The ERG clinical advisor agrees that given current pathways in relation to the Cancer Drugs Fund (CDF) specific drug availabilities that this is a reasonable representation of the likely treatment pathway, and that few patients would be given docetaxel monotherapy as second-line treatments as indicated by the dashed line in CS Figure 1. The ERG clinical advisor has noted that for those with progression post ceritinib, docetaxel or BSC would be considered, based on clinical factors.

2.2.1. Changes to service provision (CS page 27)

The Company notes that patients eligible for treatment with ceritinib will already have had their ALK status confirmed because of the position of ceritinib as a subsequent line of therapy to crizotinib. The CS states that as such, there is no expectation that ceritinib will result in changes in service provision and management with regards to the identification of the eligible patient population. The CS describes the monitoring associated with ceritinib use and this concurs with section 4.3 of the Summary of Product Characteristics (SPC) which also describes the monitoring required in those being treated with ceritinib. Patients being treated with ceritinib are monitored regularly for liver function, hyperglycaemia and for pulmonary symptoms.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

3.1. Population

The population in the decision problem, and subsequent clinical evidence, matches the population described in the final scope. The population of relevance is adults with ALK+ NSCLC who have previously been treated with crizotinib.

3.2. Intervention

The intervention in the decision problem is ceritinib and this matches the final scope. The Company provides a description of the technology and the mechanism of action of ceritinib (CS page 24) which the ERG clinical advisor has confirmed is accurate. Ceritinib is an oral medication authorised for use in patients with NSCLC caused by a variant of the ALK gene. The variant gene can lead to over-proliferation of cells and the development of tumours. Ceritinib is a highly selective second-generation ALK inhibitor which aims to impede cell signalling and reduce cell proliferation and tumour development. Ceritinib is indicated for the treatment of ALK metastatic NSCLC in those who have progressed on, or are intolerant to, treatment with crizotinib, a first-generation ALK inhibitor.

Ceritinib has received conditional marketing authorisation from the European Medicines Agency (EMA), (gained on 6th May 2015), and the Food and Drug Administration (FDA) (gained on 29th April 2014). The CS is correct that both the FDA and EMA agree the benefits of ceritinib outweigh the risks in this population, however, the CS provides little information on the outcomes from the EMA or the FDA.

The FDA, in their overall summary review states that there is a major concern over the appropriateness of the 750mg per day dose, which is poorly tolerated and may be higher than required to achieve the observed anti-tumour effect (98% had a gastrointestinal reaction, more than 25% had fatigue, decreased appetite, constipation). In addition, the FDA report states that 80% had an increase in ALT, 75% in AST, 58% creatinine and 51% raised glucose and that serious adverse reactions included hepatotoxicity, interstitial lung disease, prolongation of corrected QT interval and hyperglycaemia. At the 750mg dose approximately 60% of patients required at least one dose reduction, mostly due to gastrointestinal (GI) toxicity and the FDA have required post-marketing trials to assess these safety issues further, using ceritinib at different doses and with or without food. Clinical advice to the ERG is that the post marketing trial starts in the last quarter of 2015.

Marketing authorisation from the EMA is conditional and further results from the ongoing studies and a comparative phase 3 study, within three years, has been requested. The ERG notes that safety outcomes presented in the European Public Assessment Report (EPAR) came from more studies than

are presented in the CS (although some with small numbers). The Company provided pooled safety outcomes in their clarification request (see Section 4.4).

Ceritinib will be assessed by the Scottish Medicines Consortium in Q3 2015.

The CS does not summarise details of the SPC in the main submission, but a link to the SPC is presented in Appendix 1. Table 4 in the CS (page 25-6) summarises administration and costs of ceritinib and information provided in this table regarding the treatment administration concur with those in the SPC. The Company refers to the SPC for recommendations for dose interruption, reduction or discontinuation but does not specify reasons for these. In Table 1 of the SPC the dose adjustments and management recommendations are provided for a number of criteria; these include adjustments for alanine amino transferase (ALT) or aspartate aminotransferase (AST) elevation at different thresholds, QT corrected for heart rate at different thresholds, bradycardia, treatment related pneumonitis, hyperglycaemia and severe or intolerable nausea, vomiting or diarrhoea despite treatment.

3.3. Comparators

The comparator described in the decision problem is BSC. This is appropriate to the NICE scope, although the source of the evidence on BSC is from a small subgroup of a retrospective study which has been naively indirectly compared with ceritinib (see Section 4.3 for more detailed critique).

3.4. Outcomes

The outcomes reported in the decision problem match the NICE scope. These are overall survival (OS), progression-free survival (PFS), overall response rate (ORR), adverse effects and health-related quality of life (HRQoL).

3.5. Other relevant factors

The CS makes a case for innovation. On page 28 and 30, the CS states that the innovative nature of ceritinib has been recognised by the Medicines and Healthcare Products Regulatory Authority by being granted a Promising Innovative Medicine designation. This allows earlier access to treatments for those with life-threatening conditions. The CS states that ceritinib offers a step-change in the management of people with ALK+ NSCLC following treatment with crizotinib. The CS notes the unmet need for the population of relevance to the scope, without ceritinib the only treatment available is BSC; that is no active treatment, with the exception of some who may be given docetaxel. The CS states that ceritinib offers clinical benefits in terms of extension to life of approximately [redacted] (based on evidence from single arm cohort studies discussed further in Section 4). On

page 30 of the CS a discussion of the potency of ceritinib is provided, from enzymatic assay studies, which show that ceritinib is more potent than crizotinib. The CS states that this allows clinicians with a wider choice of treatments for treating this subtype of NSCLC. The CS does not discuss any further factors to make the case for innovation, such as any specifics of the drug development programme they have undertaken, or the clinical study programme.

The CS states that ceritinib fulfils the end-of-life criteria. This is discussed by the ERG in Section 6.

4. CLINICAL EFFECTIVENESS

4.1. Critique of the methods of review

The CS undertook a systematic review for evidence of clinical effectiveness of relevance to the decision problem. The review included a search for studies on the intervention and for any comparator studies (for a naïve indirect comparison).

The overall quality of the CS systematic review, based on CRD quality assessment questions for systematic reviews,[9] was reasonable (see Table 1). The submitted evidence generally reflects the decision problem defined in the CS.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	ERG response
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	1. Uncertain. Inclusion/exclusion criteria are reported, these are broader than the decision problem for the review, and secondary criteria are then applied. Studies just reporting adverse events or HRQoL could have been missed.
2. Is there evidence of a substantial effort to search for all relevant research?	2. Yes
3. Is the validity of included studies adequately assessed?	3. No. The CS uses the NICE questions for RCTs and applies these questions to two of the included studies only. Neither of the studies is an RCT. In addition, the CS does not discuss the findings of their critical appraisals in the text. The ERG have applied quality questions modified from the Down & Black criteria.[10]
4. Is sufficient detail of the individual studies presented?	4. Yes
5. Are the primary studies summarised appropriately?	5. Yes

4.1.1. Searches

The Company reports one broad set of searches for both RCTs and non-RCTs of subsequent line therapies in patients with advanced or metastatic NSCLC. These searches were undertaken on 20th March 2015 in the following medical databases (MEDLINE and Embase (via EMBASE.com); MEDLINE In-process (via Pubmed); and CENTRAL (via the Cochrane Library)). A few broad terms

for BSC were included and justification for the inclusion of drugs other than ceritinib is provided on CS pages 39 and 42. The searches were well-constructed. Mistakes in some lines (e.g. cellcancer and celllung on lines 1, 4 and 6 of the MEDLINE/Embase search and cellor and celling on line 4 of the Cochrane search, see CS Appendix 3) that may have affected the retrieval performance of the search were corrected in the version supplied in response to clarification request A1. The ERG does not have access to EMBASE.com and therefore checked the performance of these lines via a different platform (Ovid). The numbers retrieved were similar to those provided in response to clarification request A1, indicating that the mistakes were due to a reporting error rather than an error in the searches themselves. The MEDLINE thesaurus heading for the condition of interest (Carcinoma, Non-Small-Cell Lung) was absent from the MEDLINE/Embase search, but mapping to it from other terms is likely to have occurred in the database platform used (EMBASE.com). The ERG sought to verify this through searches in these databases via the Ovid platform and are confident that the absence of this key term is not a cause for concern.

The Company sought conference abstracts directly from four sources:

- American Society for Clinical Oncology (ASCO) Annual Meeting (2011-2014)
- European Society of Medical Oncology (ESMO) Congress (2012, 2014)
- European Lung Cancer Conference (ELCC) (2012, 2014)
- World Conference on Lung Cancer (WCLC) (2011, 2013)
- The ERG checked two more recent conferences (ASCO 2015 and ELCC 2015).

The ERG checked the studies reported in CS Appendix 4, and the references lists supplied as part of clarification request A1, for any additional studies of relevance to the decision problem. None were identified. In addition, the ERG undertook targeted searches for studies reporting a comparator arm that could be classed as BSC, however, no studies were identified.

4.1.2. Inclusion criteria

The inclusion criteria for the systematic review were clearly stated on page 39-40 of the CS. The inclusion criteria were broader than the decision problem for both the participants and the interventions. It is stated (CS page 43) that the reason for using criteria that were broader than the decision problem was “to ensure that all potentially relevant articles were captured by the searching”. The inclusion criteria were narrower than the decision problem in terms of outcomes. Any study design was eligible and no limits were placed on the quality of studies.

4.1.2.1. Participants

The criteria were broad to include studies involving all adults with advanced or metastatic NSCLC (stage 3B or 4), therefore not restricted to just those with ALK+ status. The inclusion criteria also potentially allowed for the inclusion of studies of participants with earlier stages of NSCLC if the outcomes were reported specifically for the advanced or metastatic stages.

4.1.2.2. Interventions

The inclusion criteria included other therapies not specified in the scope (potentially eligible interventions as monotherapies or combination therapies were listed in Table 6 (CS page 39-40); these included ceritinib (listed as LDK378), crizotinib and BSC.

4.1.2.3. Outcomes

The CS sets out in its eligibility criteria for the systematic review to include studies that included at least one of the outcomes of response rate (ORR), overall survival (OS), time to progression (TTP), time to treatment failure (TTF) and progression free survival (PFS). Although the outcomes of OS, PFS and ORR coincide with those outlined in the NICE scope/decision problem, the systematic review eligibility criteria fail to mention adverse events of treatment and HRQoL. In addition, TTP and TTF are included although they are not specified in the NICE scope/decision problem. Overall, the inclusion criteria broadly incorporates the decision problem and the licensed indication for ceritinib. The ERG requested details of the articles excluded at level 1 screening to ensure no studies of HRQoL or adverse events had been missed because the inclusion criteria did not specify these as eligible outcomes. No studies of relevance were, however, identified in the references supplied by the Company.

A PRISMA diagram was submitted (Figure 2, CS page 42). 126 RCTs and 147 non-RCTs were reported to have met the inclusion criteria. Three studies were identified subsequently (from other sources, details were not stated); Gainor et al. (2015)[11] had not been indexed in Ovid at the time of the search; Camidge et al. (2012)[12] and Lee et al. (2013)[13] had been missed because the study was indexed as a Phase 1 trial and the study population did not state it was advanced disease respectively.

The numbers of studies reported to be included in the systematic review is greater than the number of studies actually presented in the CS. A second stage of eligibility was applied in the CS, to narrow down the results of the searches, where the following criteria were applied:

- RCT and non-RCT studies for ALK+ NSCLC
- RCT studies for general NSCLC with at least two treatments of interest.

The CS provides details of the studies included at this stage (n=30) in Appendix 4. The ERG requested details of the studies excluded at this stage (these were provided and no additional studies were identified). The CS then applied a further selection on these 30 studies (although not formally described as a selection process) to include those that investigated efficacy or safety of ceritinib. The ERG has checked the 30 references and agrees that no further studies meet the decision problem.

Only two published studies identified from the searches were selected which were those by Gainor et al. (2015)[11] and Shaw et al. (2014)[14] The CS subsequently searched their internal databases and this identified three additional studies. These are described in CS Table 8 (CS page 44) but do not appear in the PRISMA flowchart.

The CS has not included studies that do not appear to meet the decision problem. Only one subgroup (applying to 163 of the 255 patients) in the ASCEND-1 study, and the full population in the ASCEND-2 study are relevant to the decision problem. A further study was identified by the CS, ASCEND-3, however, this is not relevant for efficacy and is only included by the CS for the assessment of safety (see below), as is the total group from the ASCEND-1 study.

The CS reports that two researchers reviewed all citations independently, with disagreements resolved by discussion or a third reviewer.

4.1.3. Critique of data extraction

The CS does not state what processes for data extraction were used. The CS has extracted data and has summarised study methodology (including duration, outcomes, duration of follow-up, diagram of phases/timings, CS pages 50-53), eligibility criteria (CS pages 54-60), outcomes and definitions (CS pages 61-63), statistical analyses (CS page 64), flow-charts of study numbers (including withdrawals with reasons, CS pages 65-67), baseline characteristics (CS pages 67-68), and results (CS pages 69-76) appropriately. These are discussed in more detail as relevant below.

4.1.4. Quality assessment

The relevant studies for assessment of quality are ASCEND-1 (163 patients with profile and treatment relevant to the decision question) and ASCEND-2 (all 140). These are quality assessed in the CS but the Company uses the NICE suggested criteria for RCTs (see CS Appendix 7). The CS does not outline the processes used for quality assessment. As these studies are uncontrolled, most questions were answered with ‘not applicable’. Only three questions were relevant to these types of studies, these were ‘blinding of care providers, participants and outcome assessors’, ‘selective reporting of outcomes’ and ‘intention to treat analysis’. These were all rated positively by the CS for both the ASCEND-1 and ASCEND-2 studies. For blinding the CS assessed both studies as meeting the

criteria, based on the outcome assessment by the Blinded Independent Review Committee, BIRC, (blinding of care providers and participants is not applicable). The ERG note that the BIRC assessment was not provided for all outcomes and would have rated this as unclear.

The ERG has applied a more appropriate set of questions based on the Down & Black Checklist,[10] as seen in Table 2.

Table 2: ERG quality assessment of the ASCEND-1 and ASCEND-2 studies

Quality criteria for the assessment of uncontrolled studies in the CS	**ASCEND-1**	**ASCEND-2**
Are the characteristics of the patients included in the study clearly described?	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes
Are the main findings of the study clearly described?	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	Yes	Yes
Were the subjects in the study representative of the entire population from which they were recruited?	Unclear	Unclear
Where applicable, were patients in different intervention groups recruited from the same population?	N/A	N/A
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unclear	Unclear
Do the analyses adjust for different lengths of follow-up of patients?	Yes	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Were losses of patients to follow-up taken into account?	Unclear	Unclear

Overall, the ERG rate these single arm cohort studies as of reasonable quality, where the studies describe the participants, interventions and results adequately. Key areas of uncertainty include whether the participants were representative of the population of ALK+ NSCLC who have failed second line treatment with crizotinib, whether there were differences in the care and treatment of the participants in the study compared with what would be expected to be in usual care, and uncertainties

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 or -2 studies). 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. Prior treatment with a prior ALK inhibitor was required, and the first dose of ceritinib was expected to be within 60 days since the last dose of the initial ALK inhibitor. Inclusion criteria for the subset of ASCEND-1 which is of relevance to the decision problem NSCLC patients with advanced tumours who were required to have at least one prior regimen including crizotinib and have received ceritinib at a dose of 750mg. 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] 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 56.3% of participants had received 3rd line therapy or beyond.

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 65 and 67. 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 =382 (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 (20.6)

4.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS identified a retrospective study[1] analysing data from two single arm studies of crizotinib in advanced ALK+ NSCLC (expansion cohort of phase I trial (PROFILE 1001)[15] and a phase II trial (PROFILE 1005)[16]) to assess the effects on patients receiving BSC. The study, which was sponsored by Pfizer Inc (the Company which produces crizotinib), was considered by the CS to be the only relevant comparator study available and was the basis for a naïve indirect comparison (see Section 4.4).

Details of the study are outlined in the CS and these directly reflect those provided in the study publication. The retrospective study was based on a selective analysis of the PROFILE 1001 cohort of 153 patients who could be either treatment naïve or received prior therapy (including first-line crizotinib) and the PROFILE 1005 study of 261 patients who must have failed at least one line of treatment. Ou et al. (2014)[1] only focused on those patients who had received crizotinib therapy (250mg twice daily starting dose with modification as required) as second or subsequent line of therapy and who had experienced progressive disease on crizotinib following either complete response (CR), partial response (PR) or stable disease. Those having first line crizotinib therapy, (n=11) and those with progressive disease as their best overall response to initial crizotinib treatment (n=24) were excluded. The CS indicates that the exclusion of patients who received crizotinib as first line treatment from the final cohort in the Ou et al. (2014)[1] study was to ensure comparability between the PROFILE 1001 and 1005 studies. The CS also reports that those whose best overall response (from RECIST criteria, defined as best response recorded from the start of the treatment until disease progression/recurrence) to initial crizotinib treatment was progressive disease were excluded to avoid introducing bias into the analysis. The ERG agrees that the exclusion of the subgroup who continued to be treated with crizotinib is appropriate to the decision problem. The exclusion of those who had progressive disease as their best overall response may mean that some participants in the Ou et al. (2014)[1] study who would be of relevance to the comparator in the decision problem are not included in the analysis.

The CS focuses on two subgroups from the Ou et al. (2014);[1] those who did not continue crizotinib therapy beyond progressive disease but received BSC (n=37), and those who did not continue crizotinib beyond progressive disease but received systemic chemotherapy (n=37). The systemic chemotherapy patients only were included in the CS as characteristics of the patients, but some outcomes, were presented for the combined group of BSC and for systemic chemotherapy patients in the publication by Ou et al. (2014).[1] These can be seen in Table 29 of the CS (page 79). The CS states on page 80 that the latter group are of relevance to a scenario analysis in the economic evaluation (see

ERG report Section 5). The ERG note uncertainty given the limited numbers in the final sample, however, the ERG clinical advisor confirms that despite the limitations these are the most relevant data.

The Ou et al. (2014)[1] study presents estimates of TTP and OS (95% confidence intervals; CI), however only OS was estimated for the sub-groups of BSC and systemic chemotherapy separately. OS was estimated using the Kaplan-Meier method with two sided 95% CIs using the Brookmeyer-Crowley method, which the ERG consider reasonable because there do not appear to be large numbers of tied survival times). The CS presents baseline characteristics for the combined patient group receiving either BSC or systemic chemotherapy as reported by Ou et al. (2014)[1] (see Table 4).

Table 4: Baseline characteristics from the Ou et al study

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 progression, 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, given BSC or systemic chemotherapy							
Ou et al. (2014)[1] 74 (37 BSC and 37 systemic chemotherapy). No baseline data available for BSC alone.	52.0 (54) min 28 max 78	Male 35 (47) Female 39 (53%)	Caucasian 34 (46) Asian 34 (46) Other 6 (8)	Not reported	0 = 18 (24) 1 = 43 (58) 2+ = 10 (14) Missing = 3 (4)	Not reported	1=15 (20) ≥2=59 (80)

Since a retrospective study was acting as the control arm, a comparison of patient characteristics was made in the CS (CS Table 30, page 80) with the ASCEND-1 and ASCEND-2 studies. The comparison was limited to the characteristics of sex, age, ECOG performance status, smoking history and prior lines of therapy for advanced or metastatic disease. The CS indicates on page 80 that there are no key differences in baseline characteristics between studies, noting that there was a slightly higher proportion of patients in the group from Ou et al. (2014)[1] (BSC and systemic chemotherapy) that were in the ECOG performance status grade 1 and 2+ than in ASCEND-2 study (combined BSC and systemic chemotherapy group: grade 1 65%, grade 2+ 16%; ASCEND-1: grade 1 63.8%, grade 2+ 12.9%; ASCEND-2: grade 1 55.7%, grade 2+ 14.3%). Also, the ASCEND-2 study had a higher proportion of patients receiving ≥2 prior lines of therapy than either the ASCEND-1 study or combined BSC + chemotherapy group (combined BSC + chemotherapy group: 1 line 20%, 2 line 80%; ASCEND-1: 1 line 16%, 2 lines 84%; ASCEND-2: 1 line 0%, 2 lines 100%). The CS states on page 80 that the differences in baseline characteristics are not considered to make the naïve indirect comparison inappropriate. The ERG has undertaken an analysis of the differences between reported baseline characteristics between the ASCEND-1 and -2 studies and Ou et al. (2014)[1] and also found no statistically significant differences. However, the ERG also notes that the baseline characteristics of the BSC group from Ou et al. (2014)[1] are unknown. Clinical advice to the ERG suggests that these patients were similar to those entering the ASCEND studies, although see below for discussion of brain metastases.

Ou et al. (2014)[1] state that the key inclusion and exclusion criteria of the PROFILE 1001 study were similar to those of PROFILE 1005, the major difference being the line of treatment eligible (as described above). Inclusion criteria from the PROFILE 1001 and 1005 studies from Clinical Trials.gov are as follows:

Profile 1001, NCT 00585195: Histologically confirmed advanced malignancies sensitive to ALK inhibition; measurable disease; adequate blood cell counts, kidney function, liver function and ECOG score of 0 or 1 (for the Recommended Phase 2 Cohort, a ECOG score of 2 may be allowed on a case-by-case basis). Exclusion Criteria: major surgery, radiation therapy or anti-cancer therapy within 2 to 4 weeks of starting study treatment, prior stem cell transplant (except patients with neuroblastoma, lymphoma or myeloma), active or unstable cardiac disease or heart attack within 3 months of starting study treatment.
Profile 1005, NCT00932451: histologically or cytologically proven NSCLC, positive for the ALK fusion gene, may have received pemetrexed or docetaxel from a previous study and have Response

Evaluation Criteria In Solid Tumors (RECIST)-defined progression or once the previous study analysed without RECIST-defined progression, measurable or non-measurable tumour.

Exclusion Criteria: prior treatment crizotinib, received no prior systemic treatment, chemotherapy or EGFR tyrosine kinase inhibitor.

There are differences between the selection criteria for participants in the ASCEND-1 and -2 studies of ceritinib and the PROFILE 1001 and 1005 studies used by Ou et al. (2014)[1] to assess the comparator BSC. All studies included ALK+ patients. The ASCEND-1 and -2 studies focus on patients aged 18 years or over with locally advanced or metastatic NSCLC (grade IIIB or IV) who had progressed on standard therapy and had had prior treatment with an ALK inhibitor. In contrast, PROFILE 1001 specified that patients should have locally advanced or metastatic malignancy (grade III and IV) and an ECOG performance of ≤ 2, but it does not state criteria concerning prior treatment. PROFILE 1005 stated that patients should have NSCLC, progressed on standard therapy and not had prior crizotinib. Clinical advice to the ERG is that in the PROFILE studies patients were excluded if they had symptomatic brain metastases. This is different from the ASCEND studies, where those with symptomatic brain metastases could be included if they were stable (see Section 4.3.1 and 4.5).

No other comparator studies have been included in the CS and the ERG targeted searches has not identified any further studies.

No assessment of study quality was undertaken for Ou et al. (2014)[1] by the CS. The ERG has applied a set of quality assessment criteria modified from the Down and Black criteria,[10] see Table 5. The ERG note there is a risk of bias associated with the study as it is retrospective and limited information is given regarding potential confounding factors that can be compared with the studies used to assess the effectiveness of ceritinib. The retrospective study was based on two studies of advanced ALK-positive NSCLC, excluding patients who had received crizotinib as first-line treatment and those whose best overall response to initial crizotinib treatment was progressive disease to ensure comparability and avoid introducing bias. In addition, the evidence of relevance to the scope and decision problem included only 74 patients (BSC, n=37; systemic chemotherapy, n=37). A comparison was made of a limited set of characteristics between this study and the two relevant intervention studies that may act as confounders. While there were differences in ECOG performance and previous treatment, other characteristics were similar. Outcomes were objective and withdrawals/dropouts were only relevant to the primary studies. Limited information was provided as regards what constituted both BSC and systemic chemotherapy, which may influence the naïve comparison of OS.

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 ALK+ 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

NSCLC (mostly platinum based) are more toxic and have greater efficacy in East Asian populations than in Caucasian populations.[18]

The Asian group is 37.9% and 28.8% respectively for ASCEND 2 and 1 (from CSRs). The Asian population in the UK is approximately 7.5%.[19] The ERG has examined potential differences in the occurrence of Grade 3/4 adverse events from the two studies between Asian and Caucasian participants (see Section 4.5).

Another consideration is that in the PROFILE studies (feeding into the Ou et al., 2014[1] for BSC) participants could be included if they had asymptomatic brain metastases. In the ASCEND studies patients could be included if they had asymptomatic or treated and stable brain metastases. Clinical advice to the ERG is that crizotinib may be used in the National Health Service (NHS) in patients with symptomatic brain metastases. The reported benefits of ceritinib potentially include specific effects on brain metastases, and although not relevant to the NICE scope or decision problem, the ERG have identified some published data on the effects of ceritinib in those with brain metastases. These data are discussed in terms of the generalisability of participants in the respective crizotinib and ceritinib studies, in Section 4.5.

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

The evidence synthesis presented in the CS focused on a narrative review of reported outcomes for ceritinib and BSC separately and a simple naïve indirect comparison was presented of the pooled OS data for the ASCEND-1 and -2 studies with the data for the comparators of BSC and systemic chemotherapy from Ou et al. (2014).[1] Such naïve indirect comparisons have limitations particularly around uncertainties in the comparability of the studies (e.g. participants, treatments given, methodology used, the lack of randomisation etc.). Having identified the limitations, it is evident that there was insufficient data to undertake an appropriate indirect or network meta-analysis.

The naïve indirect comparison focused on comparing the observed absolute difference in overall median survival (95% CI) for the pooled estimate of effect reported for the two studies of ceritinib (ASCEND-1 and -2) with that reported for the BSC comparator. No other outcomes were reported in the two studies of ceritinib and the retrospective study of BSC to allow other comparisons to be made. The naïve indirect comparison was based on observation of the data only.

A pooling of median OS (95% CIs) was undertaken for the ASCEND-1 (data cut point 14th April 2014) and ASCEND-2 (data cut point 13th August 2014) studies to provide an estimate for ceritinib. Although no details are provided of the methods used for the meta-analysis in the CS, the Company

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-1) 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 AIC.

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

than that reported by the investigators for the individual trials (ASCEND-1: 6.93 months (95% CI 5.55; 8.67); ASCEND-2: 5.7 months (95% CI: 5.4, 7.6)). The ORR for patients receiving ceritinib varied from 35.7% (95% CI 27.8, 44.2) from the BIRC to 38.6% (95% CI 30.5, 47.2) from the Investigator Assessment in ASCEND-2 and from 46.0% (95% CI 38.2, 54.0) from the BIRC to 56.4% (95% CI 48.5, 64.2) from the Investigator Assessment in ASCEND-1. DOR differed from 8.25 months (95% CI 6.80, 9.69) from the Investigator Assessment to 8.77 months (95% CI 5.98, 13.11) from the BIRC in ASCEND-1 and from 9.7 (95% CI 5.6, 12.9) from the BIRC to 9.7 (95% CI 7.1, 11.1) from the Investigator Assessment in ASCEND-2.

DCRs and TTR were reported in the ASCEND-2 study only. The DCR ranged from 62.9% (95% CI 54.3, 70.9) to 77.1% (95% CI 69.3, 83.8) for the BIRC and Investigator assessments respectively. Median time to response in ASCEND-2 for the Investigator Assessment was 1.8 months (95% CI 1.6, 5.6) and for BIRC was [redacted]).

4.4.1. Summary of key outcomes and results

The CS reports the cut-off date for the results and whether they are the primary or updated analyses. For the ASCEND-2 study the analysis focuses on an updated data set (August 2014 – 48 weeks) rather than the primary analysis cut-off date of February 2014 (24 weeks) for the outcomes of ORR, DCR, DOR, TTR, PFS, OS and adverse events, indicating that there was limited difference in the results. HRQoL was assessed at the primary analysis cut-off date of February 2014 for the ASCEND-2 study. Similarly the ASCEND-1 study reports outcomes at the updated analysis of April 2014 rather than the primary analysis cut-off of August 2013, except for adverse events which used data from August 2013 cut-off. The ERG is unclear if these data cuts were defined *a priori*.

The CS presents the outcomes of ORR, DCR, DOR, TTR, PFS, OS and adverse events as numbers, proportions, medians and 95% CIs, with the outcomes of PFS and OS for the ASCEND-1 and ASCEND–2 studies pooled. Time to event data was presented as Kaplan Meier curves. The outcomes of TTP, definition provided in Table 14 (CS page 61) was not reported in the CS. OIRR was not reported in the CS, but this outcome is not relevant to the decision problem (however, see Section 4.5).

The ERG requested information on any subsequent treatment post progression in the ASCEND-1 and ASCEND-2 studies as this may have a bearing on the key outcomes. The Company response was that for the relevant group in ASCEND-1

[redacted]

[redacted] In ASCEND-2 rates were [redacted] Although approximately [redacted] participants had other treatments post progression in both studies, clinical advice to the ERG is that these additional treatments will at best have a minor effect on the survival of these patients.

Additional data were assessed through the retrospective study by Gainor et al. (2015)[11] for patients receiving sequential treatment with crizotinib and ceritinib on PFS and OS. Ou et al. (2014),[1] which provided outcome data for the comparator of BSC and systemic chemotherapy, assessed the outcome measures of OS and TTP, although only the outcome of OS was reported in the CS.

The CS provides a brief summary of results from Gainor et al. (2015)[11] on page 77. The ERG agrees with the CS that as all but two participants had been included in the ASCEND-1 study that data from this additional real-world evidence is similar in magnitude to those presented in the CS and have not reproduced these data here.

The ERG present the data from the CS, focusing on the BIRC outcome data as the most reliable evidence. All data has been checked with the CSRs and publications where available. The ERG notes that these data have not been published in peer review publications, and are interim data from ongoing studies.

4.4.2. Overall survival estimates

The definition of OS is the time from first treatment to death due to any cause (CS page 61) and the ERG considers this to be the most reliable outcome. As can be seen in Table 6 the number of deaths for ASCEND-2 (n=140) and for the relevant population of ASCEND-1 (n=163) were 59 [redacted] and 63 (38.7%) at the defined cut-off points of 13th August and 14th April, respectively. The number of patients censored at these respective cut-off dates were 81 (57.9%) and 100 (61.3%) for ASCEND-2 and ASCEND-1 respectively. Median survival in months was 14.9 (95% CI 13.5, NE) for the ASCEND-2 study and 16.72 (95% CI 14.78, NE) for the ASCEND-1 study. The pooled estimate was [redacted]. For ASCEND-1 and ASCEND-2, respectively, the 12 month survival rate was [redacted] and 67.2 (95% CI 58.9, 74.1).

Table 6: Overall survival in the ASCEND 1 and ASCEND 2 studies and the pooled estimate

	ASCEND-2 Ceritinib 750mg (data cut 13th August 2014)[a]	**ASCEND-1 Ceritinib 750mg (data cut 14th April 2014)[a]**	**Pooled ASCEND 1 and ASCEND 2 results (BIRC assessment)**
Numbers	140	163	303
No. of deaths, n (%)	59 [redacted]	63 (38.7)	-
No. patients censored, n (%)	81 (57.9)	100 (61.3)	-
Median Survival, months (95% CI)	14.9 (13.5, NE)	16.72 (14.78, NE)	[redacted]
12-month survival rate, % (95% CI)	[redacted]	67.2 (58.9, 74.1)	-

[a]investigator assessment

Median durations of follow-up were 11.3 months (range 0.1–18.9) for ASCEND-2 and [redacted] for ASCEND-1

For Ou et al. (2014)[1] the median survival in months from the date of initial crizotinib treatment for both BSC and BSC with chemotherapy combined (as seen in Table 7) was 2.2 (95% CI 1.1, 3.8) for the BSC only group (n=37) and 5.4, (95% CI 3.8, 12.3) for the BSC and chemotherapy group (n=37). The probability of twelve month survival among patients who had either BSC or BSC with chemotherapy was 23.9% (95% CI 13.3–36.1).

Table 7: Overall survival in the Ou et al. (2014)[1] study

	BSC	**Chemotherapy**	**BSC + Chemo combined**
Numbers	37	37	74
No. of deaths, n (%)	-	-	-
No. patients censored, n (%)	-	-	-
Median Survival, months (95% CI)	2.2 (1.1, 3.8)	5.4, (3.8–12.3)	3.9 (2.7, 5.1)
12-month survival rate, % (95% CI)	-	-	23.9 (13.3, 36.1)

4.4.3. Progression free survival estimates

PFS is defined as the time from treatment to the date of disease progression or death. Table 8 shows the BIRC assessment of median PFS in ASCEND-2 was 7.2 (95% CI 5.4, 9.0) at the August 2014

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)	6.97 (5.65, 8.67)	[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]

4.4.4. 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 minimum 20mm for spiral computed tomography; v1.1 minimum 10mm for all radiological methods). The Company

contends that despite the possibility that the differences in RECIST criteria used may underlie differences in the response rates observed between ASCEND-1 and ASCEND-2, the studies both show similar benefit in DCR, median DOR, median PFS and in waterfall plots of best percentage change from baseline in measureable lesions (CIC Figures provided by the Company but not reproduced here). The measures of response were not pooled in the CS, but were reported for each study separately.

For the ASCEND-2 study this was defined as the proportion of patients with a best overall confirmed CR or PR, as assessed per RECIST 1.1. Both CR and PR were confirmed by repeat assessments performed not less than four weeks after the criteria for response were first met. For ASCEND-2 ORR was 35.7% (95% CI 27.8, 44.2) by BIRC assessment (Table 9). ORR was the primary endpoint in the ASCEND-2 study.

For ASCEND-1 the ORR was 46.0% (95% CI: 38.2, 54.0) as per BIRC assessment using RECIST 1.0 in the 750 mg dose group (Table 9).

ORR from the investigator assessed outcome was 38.6% (95% CI 30.5, 47.2) for ASCEND-2 and 56.4% (95% CI 48.5, 64.2) for ASCEND-1.

The CS states that ASCEND-2 results were consistent with the February 2014 cut-off. The ERG was provided with data for the ASCEND-2 26th February cut-off, BIRC assessment of ORR in the response to clarifications. The ERG agrees that the rate of 34.3% (95% CI: 26.5, 42.8) is similar to the most recent cut-off.

Table 9: ORR in the ASCEND-1 and ASCEND-2 studies

	ASCEND-2 Ceritinib 750mg (BIRC assessment data cut 13th August 2014)	**ASCEND-1 Ceritinib 750mg (BIRC assessment data cut 14th April 2014)[a]**
Numbers	140	163
ORR, n (%) [95% CI]	50 (35.7) [27.8, 44.2]	75 (46.0) [38.2, 54.0]
Complete response (%)	0	[redacted]
Partial response (%)	50 (35.7)	[redacted]

[a]uses the RECIST 1.0 criteria

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

No data on ORR was presented by Ou et al. (2014)[1] for the comparator BSC.

4.4.5. Time to Tumour Response estimates

TTR was defined as the time from treatment to CR or PR. No data on TTR was presented in the ASCEND-1 study or the study by Ou et al. (2014)[1] for the comparator BSC. Table 10 shows that the TTR in ASCEND-2 was [redacted] for the BIRC assessment. For the investigator assessed outcome TTR was [redacted] 1.8 (1.6, 5.6).

Table 10: TTR in the ASCEND-2 study

	ASCEND-2 **Ceritinib 750mg (BIRC assessment data cut 13th August 2014)**
Numbers	140
TTR, median (95% CI) months	[redacted]

4.4.6. Disease control rate

DCR was reported only in ASCEND-2. This is defined as the proportion of patients with best overall response of CR, PR or stable disease (not meeting PR or progressive disease criteria). Table 11 shows that the BIRC assessment of DCR in ASCEND-2 was 62.9% (95% CI 54.3, 70.9). The BIRC DCR from the February 2014 cut-off was similar at [redacted].The investigator assessed DCR rate was 77.1% (95% CI 69.3, 83.8).

Table 11: DCR in the ASCEND-2 study

	ASCEND-2 **Ceritinib 750mg (BIRC assessment data cut 13th August 2014)**
Numbers	140
DCR, n (%) [95% CI]	88 (62.9) [54.3, 70.9]

4.4.7. Duration of response estimates

Duration of response (DOR) applies to those patients who had a response to ceritinib. This applied to 50 of the original 140 in the ASCEND-2 trial and the median DOR was 9.7 months (95% CI 5.6, 12.9). For the February 2014 cut-off date for ASCEND-2, the DOR was similar at 9.2 months (95% CI: 5.5, NE) by BIRC, for the 48 patients with a confirmed CR or PR (Table 12). For ASCEND-1 for the 75 people who had a response median DOR was 8.77 months (95% CI 5.98, 13.11). The 12 month DOR rate was [redacted] for ASCEND-2 and [redacted] for ASCEND-1.

Table 12: DOR in the ASCEND-1 and ASCEND-2 studies

	ASCEND-2 Ceritinib 750mg (BIRC assessment data cut 13th August 2014)	**ASCEND-1 Ceritinib 750mg (BIRC assessment data cut 14th April 2014)**
Numbers[a]	50	75
No. of events, n (%)	-	[redacted]
Progression	-	[redacted]
Death		[redacted]
No. patients censored, n (%)	-	[redacted]
DOR, median, months, (95% CI)	9.7 (5.6, 12.9)	8.77 (5.98, 13.11)
12-month **DOR** rate, % (95% CI)	[redacted]	[redacted]

[a]the total number with confirmed CR or PR. Note in Table 19 these numbers are reported to be 140 and 163 for the ASCEND-2 and ASCEND-1 studies respectively, assume a typo.
Data checked with CSRs and posters by Mok et al. (2015)[20] and Felip et al. (2014)[21]

For comparison with the BIRC assessment the investigator assessed median DOR was 9.7 (95% CI 7.1, 11.1) in the ASCEND-2 and was 8.25 (95% CI 6.80, 9.69) in ASCEND-1. In the ASCEND-1 study the investigator assessed number of events was [redacted]; the number progressed was [redacted]; the number of deaths was [redacted] and the number censored was [redacted]

4.4.8. Quality of life

HRQoL was measured in the ASCEND-2 study using the European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) and lung cancer specific questionnaire (QLQLC13, version 1.0), focusing specifically on patient reported outcome (PRO) measures of health-related QoL, functioning, disease symptoms and treatment-related side effects (Section 5.4.1 in CS). Change in reported outcomes were recorded every eight weeks in ASCEND-2. Patients with a clinically significant change were those who changed score by +or – 10 points. EORTC is considered to be a validated measure.

ASCEND-1 did not evaluate HRQoL.

4.4.9. Adverse events

The CS presents data on adverse events from the ASCEND-2 study (CS page 81-3) for the period up to 48 weeks including deaths, on treatment deaths, all grade and grade 3/4 adverse events and serious

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 86. 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	140 (100.0)	163 (100.0)	[redacted]	[redacted]
Suspected to be Drug Related	[redacted]	[redacted]	[redacted]	[redacted]
Serious Adverse Events	57 (40.7)	[redacted]	[redacted]	[redacted]
Suspected to be Drug Related	24 (17.1)	[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 after the last dose of study drug.

[b] Deaths occurring more than 30 days 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.

Missing grades are included under 'All grades' column.

The CS also provides a pooled analysis of grade 3/4 adverse events suspected of being drug related from the ASCEND-2 and ASCEND-1 studies as these are used to inform the economic evaluation (see Section 5). The ERG has reproduced the pooled analyses in Table 14. The ERG requested clarification over how events were classified as being treatment related. In the response the Company stated that this was by the judgement of the study investigator and that definitions are provided in the CSR for ASCEND-2 and the protocol for ASCEND-1. The ERG are satisfied that these events were pre-defined. The Company also states that adverse events were categorised as "Yes" or "No" in terms of whether there was a 'reasonable possibility that AE is related' [to the study treatment].

Table 14: Pooled analysis of treatment related adverse events occurring in 5% or more patients

Adverse Events	**Pooled Analysis ASCEND-1 and ASCEND-2 n=303 Grade 3/4 n (%)**
Alanine aminotransferase increased	[redacted]
Aspartate aminotransferase increased	[redacted]
Blood alkaline phosphatase increased	[redacted]
Diarrhoea	[redacted]
Gamma-glutamyltransferase increased	[redacted]
Nausea	[redacted]

The ERG considered that it would be informative to the appraisal to have pooled data on adverse events for all patients who have received ceritinib, to include those from ongoing studies and the treatment-naïve populations. The Company have provided a summary table of adverse events for 525 ALK+ patients who have been treated with 750mg ceritinib (10 with other malignancies) across four clinical studies. The median duration of exposure to ceritinib was 33.0 weeks (range: 0.3 to 106.1 weeks). Adverse events with an incidence of ≥10% were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, constipation, rash, blood creatinine increased, oesophageal disorder and anaemia. Grade 3-4 adverse events with an incidence of ≥5% were liver laboratory test abnormalities, fatigue, diarrhoea, nausea and hyperglycaemia. Table 15 shows the frequency of adverse events in these studies. The Company also provided a ranking of the frequency of the adverse, within each Medical Dictionary for Regulatory Activities (MedDRA) system organ class. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse event: very common (≥1/10); common (≥1/100 to

<1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data). See also Table 25 which lists grade 3/4 adverse events from ASCEND-1 and ASCEND-2 and used in the health economic analysis.

Table 15: Frequency of adverse events with ceritinib 750mg

System organ class **Preferred term**	**Ceritinib** **N=525** **%**	**Frequency category**
Blood and lymphatic system disorders		
Anaemia	11.4	Very common
Metabolism and nutrition disorders		
Decreased appetite	41.1	Very common
Hyperglycaemia	7.8	Common
Hypophosphataemia	5.3	Common
Eye disorders		
Vision disorder[a]	7.4	Common
Cardiac disorders		
Pericarditis[b]	5.9	Common
Bradycardia[c]	1.9	Common
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[d]	3.2	Common
Gastrointestinal disorders		
Diarrhoea	83.8	Very common
Nausea	79.8	Very common
Vomiting	62.9	Very common
Abdominal pain[e]	48.2	Very common
Constipation	25.1	Very common
Oesophageal disorder[f]	15.0	Very common
Hepatobiliary disorders		
Abnormal liver function tests[g]	2.1	Common
Hepatotoxicity[h]	0.6	Uncommon
Skin and subcutaneous tissue disorders		
Rash[i]	19.0	Very common
Renal and urinary disorders		
Renal failure[j]	2.1	Common

Renal impairment[k]	1.3	Common
General disorders and administration site conditions		
Fatigue[l]	50.5	Very common
Investigations		
Liver laboratory test abnormalities[m]	50.5	Very common
Blood creatinine increased	17.7	Very common
Electrocardiogram QT prolonged	6.5	Common
Lipase increased	4.6	Common

Includes cases reported within the clustered terms:

[a] Vision disorder (vision impairment, vision blurred, photopsia, vitreous floaters, visual acuity reduced, accommodation disorder, presbyopia)

[b] Pericarditis (pericardial effusion, pericarditis)

[c] Bradycardia (bradycardia, sinus bradycardia)

[d] Pneumonitis (interstitial lung disease, pneumonitis)

[e] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)

[f] Oesophageal disorder (dyspepsia, gastro-oesophageal reflux disease, dysphagia)

[g] Abnormal liver function test (hepatic function abnormal, hyperbilirubinaemia)

[h] Hepatotoxicity (drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, hepatotoxicity)

[i] Rash (rash, dermatitis acneiform, rash maculopapular)

[j] Renal failure (renal failure acute, renal failure)

[k] Renal impairment (azotaemia, renal impairment)

[l] Fatigue (fatigue, asthenia)

[m] Liver laboratory test abnormalities (alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal)

4.5. Additional work on clinical effectiveness undertaken by the ERG

The ERG undertook searches for ongoing studies of relevance to the decision problem. No studies of relevance were identified.

4.5.1. Adverse events between Asian and Caucasian participants in the ASCEND-2 and -1 studies

The ERG examined potential differences in the occurrence of adverse events (Grade 3-4) between Asian and Caucasian patients reported in the two studies (information provided in response to clarification request). For both ASCEND-2 and ASCEND-1 Caucasian patients were more likely to have a grade 3-4 adverse event than Asian patients [redacted]. Whether this reflects differences in

clinical practice or reporting between centres or real 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 72% (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 active 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]
Median Progression	5.4 [4.7, 7.2]	11.3 [5.7, 15.6]	5.7 [5.4, 7.6]

Free Survival - months [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 higher than those reported for the total sample (N=163, 46.0% (95% CI: 38.2, 54.0)) as per BIRC assessment for the ORR, see Table 9 and lower than those reported for the total sample (by BIRC assessment) for DOR (N=75, 8.77 (5.98, 13.11), 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 studies (population in Ou et al., 2014[1]) were excluded in 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 89); 236 participants have been recruited.

As noted above, the ERG has not identified any other ongoing studies of relevance.

4.6. Conclusions of the clinical effectiveness section

The CS presents a reasonable quality systematic review of the clinical effectiveness of ceritinib. Two ongoing studies of ceritinib (one a subgroup), providing evidence that is from the most recent data cut, were identified and included in the review. The summarised evidence of clinical effectiveness and adverse events has been accurately presented. Outcomes of response rates, measures of survival and adverse events are presented from both an investigator assessment and from a BIRC assessment. The ERG considers the BIRC assessments likely to be less biased. 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. The retrospective nature of the study used for the BSC arm means there is a high risk of bias. However, the ERG agrees there does not appear to be any other available data. In the only comparison of ceritinib with BSC the pooled median overall survival was shown to be higher (estimated to be [redacted] for ceritinib than seen for BSC (2.2 months (95% CI: 1.1, 3.8)). Caution is recommended in the interpretation of the results seen as there is no adjusted indirect comparison of data. Data are compared through observation only. It is also unclear how comparable the populations are. The generalisability of all study populations to the UK population is uncertain.

5. COST-EFFECTIVENESS

5.1. ERG comment on Company's review of cost-effectiveness evidence

The Company has provided an appropriate description of the cost-effectiveness systematic review undertaken including the search strategy, inclusion/exclusion criteria and description of included and excluded studies.

The Company searched MEDLINE (via Ovid), Embase (via Ovid) and the Cochrane Library (incorporating the NHS Economic Evaluation Database and the Health Technology Assessment database) via EBM Reviews for economic models in advanced or metastatic NSCLC. Papers from 1st January 2004 to the 16th March 2015 were sought in the MEDLINE and Cochrane search, but the Embase search was limited to 2004 to 2013 (see response to clarification request B1). Conference articles were sought from 2012 onwards, but it is unclear which conferences were searched. A summary of the inclusion and exclusion criteria are given in Table 17.

Table 17: Inclusion and exclusion criteria for the economic evaluation reviews

Category	Inclusion Criteria	Exclusion Criteria
Population	Advanced or metastatic NSCLC	Advanced or metastatic SCLC, early stage NSCLC
Interventions	NA	NA
Comparators	NA	NA
Outcomes	Economic outcomes (costs, healthcare resource use, work productivity)	Studies with no outcomes of interest
Study type	Economic models	Interventional or observational study designs (registry, chart review, HER, administrative claims)
Language Restrictions	English	Non-English
Country	Full-text articles published from 2004 onwards	Full-text articles published before 2004

Abbreviations: NA, not applicable; NSCLC: non-small cell lung cancer

Using this fairly broad search, 10 studies were found that evaluated the ALK+ NSCLC population, of which six were cost-effectiveness studies. However, none of these studies evaluated ceritinib, and none were in the population of interest for the submission, namely advanced ALK+ NSCLC patients previously treated with crizotinib.

The ERG does not believe that any important cost-effectiveness evidence was missed, mainly due to the established scarcity of evidence in this area. No additional relevant cost-effectiveness studies were identified by the ERG, either from the list of excluded studies provided by the Company, or from any additional searches undertaken.

ERG summary:

- Despite the cost-effectiveness review undertaken having some restrictions placed upon it (date of publication, language and study type restrictions), there is no evidence that any important information which would improve the cost-effectiveness analysis has been missed.

5.2. Summary and critique of the Company's submitted economic evaluation by the ERG

5.2.1. NICE reference case checklist

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice for the two populations	BSC. As per the NICE final scope, patients receive no active treatment but receive passive therapy aimed at symptom management and palliative care Post crizotinib treatment with docetaxel was considered in a sensitivity analysis
Patient group	As per NICE final scope	Adult patients with ALK positive NSCLC previously treated with crizotinib
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-utility analysis
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (10 years)
Synthesis of evidence on outcomes	Systematic review	Evidence on the efficacy of ceritinib (OS, PFS, response

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		rates, adverse effects of treatment, and health-related quality of life) are drawn from two clinical trials (ASCEND-1 and ASCEND-2)
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes – EORTC QLQ-C30 data from ASCEND-2 were mapped to the EQ-5D
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		A range of sensitivity and scenario analyses are presented

The cost-effectiveness evidence submitted by the Company appears to satisfy the NICE reference case, and the decision problem defined in the scope. To appraise ceritinib versus BSC for patients with ALK positive NSCLC, the Company constructed a de novo time dependent Markov model with a one month cycle length and a 10 year time horizon. The model assumes that treatment benefit continues both beyond the length of the study and after treatment discontinuation.

Four key studies formed the basis of the clinical evidence used to populate this model. OS and PFS with ceritinib were based on data from the ASCEND-1 and ASCEND-2 studies. Data on OS with

BSC were taken from a retrospective cohort study by Ou et al. (2014),[1] and finally data on PFS with BSC were taken from a study in EGFR positive NSCLC patients by Shepherd et al. (2005).[24]

5.2.2. Model structure

The Company constructed a de novo cost-utility Markov model with a one month cycle length. The model defines 3 health states, based on disease progression and death (Figure 1).

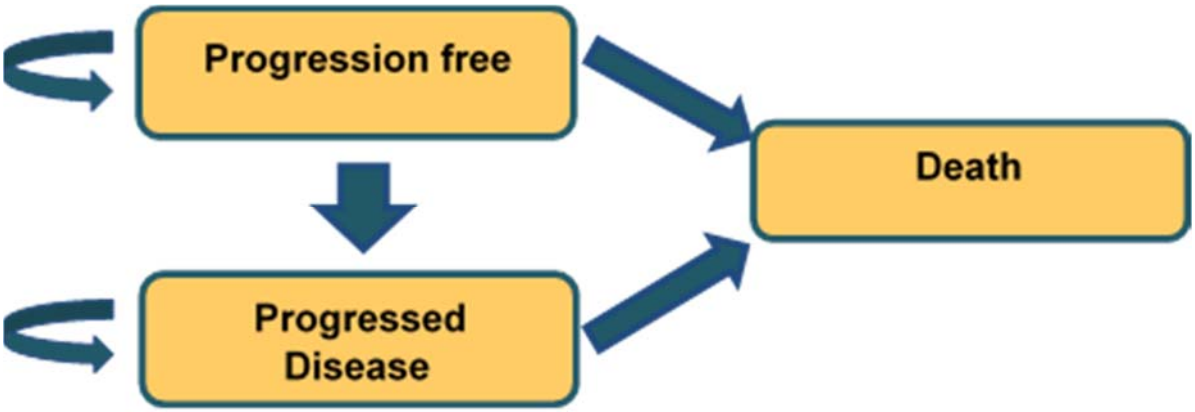


Figure 1: Overview of model structure

The model constructed used an "area under the curve" partitioned survival approach, where the number of patients in each health state at a given time is taken directly from the survival curves fitted to the clinical data.

All patients enter the model in the progression-free state. Although the eligibility criteria from ceritinib imply these patients will all have progressed on crizotinib, they do not meet the criteria of further progression since beginning the new line of treatment. Patients in the progression-free state receive ceritinib (or the comparator treatment) until disease progression. Costs of disease management, utilities and risks of death all differ between the progression-free and progressed disease states.

Patients with a CR or PR to treatment, and those who do not respond but have stable disease, are all considered to be in the PFS state. Response status does not have any impact on future disease progression. The model does not include parameters for treatment discontinuation, and consequently future disease progression is modelled as being independent of whether patients have discontinued from therapy.

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 immediately terminated until 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.

ERG summary:

- The base case analysis incorporates the appropriate comparator, taken from the NICE final scope, and scenario analyses undertaken seem appropriate given the available knowledge about possible treatment pathways.
- Since data from ASCEND-2 imply that patients would continue treatment with ceritinib for a period of time after disease progression, it seems appropriate these costs are included in the base case analysis, not as a sensitivity analysis. If post-progression treatment with ceritinib has an impact on OS, these benefits will be captured in the clinical data used to populate the model, and thus for consistency costs of this treatment should also be included.

5.2.5. Perspective, time horizon and discounting

The perspective is as per the NICE 2013 '*Guide to the methods of technology appraisal*',[25] with benefits from a patient perspective and costs from an NHS/PSS perspective.

The time horizon of the model is 10 years, which is effectively a lifetime time horizon given the life expectancy of the population of ALK+ NSCLC patient in third-line treatment. Over 99.9% of patients in both arms of the base-case model are in the death state by the end of this 10 year horizon. In the base-case, costs and benefits are discounted at an annual rate of 3.5%.

ERG summary:

- The perspective, time horizon and discount rates chosen by the Company all follow NICE recommendations, and are appropriate to the decision problem.

5.2.6. Treatment effectiveness and extrapolation

5.2.6.1. Ceritinib versus BSC

Two clinical outcomes were used to inform transitions between states in the model. There are:

- Overall survival (OS)
- Progression-free survival (PFS)

5.2.6.2. Overall survival

OS in the ceritinib arm of the model was extrapolated from Kaplan-Meier data derived by pooling, without adjustment, data from the whole ASCEND-2 study with the previously treated subgroup from the ASCEND-1 study. Such an unadjusted pooling assumes that participants in both studies are drawn from the same underlying population, with the same prognosis at baseline (see section 4.2 for information on baseline characteristic of studies). The median duration of follow-up was 11.3 months

in ASCEND-2, and [redacted] in ASCEND-1. OS in the BSC arm of the model was again extrapolated from Kaplan-Meier data, this time from the BSC arm of Ou et al. (2014).[1] Again, no adjustments are made for differences in baseline characteristics (see section 4.3). Therefore, all the results presented rely on the assumption that the populations in the ASCEND and Ou et al. (2014)[1] studies are equivalent. A potential cause for concern with this assumption is that the Ou et al. (2014)[1] study was not randomised, with patients assigned to the different treatment pathways by clinician choice. This means that those allocated to the BSC group may be those not expected to benefit from further treatment, hence representing a sicker population than that included in the ASCEND studies.

The Company tested a proportional hazards assumption for the ceritinib and BSC Kaplan-Meier data, but this was rejected due to the different shapes of the two distributions. Thus separate, independent parametric models were fitted to the two sets of Kaplan-Meier data. Exponential, Weibull, Gompertz, log-logistic and log-normal models were fitted, with the AICs and BICs generated shown in Table 18.

Table 18: AIC and BIC criteria for overall survival models

Parametric model	**OS for ceritinib**		**OS for BSC**	
	AIC	BIC	AIC	BIC
Exponential	635.05	638.80	109.88	111.35
Weibull	634.24	641.74	110.12	113.05
Gompertz	634.38	641.87	104.26	107.19
Log-logistic	636.41	643.91	103.60	106.53
Log-normal	644.23	651.73	103.19	106.12

AIC, Akaike information criterion; BIC, Bayesian information criterion

The Company states that the best-fitting curves were selected on visual inspection, AIC/BIC, internal validity (fit to observed study data) and external validity (validation with expert clinical opinion). The Weibull model was selected as the most appropriate for both the ceritinib and BSC data. This appears fully justified for the ceritinib arm, where the Weibull is indeed the best fitting model, but is more controversial for the BSC extrapolation, where both the AIC and BIC give the Weibull as the worst fit to the data. Following a request for clarification from the Company, it was stated that the Weibull model was rejected as it was deemed to give implausibly high-long term rates of survival for BSC, with patients still being alive at 240 months. The percentages of patients still alive in each arm of the model, using different survival curves, are shown in Table 19 and Table 20.

Table 19: Proportions of patients alive (%) with ceritinib using different parametric models

Year	exponential	Weibull	Gompertz	log-logistic	log-normal
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Proportions of patients alive (%) in BSC using different parametric models

Year	exponential	Weibull	Gompertz	log-logistic	log-normal
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Whilst it is true that a very small percentage of patients are still alive at 20 years [redacted] in the log-normal extrapolation (the best fitting according to the AIC and BIC criteria), a proportion this small will not make a major difference to the overall results. Furthermore, the time horizon for the base case analysis is only 10 years, at which point the percentage modelled as being alive in the BSC arm [redacted] is lower than that from the selected model for the ceritinib arm [redacted] A second reason given for choosing the Weibull curve is so the same parametric model is used in both arms. However, since the Kaplan-Meier data come from two independent, single-arm sources, and the proportional hazards assumption has already been rejected (meaning the two survival curves are not expected to follow the same shape), this alone does not seem a sufficient reason to justify the choice of model.

Therefore, in the opinion of the ERG, it would be more appropriate to use the log-normal distribution for extrapolation in the BSC arm of the model. This is the best fitting curve according to the statistical criteria presented, and gives consistent results over the time horizon used for the base case analysis.

The Kaplan-Meier OS data, together with the Company's chosen parametric curves, are shown in Figure 2. The log-normal survival function for BSC OS, preferred by the ERG, is shown in Figure 3.

Figure 2: Kaplan-Meier curves and fitted parametric functions for overall survival, base case

Figure 3: Kaplan-Meier curves and fitted parametric functions for overall survival, log-normal

It is important to note that the use of such parametric survival curves as the sole basis for transitions relies upon the assumption that the benefits of treatment persist both after the time horizon of the study, and after treatment discontinuation. All analyses undertaken by the Company assume this long-term treatment benefit, and no analyses are undertaken to test the sensitivity of the ICER to alternative assumptions, such as that the treatment benefit persists for the study time horizon, or until treatment discontinuation, but from that point onwards future progression rates are the same in the ceritinib and BSC groups. The ERG has undertaken a series of additional sensitivity analyses, with different cut-off values for the duration of treatment benefit post discontinuation, to assess the impact this has on the ICER.

5.2.6.3. Progression-free survival

PFS in the ceritinib arm of the model, as with OS, was extrapolated from Kaplan-Meier data derived by pooling data from the whole ASCEND-2 study with the previously treated subgroup from the ASCEND-1 study, without adjustment. PFS in the BSC arm of the model was also extrapolated from Kaplan-Meier data, this time from the placebo arm of an RCT of erlotinib in EGFR+ NSCLC, a genetically distinct subpopulation from those of interest in this evaluation. In response to a clarification request, the Company gave the following justification for the use of data from EGFR+ patients:

"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 BSC**		**OS for BSC**	
	AIC	BIC	AIC	BIC
Exponential	605.60	609.08	605.60	609.08
Weibull	585.21	592.17	585.21	592.17
Gompertz	607.35	614.31	607.35	614.31
Log-logistic	530.50	537.46	530.50	537.46
Log-normal	551.92	558.88	551.92	558.88

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

The percentages of patients in the PFS state whilst being treated with ceritinib or BSC, for each of the five curves fitted, are shown in Table 22 and Table 23.

Table 22: Proportions of patients progression free (%) with ceritinib using different parametric models

Year	exponential	Weibull	Gompertz	log-logistic	log-normal
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 23: Proportions of patients progression free (%) with BSC using different parametric models

Year	exponential	Weibull	Gompertz	log-logistic	log-normal
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The models selected by the Company, on the basis of the same criteria as for OS, were the log-logistic for both ceritinib and BSC. The log-logistic is also the best fitting model according to the statistical criteria presented, and hence this selection appears justified. As with OS, an assumption was made

that treatment benefit will continue post treatment discontinuation and after the time horizon of the study. This is a less important assumption than with OS, 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.

Adverse events

The base case model included grade 3/4 adverse events affecting ≥5% patients for any of the three interventions (ceritinib, docetaxel, BSC). Ceritinib adverse events from the ASCEND-1 and ASCEND-2 studies were only included if they were deemed to be study-drug related. Table 24 below shows the adverse event rates included in the base case analysis, with adverse events for BSC assumed to be zero.

Table 24: Pooled analysis of grade 3/4 adverse events from ASCEND-2 and ASCEND-1 (greater than or equal to 5%)

Grade 3/4 adverse events	**Pooled Analysis Ceritinib 750 mg (n=303) Grade 3/4 n (%)**
Alanine aminotransferase increased	[redacted]
Aspartate aminotransferase increased	[redacted]
Diarrhoea	[redacted]
Gamma-glutamyltransferase increased	[redacted]
Nausea	[redacted]

Since restricting to adverse events affecting ≥5% of patients means it is possible that rare but serious adverse events, which may have considerable cost or quality of life implications, are excluded, the ERG requested a list of all grade 3/4 events from the ASCEND studies, which was supplied by the Company. The full list of events reported following this query is shown below, and was used by the ERG for additional analyses.

Table 25: Pooled grade 3-4 adverse events from the ASCEND-1 and ASCEND-2 trials

	Pooled Analysis: Ceritinib 750 mg (n=303) Grade 3/4 n (%)
Abdominal Pain	[redacted]
Abdominal Pain Upper	[redacted]
Alanine Aminotransferase Increased	[redacted]
Amylase Increased	[redacted]
Anaemia	[redacted]
Aspartate Aminotransferase Increased	[redacted]
Asthenia	[redacted]
Blood Alkaline Phosphatase Increased	[redacted]

Decreased appetite	[redacted]
Diarrhoea	[redacted]
Dyspepsia	[redacted]
Electrocardiogram QT prolonged	[redacted]
Fatigue	[redacted]
Gamma-glutamyltransferase increased	[redacted]
Hepatic function abnormal	[redacted]
Hyperglycaemia	[redacted]
Hypophosphataemia	[redacted]
Lipase Increased	[redacted]
Nausea	[redacted]
Neutropenia	[redacted]
Pneumonia	[redacted]
Pneumonitis	[redacted]
Pruritus	[redacted]
Pyrexia	[redacted]
Transaminases Increased	[redacted]
Vomiting	[redacted]
Weight decreased	[redacted]

ERG summary:

- OS and PFS for both ceritinib and BSC were calculated as extrapolations to single-arm studies, and no adjustment for differing baseline characteristics was made. Therefore, differences between the populations in the 4 sources of data (ASCEND-1, ASCEND-2, Ou et al., 2014,[1] Shepherd et al., 2005[2]) and the applicability of these data to the UK treatment population need to be carefully considered.
- PFS, for both BSC and docetaxel, are based not on data from ALK+ NSCLC, but rather from a study in EGFR+ NSCLC. Again, no adjustment is made for possible differences between these populations.
- OS and PFS extrapolation all rely on the assumption that the benefit of treatment persists, both after the time horizon of the study and after treatment discontinuation. Any reduction in treatment benefit following either of these will result in a smaller treatment benefit for ceritinib than is currently the case.
- The ERG believes the log-normal distribution provides a better extrapolation, over the 10 year time horizon of the base case analysis, than the Weibull distribution chosen by the

Company. All additional analyses undertaken by the ERG make use of this different distributional choice.

5.2.7. Health-related quality of life

Participants in the ASCEND-2 study were asked to complete the EORTC-QLQ-C30 questionnaire, a validated measure often used in clinical studies of lung cancer. For the cost-effectiveness analysis, data from the EORTC QLQ-C30 were mapped to the EQ-5D using an algorithm by Proskorovsky et al. (2014)[27] A number of possible mapping algorithms are available for use between the two questionnaires, with this one selected as it uses a UK-specific algorithm and contains a similar sample of patient to ASCEND-2. This choice of algorithm seems a reasonable one, and there is no reason to believe the use of a different mapping algorithm would lead to more robust results. For each time point where HRQoL was measured, tumour response status was also assessed from the tumour evaluation that took place closest to the HRQoL assessment. Response status was classified as CR, PR, stable disease or progressive disease, with all participants assumed to have stable disease at baseline. CR and PR were then grouped together as responding disease, with linear mixed models, taking into account repeated measurements from the same patients, used to estimate utility values for each of the three states (Table 26).

Table 26: Mapped utility values by response state from ASCEND-2

Response state	n	Mean utility	95% CI
Stable disease	[redacted]	[redacted]	[redacted]
Responding disease	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]

The utility values for responding disease and stable disease were used in the model, but the value for progressive disease was not. The justification given for this is that since collection of the EORTC stopped after confirmed disease progression, these numbers represent the utility for those who have just progressed, not the whole group in the health state. Therefore, a systematic review was conducted, looking for studies reporting utilities for individuals with advance or metastatic NSCLC. A broad, well-constructed search of a range of appropriate databases was undertaken on 10th March 2015. The inclusion/exclusion criteria for this review are given in Table 27.

Table 27: Inclusion and exclusion criteria of the HRQoL systematic review

Inclusion criteria	**Population:** Eligible participants were patients with advanced or metastatic (stage IIIB or IV) NSCLC. If the study assessed a mixed population (e.g., early stage and advanced/late stage), included the study if the outcomes of interest were reported for population of interest (advanced or metastatic (stage IIIB or IV) NSCLC). Study design: Reports of utility elicitation exercises Reports of utility validation exercises Reports of utility mapping exercises, e.g., EORTC QLQ-C30 to EQ-5D Reports of economic evaluations using utility measures gathered during studies Utility estimates based on clinical trials Utility study requirements: Mean or median utility values or quality of life values; A standard method of utility assessment (e.g., standard gamble, time trade-off, rating scale); A description of the health state valuation instrument (e.g. was a generic preference-based measure such as the EQ-5D used or did authors value bespoke health state descriptions) **Health states**: stable disease, progressed disease, treatment response (complete or partial), treatment-related adverse events **Language restrictions:** Any studies with English abstracts but whose full reports were in languages other than English were not extracted but were listed for information only.
Exclusion criteria	Study population: Not NSCLC disease (e.g. small cell lung cancer) Early stage of NSCLC (i.e., not advanced or metastatic NSCLC or stage IIIB or stage IV NSCLC) Study design: Review studies already included in systematic literature review of clinical

	evidence **Utility studies:** Studies not including sufficient information on type of utility measure and how it was assessed **Health states:** Health states other than those listed above **Languages:** Studies not in English

Eleven unique studies met the eligibility criteria for data extraction, with two studies identified as providing utility values appropriate for use in the model. The data provided by these studies included utilities for the progressive disease health state, and utility decrements associated with specific adverse events. The utility values extracted from the studies providing data for the progressive disease state are shown in Table 28.

Table 28: Utility inputs from published literature used in the economic evaluation

Source	Utility
Chouaid (2013)[3]	Third/fourth-line progressive disease Mean: 0.46 Standard deviation: 0.38
Nafees et al. (2008)[24]	Health states: Progressive: 0.473 Responding: 0.673 (PR: 0.67, CR: 0.85) Stable: 0.653 End of life: 0.35 Death: 0.00 By health states and adverse events: Responding + diarrhoea: 0.626 Responding + fatigue: 0.599 Responding + febrile neutropenia: 0.582 Responding + hair loss: 0.628 Responding + nausea/vomiting: 0.624 Responding + neutropenia: 0.583 Responding + Rash: 0.640

	Stable + fatigue: 0.580 Stable + febrile neutropenia: 0.563 Stable + hair loss: 0.608 Stable + nausea/vomiting: 0.605 Stable + neutropenia: 0.563 Stable + diarrhoea: 0.606 Stable + Rash: 0.621

The CS (section 5.4.5) states that, in the base-case, the same utility level is assigned to each of the health states in the model, irrespective of the treatment arm, and a utility of [redacted] is quoted for the PFS state (the utility for stable disease from the mapping). However, in the actual model submitted by the Company, a different and slightly more complex methodology is applied. In this the utilities for stable and responding disease are weighted by the proportions of people who respond to treatment (taken from the ASCEND studies for ceritinib and Shepherd et al., 2005[2] for BSC), giving a PFS utility of [redacted] for ceritinib and [redacted] for BSC. Since this approach is not described in the submission, no justification is given for the validity of such a calculation.

The assumption that underlies this approach is that the differences in utility between responders and non-responders are driven by the effectiveness of treatment. An alternative possibility is that people who will go on to respond are likely to have a higher utility at baseline (pre-treatment), and under this assumption there would be no reason to assume a higher utility for PFS with ceritinib than BSC. Since no justification was provided by the Company for the approach undertaken, the ERG believe the correct, conservative, assumption would be to assume the same utility for patients in the PFS state on ceritinib or BSC, which is indeed the approach the CS asserts they have undertaken. All the additional analyses undertaken by the ERG make use of this equivalent utility value. Further, the submission states that it was not necessary to include adverse event disutilities in the model, as these would be captured by the measure used in the study. Whilst this is indeed the case for the ceritinib arm, it means that adverse event disutilities will also have been included for BSC, which is inappropriate. Therefore, the ERG's new analyses also increase the utility for patients in the PFS BSC health state, to account for the higher utility that would be expected without the drug-related adverse events, with the disutilities associated with adverse events taken from Nafees et al. (2008).[24]

For the progressive disease health state, the Company included in the model the value from the Chouaid et al. (2013)[3] paper. The reason for choosing this paper provided by the Company was that it included the EQ-5D as an instrument, used the UK specific tariff, and contained a population of patients relevant to the decision problem in this evaluation. The utility for the progressive disease

state from this paper is sufficiently similar to values from other studies (e.g. 0.473 from Nafees et al. (2008)[24]) that there is no reason to believe the use of a different source for this utility would lead to substantially different results being produced by the model. The full set of utility values and sources used in the base case model (after correction for the contradiction between the values reported in the submission and those in the provided model) are shown in Table 29.

Table 29: Summary of utility values used for cost-effectiveness analysis

State	Utility value: mean	Standard error	Reference in submission (section and page number)	Justification
Health states				
Progression free (whether on ceritinib or BSC)	[redacted]	[redacted]	Section 5.4.1	Utility based on mapped PRO values from the ASCEND-trials were used for the progression free, in order to capture the appropriate population of the submission.
Progressive disease (whether on ceritinib or BSC)	0.460	0.12		Utility based on published evidence was used as the trial-based utility for progressive disease was considered as too high after validation with clinical expert.
Adverse reactions				
Nausea	-0.04802	0.01618		Nafees et al. (2008)[24]

Diarrhoea	-0.0468	0.01553		Nafees et al. (2008)[24]
Neutropenia*	-0.08973	0.01543		Nafees et al. (2008)[24]
Febrile neutropenia*	-0.09002	0.01633		Nafees et al. (2008)[24]
Fatigue*	-0.07346	0.01849		Nafees et al. (2008)[24]
HS, health state; AR, adverse reaction				

*Included in the scenario analysis involving the composite comparator only

ERG summary:

- In the base case analysis, utilities for the pre-progression health states are calculated by mapping data from the EORTC-QLQ-C30 questionnaire, administered during the ASCEND-2 study, to the EQ-5D. Utilities for the post-progression state derived from the same sample were deemed by the Company's clinical experts to be too high, as they represent the utility immediately post progression. Therefore, data for the whole post progression health state was taken from a study by Chouaid et al. (2013)[3]
- In the base case analysis of the model provided by the Company, mapped utilities for the responding and stable disease state are weighted by the response rates for ceritinib and BSC, giving different PFS utilities for the two treatments. Since this approach is neither discussed nor justified in the CS, the ERG set all patients in the PFS state to a single utility value, regardless of treatment, in line with the methods described in the CS
- Adverse event disutilities were not included in the base case model submitted by the Company. These were added in to additional analyses by the ERG to account for the higher utility values that might be expected for otherwise identical patients receiving BSC rather than ceritinib, due to the lower rate of adverse events.

5.2.8. Resource use and costs

5.2.8.1. Intervention costs

Monthly drug costs included in the model were made up of four components; unit drug costs, dosing, proportion of planned dose consumed and drug administration costs. Ceritinib is available in sets of 3 packages of 50 capsules (each of 150mg), with the published price taken from the British National Formulary (April 2015). Not all patients taking ceritinib would be expected to take the full course of the drug, due to non-adherence as well as adverse event related dose reductions or interruptions. The average dosing intensity of ceritinib across the ASCEND-1 and ASCEND-2 studies was [redacted] and

this was applied to the cost of ceritinib to create an estimated monthly cost across the whole patient population. Drug administration costs were assumed to be 0 for ceritinib. The assumed dose intensity for docetaxel was 92.6% and costs of administration were included in this case. Unit costs for the two drugs included in the model are given in Table 30.

Table 30: Unit costs associated with the technology in the economic model

Items	Ceritinib	Docetaxel [a (scenario analysis)]
Recommended dose (per cycle)	22,500 mg [750 mg orally once daily]	192 mg [75 mg/m² once every cycle]
Cycle length	One month	21 days
Unit costs	£4,923.45 for 3 packs of 50 caps	£25.73 for 20 mg/mL vial, 4mL
Cost per month - dose intensity applied (base case)	£4,076.62	£68.07
Cost per month - dose intensity not applied (scenario analysis)	£4,995.25	£74.59 [£25.73*2*(365.25/12)/21]
Treatment duration (base case)	Until disease progression	NA
Treatment duration (scenario analysis)	1.6 months post progression	2.76 months followed by BSC

[a] *The average body surface area was considered to be 1.79m²*

In the base case analysis, ceritinib was assumed to be taken until disease progression, when individuals would move to BSC. However, data from the ASCEND studies indicate that a considerable proportion of individuals continue ceritinib treatment for a period after disease progression, with a median post progression duration of treatment of 1.6 months. Whilst the additional costs of these post progression treatments are included in a sensitivity analysis, the opinion of the ERG's clinical experts was that these post discontinuation treatments were likely to occur in clinical practice, and hence these costs should be included in the base case.

5.2.8.2. Health state costs

No studies were found by the Company providing relevant information on the resource use for people in either the pre or post progression states in the model. The ERG note that the company's search was limited by country terms, which may have resulted in relevant articles (for example, that only included terms such as NHS, pound, specific regions or hospitals) being missed. The Company used evidence from expert panels to estimate the resource use in each state, to which unit costs from appropriate sources were then applied. Costs in the pre-progression state included visits to healthcare providers (hospital, GP, cancer nurse etc.), laboratory test and procedure costs. The resource use assumptions were based on previous NICE appraisals, and related to second-line NSCLC, but are not specific to ALK+ patients. Post-progression costs included visits to healthcare providers, medication (steroids, nonsteroidal anti-inflammatory drugs etc.), laboratory test and procedure costs.

A one-off cost of terminal care was applied to patients at the time of death, representing the cost of palliative care in the community, in hospitals and in hospices. All items of resource use included, together with the estimated frequency unit cost of each time, and the total cost for each health state in the model, are given in Table 31, with all costs reported in 2013-14 GBP.

Table 31: List of health states and associated costs in the economic model

Health states	Items	Frequency	Unit cost (£)	Reference in submission
Stable disease	*Physician visits*			
	Outpatient visit	0.75 visits per month	143.04	Expert panel (resource use); Schedule of Reference Costs, all NHS trusts and NHS foundation trusts - WF01A, Non-Admitted Face to Face Attendance, Follow-up, 370 - Medical Oncology (unit costs)
	GP visit	10% of patients	56.00	Expert panel (resource use); PSSRU 2013-2014 general practitioner unit cost per patient contact lasting 17.2 minutes, including direct care staff costs, without qualification costs (unit costs)
	Cancer nurse	20% of	64.51	Expert panel (resource use);

Health states	Items	Frequency	Unit cost (£)	Reference in submission
		patients 1 per month		Schedule of Reference Costs, all NHS trust and NHS foundation trusts - Other Currencies Data, N10AF - Specialist Nursing - Cancer Related, Adult, Face to face (unit costs)
	Tests and procedures			
	Complete blood count	0.75 per month	3.00	Expert panel (resource use); Schedule of Reference Costs, directly accessed pathology Services, DAPS05- Haematology (unit costs)
	Serum chemistry	0.75 per month	1.18	Expert panel (resource use); Schedule of Reference Costs (unit costs), directly accessed pathology Services, DAPS04 - Clinical Biochemistry
	CT scan	30% patients 0.75 per month	132.24	Expert panel (resource use); Schedule of Reference Costs, total HRG data, RA13Z - Computerised Tomography Scan, three areas with contrast (unit costs)
	X-ray	0.75 per month	29.60	Expert panel (resource use); Schedule of Reference Costs, total HRG data, DAPF - Direct Access Plain Film (unit costs)
	Total cost per month, Stable disease			£180.88
Progressive disease	*Physician visits*			
	Outpatient visit	1 visit	143.04	Expert panel (resource use); Schedule of Reference Costs, all NHS trusts and NHS foundation trusts - WF01A,

Health states	Items	Frequency	Unit cost (£)	Reference in submission
				Non-Admitted Face to Face Attendance, Follow-up, 370 - Medical Oncology (unit costs)
	Cancer nurse	10% patients (1 visit)	64.51	Expert panel (resource use); Schedule of Reference Costs, all NHS trust and NHS foundation trusts - Other Currencies Data, N10AF - Specialist Nursing - Cancer Related, Adult, Face to face (unit costs)
	GP visits	28% patients (1 visit)	56.00	Expert panel (resource use); PSSRU 2013-2014 general practitioner unit cost per patient contact lasting 17.2 minutes, including direct care staff costs, without qualification costs (unit costs)
	Tests and procedures			
	Complete Blood Count	All patients, 1 per month	3.00	Expert panel (resource use); Schedule of Reference Costs, directly accessed pathology Services, DAPS05- Haematology (unit costs)
	Serum chemistry	All patients, 1 per month	1.18	Expert panel (resource use); Schedule of Reference Costs (unit costs), directly accessed pathology Services, DAPS04 - Clinical Biochemistry
	CT scan	5% of patients, 0.75 per month	132.24	Expert panel (resource use); Schedule of Reference Costs, total HRG data, RA13Z - Computerised Tomography Scan, three areas with contrast

Health states	Items	Frequency	Unit cost (£)	Reference in submission
				(unit costs)
	X-ray	30% of patients, 0.75 per month	29.60	Expert panel (resource use); Schedule of Reference Costs, total HRG data, DAPF - Direct Access Plain Film (unit costs)
	Home oxygen	20% of patients, 1 per month	194.00	Expert panel (resource use); Schedule of Reference Costs (unit costs),total HRG data, DZ33Z - Hyperbaric Oxygen Treatment
	Medications			
	Steroids (dexamethasone)	80 [50% of patients, 0.5mg x 160]	0.35	Expert panel (resource use); BNF (unit costs) Oral solution, 2 mg/5 mL, 150-mL = £42.30
	NSAIDS	18 [30% of patients, 200mg x 60]	0.08	Expert panel (resource use); BNF (unit costs) Aspirin, Tablets, 75 mg, 56-tab pack = £1.58
	Morphine	5.25 [75% of patients, 60mg x 7]	7.07	Expert panel (resource use); BNF (unit costs) Morphine Sulfate (Non-proprietary), Intravenous infusion, morphine sulfate 1 mg/mL, 50-mL vial = £5.89
	Bisphosphonate (alendronate)	2.10 [7.5% of patients, 5mg x 28]	0.41	Expert panel (resource use); BNF (unit costs) Alendronic acid (Non-proprietary, Oral solution, 70 mg/100 m,4 × 100-mL = £22.80
	Dietary supplement	8 [40% of patients, 350g x 20]	3.30	Tarceva (erlotinib) NICE submission (resource use and unit costs)
	Total cost per month, Progressive disease			£ 313.70

Health states	Items	Frequency	Unit cost (£)	Reference in submission
Death	Terminal care	Cost applied only once	6,079.40	Coyle D, Small N, Ashworth A *et al.* (1999). Costs of palliative care in the community, in hospitals and in hospices in the UK. Critical Reviews in Oncology/Hematology.32 (2): 71–85. The costs were inflated to 2014 GBP
	Total cost per month, Death			£ 6,079.40

Abbreviations: GP, general practitioner; NSAID, nonsteroidal anti-inflammatory drug

Adverse events

In the base case model, costs were applied to grade 3/4 adverse events affecting ≥5% of people in a given arm of the model. Costs of lab abnormalities (ALT elevation, AST elevation, blood alkaline phosphate increase) were assumed to be zero as they would be managed by dose reductions. The cost of managing fatigue was also assumed to be zero, whilst costs of nausea, diarrhoea and neutropenia were derived from 2012/13 NHS reference costs.[28] All adverse events were assumed to occur in the first month of treatment. Following a request for clarification to the Company, the following justification was provided for this approach:

"In the ASCEND-2 study, the median time to first dose interruption was 1.4 months (range: 0.1 to 7.5 months); therefore, it was felt a reasonable assumption to include all AEs in the first cycle of the economic model. Also this ensured that all the AE's would be captured in the analysis as a one-off (rather than trying to estimate how many AEs would occur each month in the progression-free health state)."

It should be noted that, if adverse events would be expected to continue over a longer period, the model will be underestimating the cost of managing these events, as adverse events occurring after the time horizon of the study will not be included. The ERG made a number of modifications to the adverse event costing assumptions made by the Company. First, a request was made to include the costs of all adverse events, not just those occurring in ≥5% of patients. In response, the Company provided new data on costs assumed for each event occurring, which are given in Table 32.

Table 32: Pooled grade 3-4 adverse events from the ASCEND-1 and ASCEND-2 trials

Adverse events	Unit Cost (£)	Source
Abdominal Pain	£0.00	Assume no cost
Abdominal Pain Upper	£0.00	Assume no cost
Alanine Aminotransferase Increased	£0.00	Assume no cost
Amylase Increased	£0.00	Assume no cost
Anaemia	£2,065.62	NHS Reference Costs 2012-13 NHS Trust HRG data Average Iron Deficiency Anaemia (SA04G- SA04L)
Aspartate Aminotransferase Increased	£0.00	Assume no cost
Asthenia	£2,065.62	Assume same as Anaemia
Blood Alkaline Phosphatase Increased	£0.00	Assume no cost
Decreased appetite	£0.00	Assume no cost
Diarrhoea	£617.81	As per submission
Dyspepsia	£0.00	Assume no cost
Electrocardiogram QT prolonged	£0.00	Assume no cost
Fatigue	£0.00	Assume no cost
Gamma-glutamyltransferase increased	£0.00	Assume no cost
Hepatic function abnormal	£0.00	Assume no cost
Hyperglycaemia	£0.00	Assume no cost
Hypophosphataemia	£0.00	Assume no cost
Lipase Increased	£0.00	Assume no cost
Nausea	£693.23	As per submission
Neutropenia	£38.16	As per submission
Pneumonia	£1,064.69	NHS Reference Costs 2012-13 NHS Trusts HRG Data Average Upper Respiratory Tract Disorders (PA65A - PA65C)
Pneumonitis	£1,064.69	Assume same as Pneumonia
Pruritus	£0.00	Assume no cost
Pyrexia	£3,633.60	NHS Reference Costs 2012-13 NHS Trusts HRG data Pyrexia of Unknown Origin with length of stay 5 days or more (WA05Z)
Transaminases Increased	£0.00	Assume no cost
Vomiting	£0.00	Included in the cost of managing nausea

Weight decreased	£0.00	Assume no cost
TOTAL Cost	£145.46	

Secondly, the assumption that dose adjustments to account for lab abnormalities would incur no cost appeared overly optimistic, as these are likely to involve both clinician time and additional testing. Therefore, again after clarification was requested from the Company, these adverse events were assumed to incur a cost equivalent to two additional blood tests and two additional outpatient visits.

ERG summary:

- In the Company's base case, costs for ceritinib are accrued until disease progression or death, using a dosing intensity estimated the ASCEND-1 and ASCEND-2 studies. The ERG believe this should be modified to also include the costs of post progression ceritinib use, estimated from the ASCEND studies.
- No primary data were available on resource use for either the pre-progression or progressive health states, so resource use estimates were taken from previous NICE appraisals (based on expert panels), to which unit costs were then attached. Although the ERG has no specific concerns about the values included in the model, these estimates were based on NSCLC, but not on ALK+ patients, so any expected differences in resource use between the ALK+ and the whole population should be considered.
- In the Company's base case, costs were only applied to adverse events affecting ≥5% of patients, and no costs were assumed for managing lab abnormalities. The ERG's preferred analysis includes all adverse events and costs of managing lab abnormalities.

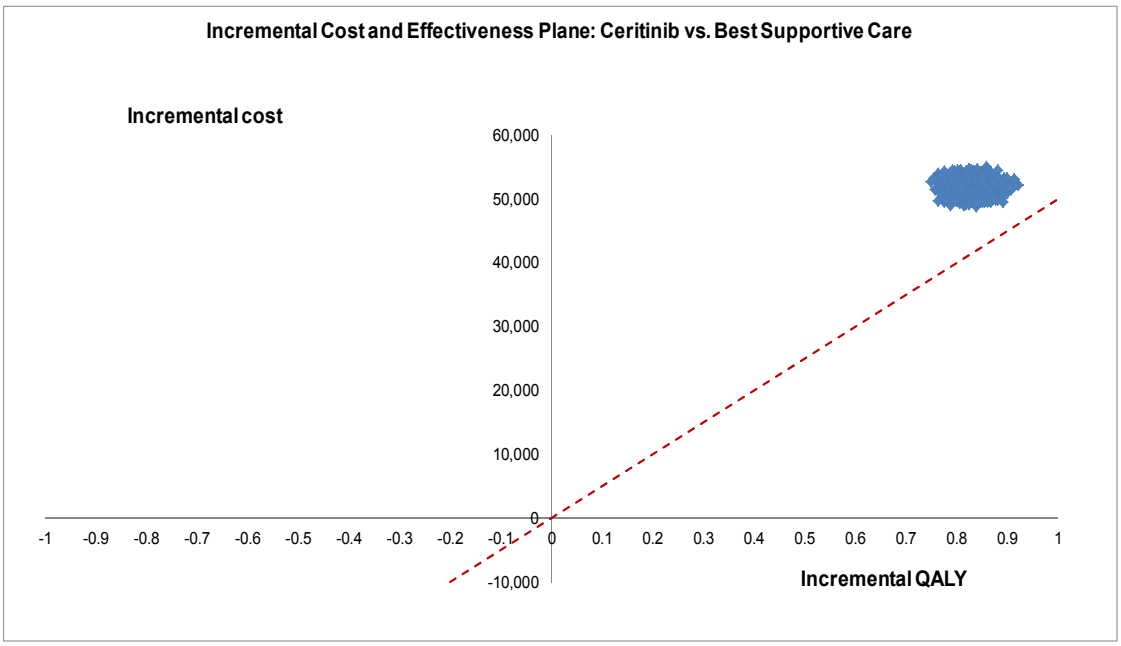
5.2.9. Cost-effectiveness results

For the base case comparison of ceritinib versus BSC, ceritinib produced more QALYs than BSC (1.08 vs. 0.25), but was also associated with higher costs (£59,155 vs. £7,203). The incremental cost-effectiveness ratio (ICER) for ceritinib versus BSC was £62,456 per QALY (Table 33).

Table 33: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	7,203	0.42	0.25				
Ceritinib	59,155	1.77	1.08	51,952	1.35	0.83	62,456

The corresponding result from the mean of the probabilistic analyses is very similar, with an ICER of £62,460 per QALY. There is a 0% chance of ceritinib being cost-effective versus BSC, at a willingness to pay (WTP) threshold of £50,000 per QALY. Figure 5 and Figure 6 present, respectively, figures from the company submission showing the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) for ceritinib versus BSC derived from the same PSA. The CEAC shows the proportion of the simulations for which the ICER falls below a given WTP threshold.



Treatment	Ceritinib	**Average Δ costs**	£51,921
Comparator	Best Supportive Care	**Average Δ QALYs**	£1
Time horizon	10 years	**Average ICER**	£62,460
		% cost-effective at WTP of £50K	0.0%

Figure 5: Probabilistic sensitivity analyses – scatter plot - ceritinib vs. BSC

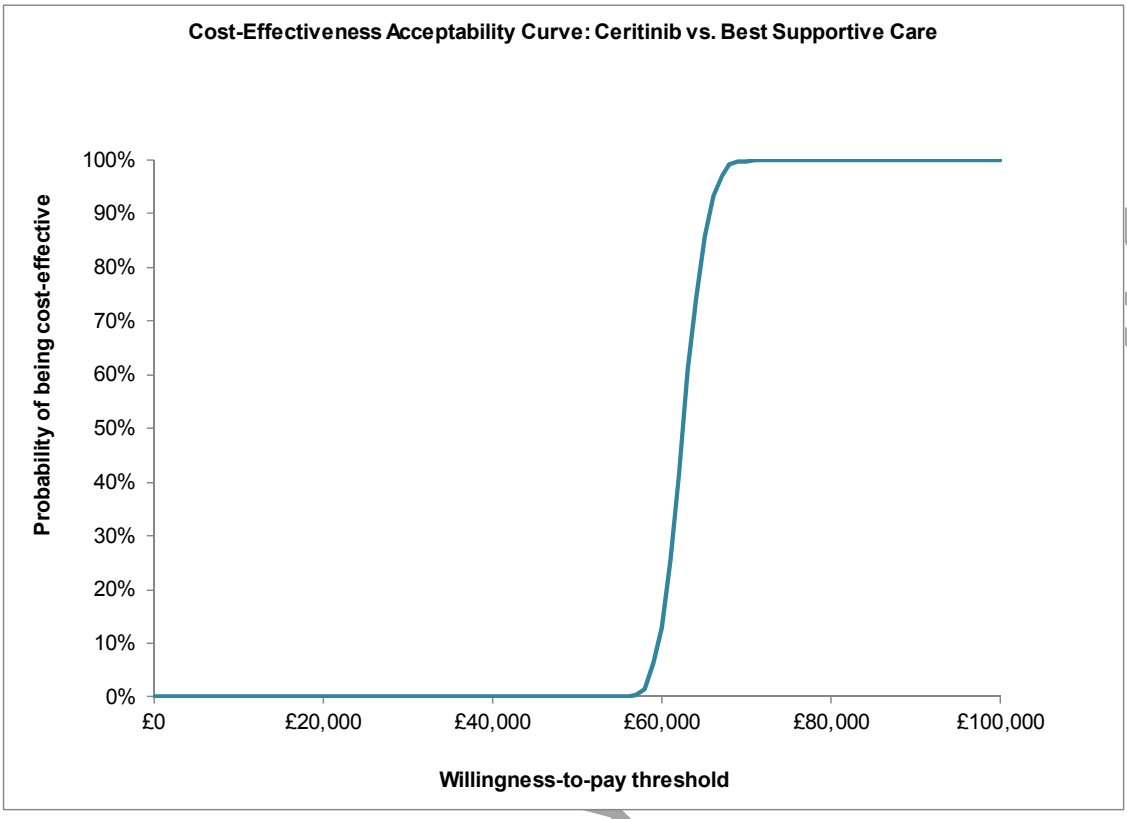


Figure 6: Cost-effectiveness acceptability curve for ceritinib vs. BSC

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	0.16	0.16	67.6%
Post-progression survival	0.36	0.09	0.09	0.09	32.4%
Total	1.08	0.25	0.25	0.25	100.0%

Table 35: Summary of costs by health state

Health state	Cost (£) ceritinib	Cost (£) BSC (no active treatment)	Increment (£)	Absolute increment (£)	% absolute increment
Progression-free survival	50,517	485	50,033	50,033	96.3%
Post-progression survival	2,944	735	2,209	2,209	4.3%
Terminal care	5,694	5,983	-289	-289	-0.6%
Total	59,155	7,203	51,952	51,952	100.0%

Table 36 shows a breakdown of the total costs for each strategy into drug and administration costs, adverse event costs, terminal care costs, and costs of disease management in the pre- and post-progression states. A large proportion of the incremental costs associated with ceritinib (93%) come from drug and administration costs, with once again terminal care the only category where costs are higher for BSC than ceritinib.

Table 36: Summary of predicted resource use by category of cost

Item	Cost (£) ceritinib	Cost (£) BSC (no active treatment)	Increment (£)	Absolute increment (£)	% absolute increment
Drug and drug administration costs	48,304	0	48,304	48,304	93.0%
Treatment associated adverse event costs	69	0	69	69	0.1%
Pre-progression costs	2,143	485	1,659	1,659	3.2%
Post-progression costs	2,944	735	2,209	2,209	4.3%
Terminal Care costs	5,694	5,983	-289	-289	-0.6%
Total	59,155	7,203	51,952	51,952	100.0%

5.2.10. Sensitivity analyses

A number of deterministic, univariate sensitivity analyse are conducted by the Company. Costs are varied by 25% in both directions for the base case values, utilities by 10% in both directions, and discount rates of 0% and 6% were used for both costs and outcomes. It is unclear why, for parameters where the Company had data available, these fixed percentage were used rather than the more standard approach of using the upper and lower CIs for that parameter.

Table 37 shows the parameter values used in the sensitivity analyses, and Figure 7 presents a tornado plot of the results.

Table 37: Variables and ranges explored through deterministic sensitivity analysis

Variable	Range	Base Case	Lower limit	Upper limit
Ceritinib drug cost (£) per month	+/- 25%	4,076.62	3,057.46	5,095.77
Systematic therapy drug (£) cost per month	+/- 25%	68.07	51.06	85.09
Pre-progression medical cost (£) per month	+/- 25%	180.88	135.66	226.10
Post-progression medical costs per month (£)	+/- 25%	313.70	235.27	392.12
Terminal care (one time) cost (£)	+/- 25%	6,079.40	4,559.55	7,599.25
Utility of stable disease state with no toxicity (base case ± 10%)	+/- 10%	0.71	0.64	0.78
Utility of progressive disease state (base case ± 10%)	+/- 10%	0.46	0.41	0.51
Cost (£) of AEs	No AEs and 2x base case value	847.57	0	1,695.13
Discount rate: cost	0%, 6%	3.5%	0%	6%
Discount rate: effectiveness	0%, 6%	3.5%	0%	6%

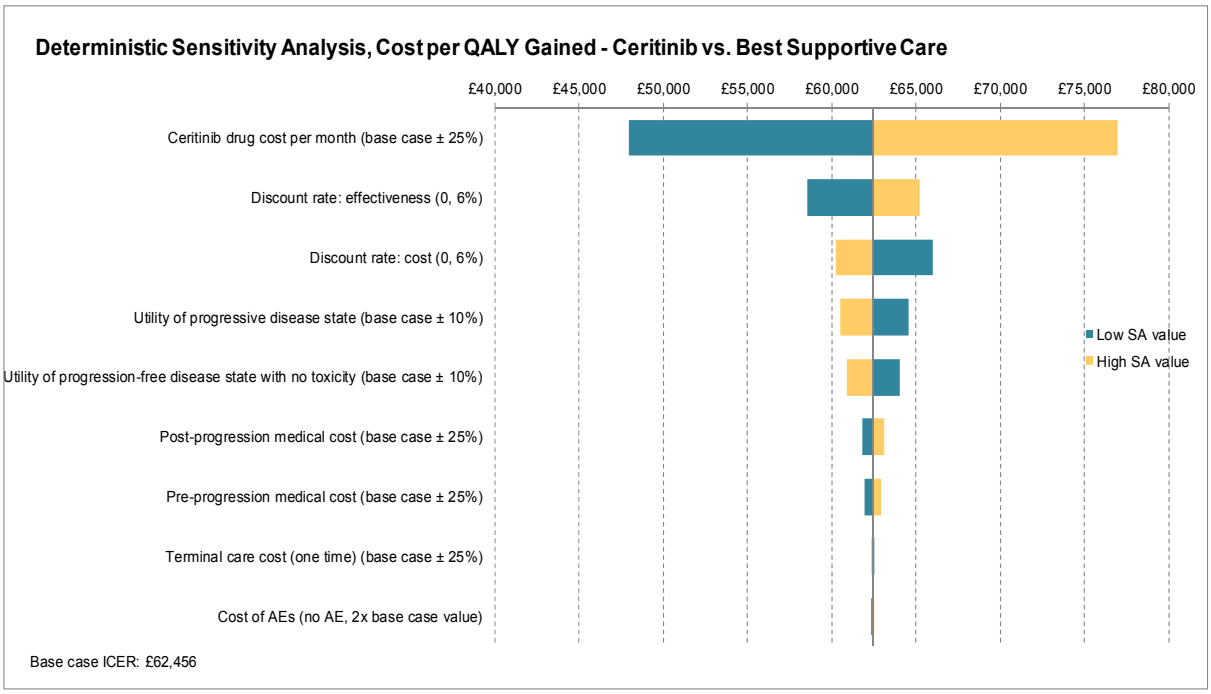


Figure 7: Deterministic sensitivity analyses for ceritinib vs. BSC

Varying the cost of ceritinib had the single largest impact on the ICER, followed the discount rates for outcomes and costs. It is important to note, however, that these analyses only consider the impact of varying one single parameter at a time, and are therefore less informative as to the overall level of uncertainty in the model than the results from the full probabilistic sensitivity analysis. It should also be noted that these analyses only consider parameter uncertainty that has been quantified within the model. Other sources of uncertainty, for example the potential biases introduced by the use of single arm studies to inform clinical effectiveness, were not quantified and hence are not included in either the univariate or probabilistic sensitivity analyses.

5.2.11. Scenario analyses

The Company also present a number of scenario analyses, looking at the impact of varying structural assumptions within the model. The full list of scenario analyses undertaken is as follows:

- 30% of patients are treated with docetaxel and 70% with BSC following progression on crizotinib, rather than 100% with BSC as in the base case
- Use data on the duration of ceritinib treatment from the ASCEND study, rather than assuming all patients discontinue immediately post-progression
- Alternative time horizons of 5 and 20 years

- Alternative survival functions for PFS and OS with ceritinib (alternative functions are not presented for BSC)
- Different sources of HRQoL data
- Assuming all patients progress immediately on BSC, with none spending any time in the progression-free state
- Including the administration cost for oral chemotherapy with the costs of ceritinib
- Assuming a does intensity of 100% for ceritinib, rather than using data from the ASCEND studies
- Taking the costs of docetaxel treatment from the British National Formulary (April 2015).

The results of all these additional analyses are presented in Table 38. The largest changes in the ICER are produced by including the costs of ceritinib treatment post progression, assuming a 100% dose intensity for ceritinib, and using alternative utility values.

Table 38: Scenario Analyses – ceritinib vs. BSC

Parameter	Base case choice	Scenario analysis	ICER (£/QALY)	% change from base case ICER
Base case			62,456	
Use systemic therapy treatment following progression on crizotinib	No	Yes (assume 30% of patients receive docetaxel and 70% BSC)	63,920	2%
Ongoing treatment with ceritinib post-progression	No	Yes (assume patients treated for a median duration of 8.8 months)[20]	76,039	22%
Time horizon	10 years	5 years	62,073	-1%
		20 years	62,473	0%
PFS function: ceritinib	log logistic	Exponential	56,898	-9%
		Weibull	54,482	-13%
		log-normal	62,610	0%
		Gompertz	54,793	-12%

Parameter	Base case choice	Scenario analysis	ICER (£/QALY)	% change from base case ICER
OS function: ceritinib	Weibull	Exponential	56,997	-9%
		Gompertz	67,423	8%
		log-logistic	48,393	-23%
		log-normal	44,011	-30%
Health state utility values	Health state utility values for progression free from ASCEND-2 trial data adjusted by ORR	Nafees et al.[24]	66,130	6%
		Chouaid *et al.*[3]	69,896	12%
		Chouaid *et* al. with ORR adjusted[3]	69,060	11%
PFS for patients on BSC	Assume patients on BSC experience PFS	Assume no PFS for patients on BSC	58,479	-6%
Administration cost for oral chemotherapy	Not Included	Include cost for ceritinib administration until disease progression	66,536	7%
Relative drug intensity - Ceritinib	As reported in the published trial (ASCEND-2)	Assumed to be 100% for ceritinib	74,519	19%
Docetaxel acquisition cost	eMIT	Use BNF cost and assume 30% of patients receive docetaxel and 70% BSC	61,678	-1%

5.2.12. Model validation and face validity check

The Company present validity checks for their model, comprising comparisons of model predicted OS and PFS with data from the studies on which those extrapolations are based (Table 39). Results from the model and studies are similar for ceritinib and PFS for BSC, but the model appears to considerably underestimate OS with BSC. This is likely due to the poorly fitting Weibull survival function selected for the BSC arm, and hence should be corrected by the alternative choice of survival function (log-normal) made by the ERG.

Table 39: Summary of modelled outcome estimates compared with clinical data

Outcome	Clinical trial result	Model result
*Ceritinib**		
Progression-free survival	9.27	9.19
Overall survival	15.63	15.60
BSC (no active treatment)[+]		
Progression-free survival	2.84	2.72
Overall survival	5.57	4.77

*Ceritinib last observation PFS (21.9 months), OS (24.1 months), [+]BSC last observation PFS (15.5 month), OS (17.75 months)

Also reported are Markov model traces, which shown proportions of people in each state of the model over time (Figure 8 and Figure 9) and QALY accumulation traces, which show the number of QALYs accumulated in each state of the model over time (Figure 10 and Figure 11). These results are consistent with data from the relevant studies (again with the exception of OS data for BSC), the model described by the Company and the expected clinical course of the disease.

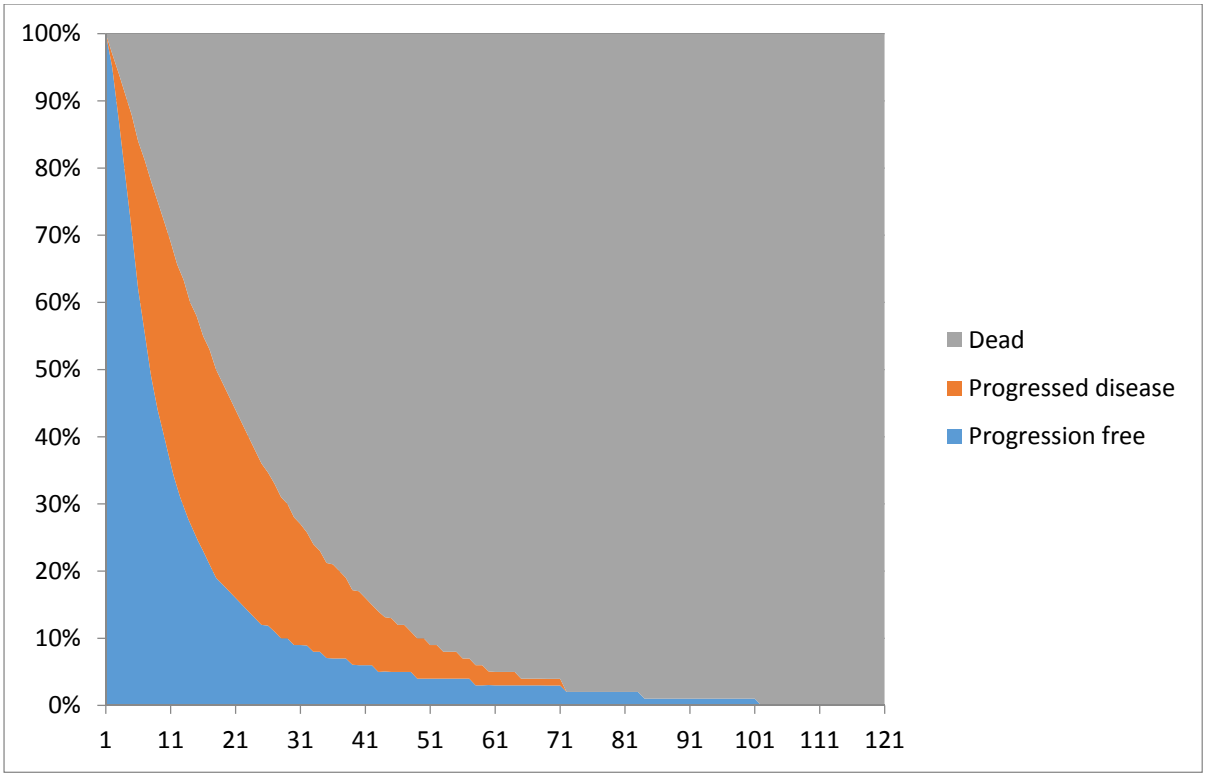


Figure 8: Markov trace, overall survival, ceritinib

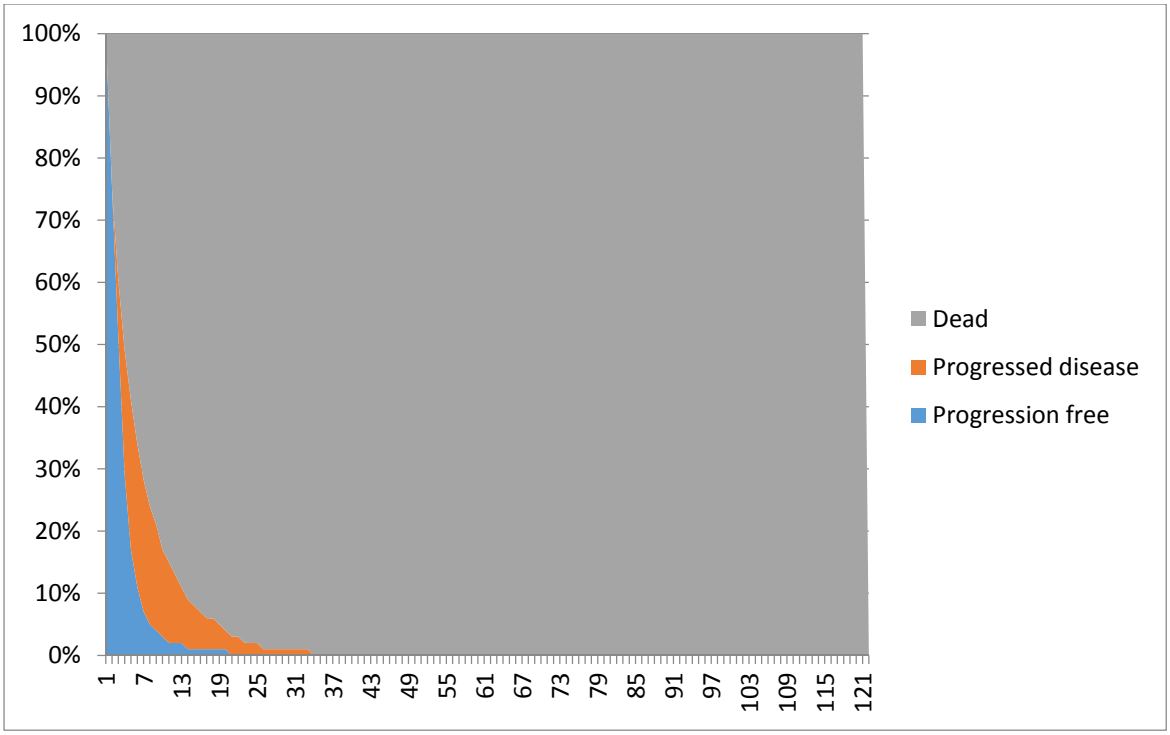


Figure 9: Markov trace, overall survival, BSC

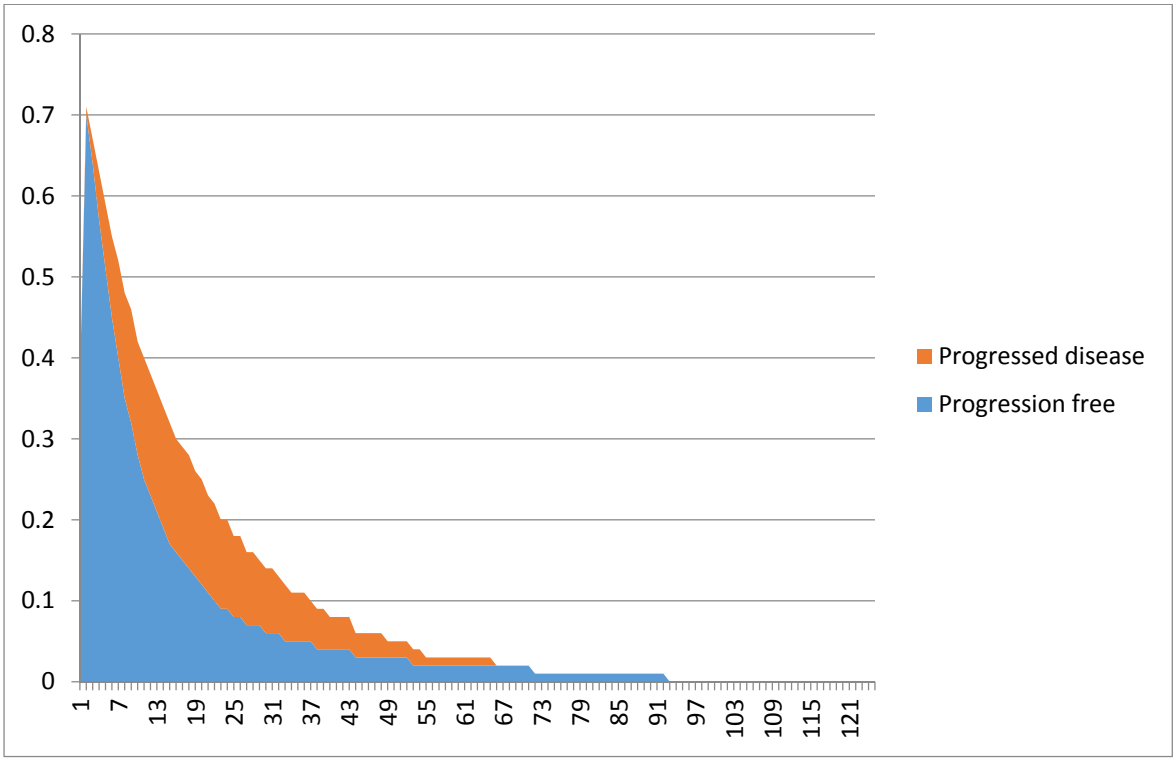


Figure 10: QALY accumulation trace, ceritinib

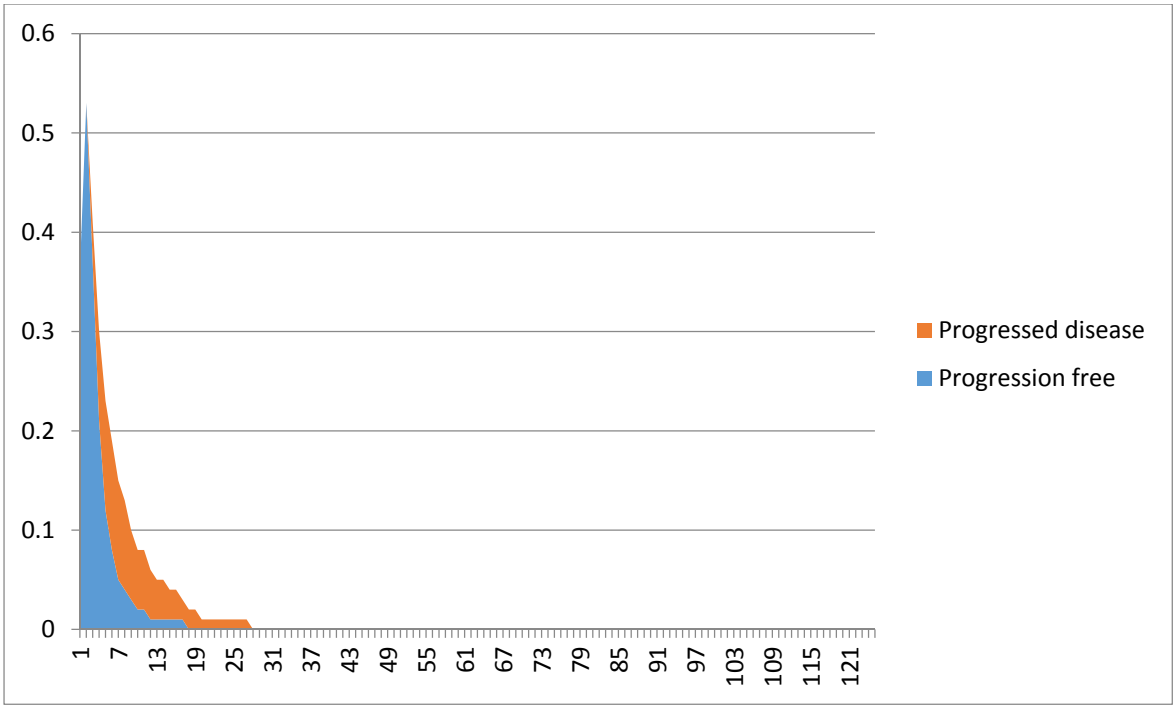


Figure 11: QALY accumulation trace, BSC

There were two discrepancies found between the models reported in the CS, and the copy of the model given to the ERG. The first, which has been mentioned previously, is the discrepancy in the method used to calculate PFS utilities, which the ERG has addressed by modifying the model so it is consistent with the method reported in the CS. The second is that the Kaplan-Meier data and survival curves presented in Figures 19 and 20 of the CS do not appear to match those produced by the model. However, the Company does report correct Kaplan-Meier data and curves in Appendix 15, so these are the curves the ERG has used when preparing this report. Other than these two issues, no discrepancies were found between the submission and the supplied model, nor were any found between the results reported and those produced by re-running analyses from the submitted model.

ERG summary:

- With the exception of the two issues highlighted above (utility values for the pre-progression state and Kaplan-Meier/survival curve plots presented in the submission), the model supplied by the Company matches that described in the submitted manuscript, and results derived from that model accurately match those reported in the manuscript. The discrepancy between PFS utility values was addressed by modifying the model to match the methodology reported in the submission.
- With the exception of the OS curve for BSC, the model results obtained are reasonable given the expected clinical progression of the disease, and have good agreement with comparable results taken directly from the study. The ERG addressed this issue by modifying the model

to use the better fitting log-normal survival cure for BSC OS, rather than the Weibull model selected by the Company.

5.3. Additional analyses undertaken by the ERG

The ERG has run a modified version of the Company's base case model, incorporating the following changes:

- The log-normal model was used for extrapolating OS for BSC, rather than the Weibull model in the original submission.
- Patients are assumed to receive ceritinib for an average of 1.6 months post progression, in line with data from the ASCEND studies, in contrast to the company base case where ceritinib treatment was considered to be discontinued at the moment of disease progression
- The full list of grade 3/4 drug-related adverse events is included in the ceritinib arm of the model, not just those which occur in ≥ 5% of patients.
- Costs, equivalent to two additional blood tests and two additional outpatient visits, were included for managing lab abnormalities, as opposed to the cost of £0 in the original model.
- Utilities for the PFS state are set to be the same in the ceritinib and BSC arms of the model (in line with the approach reported in the CS), and utilities for the BSC PFS state are then adjusted to account for the lower rates of adverse events with BSC compared to ceritinib.

Results, comparable to those reported in section 5.2.9 for the Company's base case model are given below.

Table 40: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	7,339	0.46	0.27				
Ceritinib	70,620	1.77	1.06	63,281	1.31	0.80	79,528

Results of the univariate sensitivity analyses undertaken on the ERG's preferred model are shown in a tornado plot in Figure 12, and the results of the scenario analyses are given in Table 41.

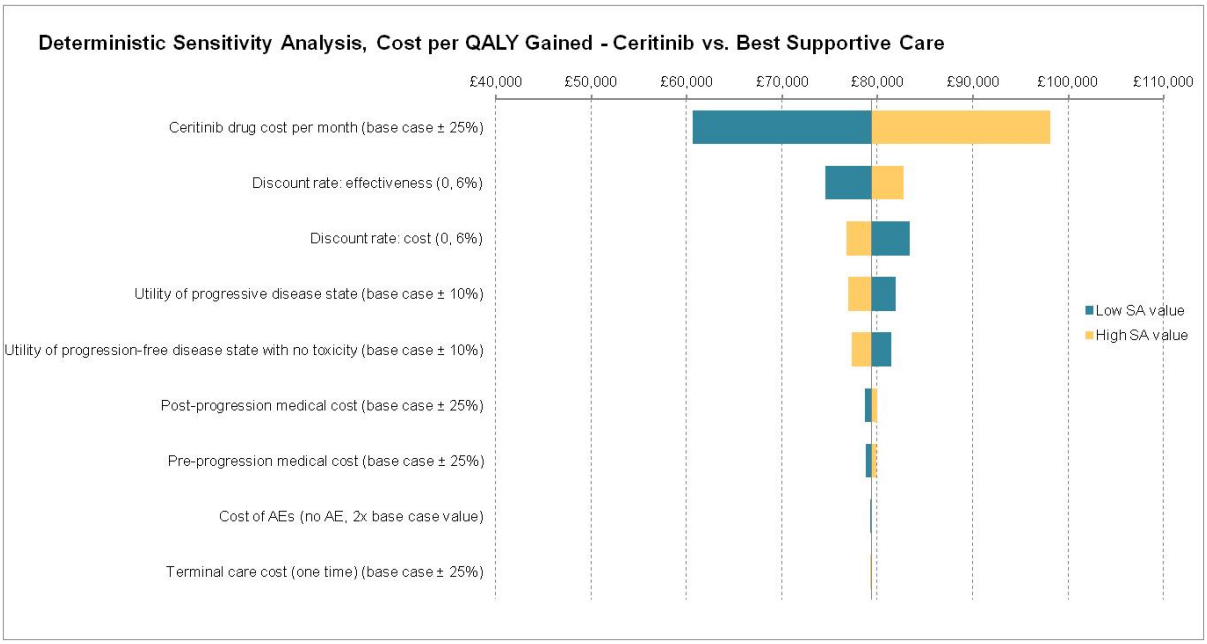


Figure 12: Deterministic sensitivity analyses for ceritinib vs. BSC

Table 41: Scenario Analyses – ceritinib vs. BSC

Parameter	Base case choice	Scenario analysis	ICER (£/QALY)	% change from base case ICER
Base case			79,528	
Use systemic therapy treatment following progression on crizotinib	No	Yes (assume 30% of patients receive docetaxel and 70% BSC)	82,755	+4%
Time horizon	10 years	5 years	79,468	-0%
		20 years	79,665	+0%
PFS function: ceritinib	log logistic	Exponential	74,331	-7%
		Weibull	72,075	-9%
		log-normal	79,673	+0%
		Gompertz	72,365	-9%
OS function: ceritinib	Weibull	Exponential	71,818	-10%
		Gompertz	87,648	+10%
		log-logistic	60,365	-24%

		log-normal	54,577	-31%
PFS for patients on BSC	Assume patients on BSC experience PFS	Assume no PFS for patients on BSC	76,645	-4%
Administration cost for oral chemotherapy	Not Included	Include cost for ceritinib administration until disease progression	84,792	+7%
Relative drug intensity - Ceritinib	As reported in the published trial (ASCEND-2)	Assumed to be 100% for ceritinib	95,091	+20%

The ERG also undertook an additional sensitivity analysis, looking at the impact on the ICER of reducing the duration of treatment benefit with ceritinib. The base case assumption is that the benefit of treatment persists for the entire time horizon of the model i.e. 10 years. An alternative assumption is to assume a certain duration of benefit, and then set risks of future transitions (progression and death) to be equal to those in the BSC arm from that point onwards. ICERs are presented for a range of possible durations of treatment benefit.

Table 42: Scenario Analyses – duration of treatment benefit

Duration of benefit	**ICER (£/QALY)**	**% change from base case ICER**
Lifetime (base case)	79,528	
9 years	79,547	+0%
8 years	79,573	+0%
7 years	79,626	+0%
6 years	79,748	+0%
5 years	80,312	+1%
4 years	82,067	+3%

3 years	86,718	+9%
2 years	99,703	+29%

ERG summary:

- The changes made by the ERG to the Company's base case assumptions increased the base case ICER for ceritinib versus BSC from £62,456 to £79,528.
- Uncertainty in the duration of treatment benefit do not appear to have a substantial impact on the ICER, provided the duration of treatment benefit with ceritinib is assumed to be at least 5 years.
- The model is not highly sensitive to any of the parameters in the probabilistic sensitivity analysis, meaning changes in these parameters are unlikely to have a substantial impact on the overall conclusion. However, there are many additional sources of uncertainty (e.g. the use of a naive indirect comparison of single arm studies) which are not captured in the probabilistic analysis.

5.4. Conclusions of the cost-effectiveness section

The CS is based around an economic analysis of ceritinib versus BSC, with key clinical evidence coming from 4 separate studies. Data on OS and PFS are based on the ASCEND-1 and ASCEND-2 studies, with the two data sets pooled together without any adjustment for baseline characteristics. OS and PFS with BSC are based, respectively, on a retrospective cohort study by Ou et al. (2014),[1] and the placebo arm of a trial in EGFR+ NSCLC by Shepherd et al. (2005).[2]

There are several important sources of uncertainty which were not quantitatively assessed in the CS. First, the use of single arm studies to inform key clinical parameters is a cause for some concern, as without randomised evidence on both treatments from within a single study, the data extracted are prone to many potential biases (e.g. selection bias). Where the use of single arm studies is unavoidable, due to the lack of any other data, it is important to adjust for differences in baseline characteristics between the included studies. However, since baseline data were not available for the specific subset of the Ou et al. (2014)[1] study relevant for this submission, no such adjustment was made/possible. Secondly, there are specific issues with the Ou et al. (2014)[1] and Shepherd et al. (2005)[24] studies, which make interpreting the data problematic. Ou et al. (2014)[1] was not randomised, meaning that patients were assigned to the different arms (BSC, systemic chemotherapy etc.) on the basis of clinician choice. This means that the BSC arm, which might be expected to contain the sickest individuals (i.e. those expected to gain least benefit from further treatment), could underestimate the expected OS for the relevant pre-treated ALK+ NSCLC population. The Shepherd et al. (2005)[24] study, meanwhile, was not conducted in ALK+ NSCLS, but rather in EGFR+ NSCLC,

and since no adjustment was made for differences between the populations, any difference in prognosis will lead to bias in the results produced.

Thirdly, the model contains an assumption that the benefits of treatment persist both after the time horizon of the study and post treatment discontinuation. No attempt is made to assess the impact of this assumption, which must be considered an optimistic one, and one which maximises the potential treatment benefit of ceritinib. An additional sensitivity analysis was conducted by the ERG, looking at the impact of varying this assumption.

In addition, there are a number of resource use parameters, specifically for disease management in the pre-progression and post-progression states, which are based not on data but clinical judgment. These are taken principally from previous NICE Technology Appraisals, and then updated to modern prices. Since, however, the main driver of differences in costs between the ceritinib and BSC arms is the drug costs associated with ceritinib itself, potentially inaccuracies in these resource use parameter estimates are unlikely to make a major difference to the overall result.

Finally, utility values for the PFS health state are based on EORTC data collected during ASCEND-2, and then mapped to the EQ-5D. Utility values for the post-progression state are taken from the literature, as no relevant data for this state were collected during either of the ASCEND studies. In the original model submitted by the Company different utilities are included, based on response status, and then weighted by the percentage of people who respond in each arm, giving a higher utility for the PFS state with ceritinib than BSC. Since this decision was not justified in the submission, the ERG modified the model to use the same base utility for the two treatments, with the utility for BSC then modified to account for the lower rate of adverse events expected in that arm. When interpreting the model results, it is important to consider the impact of these key sources of uncertainty in the ICER, and the impact that alternative assumptions would make.

5.5. Impact on the ICER of additional analyses undertaken by the ERG

Alterations to the base case assumptions made by the ERG increased the ICER for ceritinib versus BSC from £62,456 per QALY to £79,528 per QALY. This change was primarily driven by a change to the survival curve used to model OS with BSC, and the inclusion of the costs of ceritinib treatment for a period of time post disease progression. Results from the probabilistic sensitivity analysis indicate there is a 0% change of ceritinib being cost-effective at a willingness-to-pay threshold of £50,000 per QALY, a result consistent with that produced by the Company from the initial model submitted.

Key sources of uncertainty in these estimates, together with the current assumptions utilised in the model and the likely impact of varying those assumptions, are summarised in the table below (see Table 43). These additional uncertainties should be borne in mind when interpreting the ICERs given above.

Table 43: Key sources of uncertainty in ICERs

Parameter/model feature	Current assumption	Likely impact of varying assumption
Patient population	The population modelled is that from ASCEND-2 and a subgroup of ASCEND-1, which is assumed to be sufficiently similar to the UK CLL treatment population that results can be extrapolated to this group.	If the treatment benefit of ceritinib is less in the UK clinical population than in the ASCEND populations, ceritinib would become less cost-effective than it currently appears.
Naive indirect comparison of single-arm studies	Data from ASCEND-1 and ASCEND-2 are pooled, and are then directly compared to data from external single-arm studies, without any adjustment for differing baseline characteristics between the studies.	Unclear, but a failure to adjust for important baseline differences between data sources has the potential to lead to bias in the estimates of treatment efficacy.
PFS for BSC	Data on PFS with BSC are based on EGFR+ NSCLC, rather than ALK+ NSCLC	Any differences in prognosis between ALK+ and EGFR+ NSCLC will lead to potential biases in the estimate of PFS for the BSC arm of the model.
OS and PFS extrapolation over time.	Treatment benefit persists for the entire time horizon of the model (10 years in the base case).	Any reduction in the treatment benefit after progression or discontinuation will result in ceritinib becoming less cost-effective than it currently is (see Table 42)
Resource use frequency	Many items of resource use for	See Table 31

	the pre-progression and post-progression state were derived from estimates by clinicians, not data	
Treatment intensity with ceritinib	The same average proportion of prescribed ceritinib doses would be taken by patient in clinical practice as in the ASCEND studies.	If a different proportion of ceritinib doses were taken in real life, this could have a substantial impact on the ICER

With the exception of the assumption around treatment benefit, which clearly favours ceritinib in the base case, it is not clear which direction the ICER would be expected to change as a result of different potential assumptions that could be made within the model based on the above. However, there is considerable structural uncertainty around the estimates produced by this model because of the considerable number of such assumptions made.

6. END OF LIFE

The CS states that ceritinib fulfils the end-of-life criteria, providing a discussion of the NICE end-of-life criteria:

The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

One retrospective study[1] has been identified that presents survival estimates for ALK+ NSCLC patients receiving BSC following disease progression on crizotinib. This study is discussed in more detail in Section 4. Clinical advice to the ERG concurs with the CS that the life expectancy of patients post crizotinib, without any further active treatment, is shorter than 24 months.

There is sufficient evidence to indicate that the treatment offers an extension to life normally of at least an additional 3 months, compared with current NHS treatment.

The CS briefly presents details of the study results that are presented in full in the clinical effectiveness evidence, as discussed here in Section 4.5 Outcomes of overall survival and progression-free survival (PFS) from two single-arm cohort studies (interim data from ongoing studies) are presented and the pooled estimate of overall survival is [redacted] (95% Confidence Interval lower bound [redacted], upper bound [redacted]). The pooled estimate of PFS was [redacted]. The CS compares these with estimates of overall survival from the BSC study of patients post crizotinib and suggests there is an extension to life of approximately 10 months. As discussed in more detail in Section 4.5, the ERG agrees with these data, however, note that there is uncertainty owing to the comparison of these data from different studies because there is no comparator group in any study and therefore only a naïve indirect comparison can be made. The CS is aware of this as a limitation.

The CS also discusses a retrospective analysis of participants treated with crizotinib and ceritinib, the majority of which were included in the pivotal studies for ceritinib (CS, page 77). In particular the CS compares overall survival from a subgroup of the participants who reflect those defined in the decision problem (n=32, 44% of the total sample) with an overall survival estimate from a study of second-line crizotinib treatment (PROFILE 1007[29]). The CS states that results indicate an approximate 10 month extension to life with ceritinib. This is based on a naïve indirect comparison of the data (from observation of the data only) from these studies, one of which is a small sub-group from a retrospective study. The ERG also note caution in the interpretation of this comparison.

The treatment is licensed or otherwise indicated, for small patient populations.

The CS states that there are approximately 120 people eligible for treatment with ceritinib each year in England and Wales. This value is higher than presented in CS section 3.1.3 which provides estimates using two different approaches (as discussed above) which suggest either 66 or 98 patients. Despite this discrepancy, the ERG agrees that the patient population relevant under the decision problem would be small.

The CS also points out that ALK+ NSCLC tends to affect younger people, many who are of working age. The CS states that loss of productivity to society would be expected to be considerable, particularly owing to the frequency of brain metastases which are a common presentation in those with ALK+ NSCLC. The CS states that the benefits to productivity are not captured in the QALY estimates presented in their economic evaluation. The CS also makes reference to the impact on wider family and caring obligations, which they also state are not captured in the QALY calculation. Very little evidence for these factors are provided by the CS. The ERG discusses the age of the populations in the two pivotal studies of ceritinib in terms of generalisability to the UK population in Section 4.4.

7. OVERALL CONCLUSIONS

7.1. Clinical effectiveness evidence

The ERG consider that the evidence presented in the CS meets the decision problem. Overall, the presentation of evidence from two ongoing single-arm cohort studies is accurate, and the ERG consider the BIRC assessment of presented outcomes as the most reliable evidence. The key issue is the lack of comparator evidence, which means that it is difficult to ascertain what the true treatment benefit is. No formal indirect comparison can be undertaken on the data available, and comparison with evidence from a subgroup of a retrospective study can only be made through observation of the data. Therefore the evidence can only be interpreted with caution. Results of ongoing RCTs are required to be able to fully establish the treatment effect of ceritinib in those with ALK+ NSCLC who have progressed following crizotinib treatment.

7.2. Cost-effectiveness evidence

Judging both from the model submitted by the manufacturer and the ERG's modified model, which includes more conservative assumptions, ceritinib appears to provide long-term benefits over BSC, in the ASCEND study populations. This conclusion appears to be robust to all the parameter uncertainties that were included in the model. However, it is also associated with substantially higher costs (mainly due to the costs of ceritinib itself), and these increased costs are also consistent across the different model scenarios.

There are several difficulties in extrapolating the results from these analyses to the relevant decision problem in the UK. Specifically:

All the analyses included rely on the assumption that data from ASCEND-1, ASCEND 2, Ou et al. and Shepherd et al. can all be combined, without the need to make any adjustments for different patient or study characteristics, and with the assumption they all represent the appropriate treatment population for the relevant decision problem.

The treatments benefits of ceritinib on both overall and progression-free survival are both assumed to continue for the entire time horizon of the model, even though no long-term studies have been conducted in ceritinib to verify this assumption.

The presented results rely on clinical expert derived assumptions about treatment frequency, based on the whole NSCLC population, not the ALK+ subpopulation. In the absence of robust data to address these important uncertainties, it is difficult to provide robust estimates of the cost-effectiveness of ceritinib in the UK treatment population.

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