NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ceritinib for the treatment of ALK positive non-small cell lung cancer previously treated with crizotinib

Company evidence submission

File name	Version	Contains confidential information	Date
		Yes	12/06/2015

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List of abbreviations and definition of terms

AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BID	Twice daily
BIRC	Blinded independent central review committee
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
CBPD	Crizotinib beyond progressive disease
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CNS	Central nervous system
CrCL	Calculated creatinine clearance
CRD	Centre for Reviews and Dissemination
CRUK	Cancer Research UK
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
DAPF	Direct Access Plain Film
DARE	Database of Abstracts of Reviews of Effects
DBP	Diastolic blood pressure
DCIS	Ductal carcinoma in situ
DCR	Disease control rate
DFS	Disease free survival

DHFR	Dihydrofolate reductase
DOR	Duration of response
DVLA	Driver and Vehicle Licensing Agency
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluations Database
EGFR	Epidermal growth factor receptor
ELCC	European Lung Cancer Conference
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence review group
ESMO	European Society of Medical Oncology
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FISH	Fluorescence in situ hybridization
GBP	Great British Pound
GcSF	Granulocyte colony stimulating factor
GGT	Gamma-glutamyl transpeptidase
HEED	Health Economic Evaluations Database
HER	Human epidermal receptor
HIV	Human immunodeficiency virus
HORG	Hellenic oncology research group
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
JAK	Janus kinase
KFDA	Korean Food and Drug Administration
KRAS	Kirsten rat sarcoma viral oncogene homolog
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MTD	Maximum tolerated dose
NCBI	National Center for Biotechnology Information
NDS	New Drug Submission
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAIDS	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OIRR	Overall intracranial response rate
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression free survival
PIM	Promising Innovative Medicine
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year

QLQ	Quality of life questionnaire
RAS	Rat sarcoma
RCP	Royal College of Pathologists
RCT	Randomised controlled trial
RDE	Recommended dose for expansion
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SBP	Systolic blood pressure
SmPC	Summary of product characteristics
SOD	Sum of longest diameter
STA	Single technology appraisal
STAT	Signal Transducer and Activator of Transcription
TKI	Tyrosine kinase inhibitor
TTF	Time to treatment failure
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
UMVUE	Uniformly minimum variance unbiased estimate
USA	United States of America
VAT	Value-added tax
VATS	Video-assisted thoracic surgery
WCLC	World Conference on Lung Cancer
WHO	World Health Organisation

Executive summary

This submission presents the evidence for clinical effectiveness and cost-effectiveness of ceritinib for the treatment of advanced anaplastic lymphoma kinase-positive (ALK+) non-small cell lung carcinoma (NSCLC) previously treated with crizotinib. Consistent with the NICE scope for this appraisal, ceritinib is compared with the most relevant clinical comparator of best supportive care (BSC), representing no active treatment (Section 1.1).

Ceritinib is a highly selective and potent second-generation ALK inhibitor taken orally at a dose of 750 mg daily. Ceritinib has received a marketing authorisation in the European Union for the treatment of adult patients with ALK+ NSCLC previously treated with crizotinib. It is indicated for a patient population with very limited or no alternative treatment options and therefore considerable unmet medical need (Section 1.2). Its licence was granted through an accelerated approval process on the basis of efficacy and safety data presented by two uncontrolled trials, ASCEND-2 and ASCEND-1, which provide data on a total of 303 patients exactly matching the licensed indication and the indication stipulated in the decision problem.

This clinical evidence base supports good overall response rates (ORRs) that occur early and are well sustained. Treatment with ceritinib is observed to offer considerable survival benefits, with estimates for progression-free survival of [redacted] and overall survival of over [redacted] in this patient population (Section 1.3).

By contrast, the most relevant identified estimate of overall survival for patients receiving BSC (no active treatment) following progression on crizotinib is 2.2 months, suggesting an overall survival benefit with ceritinib of approximately 10 months (Section 1.3). Given the small size of the eligible population (approximately 120 patients), the poor prognosis on current BSC and the evidence for survival benefit with ceritinib, this therapy meets the end-of-life criteria.

Evidence for the cost-effectiveness of ceritinib versus BSC (no active treatment) is presented in the form of a cost-utility analysis based on a semi-markov decision analytic model, consistent with the methodology of previous economic evaluations in this disease area. In the base-case analysis ceritinib was found to be more costly (£59,155 vs. £7,203) but also more effective (1.08 QALY vs. 0.25 QALY) compared to BSC, resulting in an incremental cost per QALY of £62,456. The results of the sensitivity analyses found the model to be robust to changes in key parameters (Section 1.4).

Ultimately, ceritinib represents a novel, targeted treatment option for a patient population in desperate need of active therapies that have demonstrated significant clinical effectiveness in patients who have progressed on crizotinib. In addition, albeit not captured by the reference case, ceritinib provides a treatment option for patients who are generally young and of working age, and may help reduce productivity loss that results from ALK+ NSCLC. Funding ceritinib for the treatment of patients with ALK+ NSCLC who have progressed on crizotinib would therefore represent a valuable use of limited NHS resources.

1.1 *Statement of decision problem*

Table 1 outlines how the decision problem has been addressed in this submission.

Table 1: The decision problem

	Final scope issued by NICE(2)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with ALK positive non-small cell lung cancer previously treated with crizotinib	Adult patients with ALK positive non-small cell lung cancer previously treated with crizotinib	N/A
Intervention	Ceritinib	Ceritinib 750 mg once daily	N/A
Comparator (s)	Best supportive care (BSC)	Best supportive care (BSC)	N/A BSC is considered to mean that patients receive no active treatment but receive passive therapy aimed at symptom management and palliative care.
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 outcome measures presented in this submission include: - overall survival - progression-free survival - overall response rate - adverse effects of treatment - health-related quality of life (within cost-effectiveness section)	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	The cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year. The time horizon of the model is 10 years, which is sufficient for this patient population to reflect any differences in costs or outcomes between the	

	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	technologies being compared. Costs have been considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	None	None	N/A
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. The implications of additional testing requirements should be considered.	Clinical and economic evidence is submitted on the population covered by the marketing authorisation. No additional testing for ALK positivity has been considered.	No additional testing for ALK positivity would be required, as patients must have been tested prior to receiving crizotinib, the agent that must be used prior to ceritinib under ceritinib's marketing authorisation.

[a] Percentages are based on expert clinical opinion gathered through teleconference
Abbreviations: ALK, anaplastic lymphoma kinase; BSC, best supportive care; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence
Source: as indicated

1.2 *Description of the technology being appraised*

Ceritinib is an orally available, highly selective and potent second-generation ALK inhibitor. Ceritinib directly targets the ALK protein in an adenosine triphosphate (ATP)-competitive manner and acts as a tyrosine kinase inhibitor to inhibit autophosphorylation of ALK and ALK-mediated phosphorylation of downstream signaling proteins.(3) This results in inhibition of cell signaling that would otherwise promote cell proliferation and consequential development of tumours. Structural differences in the binding of ceritinib to ALK protein, and greater affinity and specificity, compared to the binding of the first-generation ALK inhibitor crizotinib to ALK protein appear to provide a basis for the greater potency and specificity of ceritinib observed in pre-clinical studies. Ceritinib has also shown efficacy on crizotinib resistant mutations in preclinical models and clinical trials.(4, 5)

Ceritinib represents a targeted treatment option for a patient population who has a considerable unmet medical need and meets the end-of-life criteria. Current treatment options for those patients with ALK+ NSCLC who have progressed on crizotinib are restricted to systemic chemotherapy followed by best supportive care, or best supportive care only. By providing a novel, active treatment option that has demonstrated efficacy in this specific patient population, ceritinib provides an innovative and suitable treatment option.

Table 2: Technology being appraised

UK approved name and brand name	Ceritinib (Zykadia®)
Marketing authorisation/CE mark status(6)	Ceritinib (Zykadia®) holds a marketing authorisation in the European Union for *the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.*
Indications and any restriction(s) as described in the summary of product characteristics(7)	Ceritinib is indicated only for the treatment population described above; that is for *the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.*
Method of administration and dosage(7)	Ceritinib (Zykadia®) is administered orally. Ceritinib is taken at a dose of 750 mg daily, consisting of 5 separate 150 mg capsules, taken at the same time.

Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer
Source: as indicated

1.3 *Summary of the clinical effectiveness analysis*

Ceritinib received a marketing authorisation from the European Medicines Agency (EMA) based on uncontrolled phase I and II data.(6) This accelerated approval demonstrates the enormous unmet clinical need in the population who have progressed whilst on crizotinib and that the single-arm trials showed unprecedented benefit of ceritinib compared to what would have been expected for patients if they had not received ceritinib.

Evidence of the clinical effectiveness of ceritinib in patients with ALK+ NSCLC previously treated with crizotinib for this submission is therefore provided by two, open-label, single-arm trials: ASCEND-2 (n=140) and ASCEND-1 (n=163 in the relevant patient subgroup) that evaluated the exact patient population under consideration in the decision problem.(5, 8)

The ASCEND-2 trial was a phase II trial that recruited patients (n=140) with ALK+ NSCLC previously treated with crizotinib in a number of centres globally, including 1 centre in the UK.(8) The ASCEND-1 trial was a phase I dose-escalation and expansion trial that recruited a broader population of NSCLC patients but included 163 patients with ALK+ NSCLC previously treated

with crizotinib.(5) These two trials therefore provide an evidence base for the clinical efficacy and safety of ceritinib in the precise patient population defined in the decision problem of the submission across a total of 303 patients.

Both of these trials considered overall response rate, defined as achieving either a complete response (CR) or partial response (PR) according to RECIST criteria, as a primary endpoint. In addition, the trials also evaluated progression-free survival and overall survival as secondary endpoints, amongst others. Assessment of response and progression-free survival was assessed by both Investigator assessment and Blinded Independent Review Committee (BIRC) Assessment.

Response: overall response rate (ORR), time to response (TTR) and duration of response (DOR)

- Patients demonstrated a good overall response rate (ORR) in both the ASCEND-2 and ASCEND-1 trials. Ceritinib demonstrated an ORR of 38.6% (95% CI: 30.5, 47.2) and 56.4% (95% CI: 48.5, 64.2) for ASCEND-2 (n=140) and ASCEND 1 (n=163), respectively, when considering the Investigator assessment (ie. the primary endpoints of the two trials).(9, 10)ORR was seen to be consistent when using the alternative BIRC assessment measure (secondary end points in both studies).

- Importantly, responses were found to occur early following treatment with ceritinib, with a median time to response (TTR) of 1.8 months (95% CI: 1.6, 5.6) in ASCEND-2, based on Investigator assessment.(9) Median time to response was also [redacted] using BIRC assessment.(11)

- Response to ceritinib was not only observed to occur relatively soon after treatment but was also well sustained. The median duration of response was 9.7 months (95% CI 7.1, 11.1) and 8.3 months (95% CI 6.8, 9.7) based on Investigator assessment for ASCEND-2 (n=54 patients with complete response [CR] or parital response [PR]) and ASCEND-1 (n=92 patients with complete response [CR] or partial response [PR]), respectively.(9)

Ceritinib provides clinically meaningful progression-free survival (PFS) and overall survival (OS) in a patient population for whom the current prognosis is poor

- The median PFS for patients who received ceritinib was 5.7 months (95% CI: 5.4, 7.6) in ASCEND-2 and 6.9 months (95% CI: 5.6, 8.7) in ASCEND-1.(9, 10)
    - A pooled analysis of ASCEND-2 and ASCEND-1 resulted in a median PFS of [redacted].

- The median overall survival (OS) for patients treated with ceritinib was 14.9 months (95% CI: 13.5, NE) in ASCEND-2 and 16.7 (95% CI: 14.8, NE) in ASCEND-1.(7, 9)
    - A pooled analysis of ASCEND-2 and ASCEND-1 resulted in a median OS of [redacted].

Comparative effectiveness: naïve indirect comparison

- A systematic literature designed to capture clinical evidence relevant to the population of ALK+ NSCLC patients previously treated with crizotinib identified only a single study providing efficacy data for the relevant comparator of BSC (no active treatment) in this population specifically. This study was a retrospective analysis that presented OS data for this patient population. (1)

- This study found median OS to be 2.2 months (95% CI: 1.1, 3.8) for patients who received BSC (no active treatment). For patients who received systemic chemotherapy followed by BSC (no active treatment), median OS was observed to be 5.4 months (95% CI: 3.8, 12.3).
    - The median OS across both these patient groups together was 3.9 months (95% CI: 2.7, 5.1).

- In comparison, the OS of ceritinib based on a pooled analysis of ASCEND-2 and ASCEND-1 was [redacted].

Safety

- Across both ASCEND-2 and ASCEND-1, ceritinib was associated with a low rate of AEs leading to discontinuation (7.9% and [redacted], respectively).(9, 11)

- The adverse event profile was consistent with that previously observed for ceritinib; the most commonly observed AEs were nausea, vomiting and diarrhoea, most of which occurred with grade 1 or grade 2 severity.

1.4 *Summary of the cost-effectiveness analysis*

To investigate the cost-effectiveness of ceritinib, a *de novo* model was developed using an "area under the curve" partitioned survival semi-Markov type analysis. The patient population modelled consists of patients with ALK+ advanced NSCLC previously treated with crizotinib, in line with the population defined in the NICE scope and the decision problem presented in this submission, as well as the marketing authorisation for ceritinib.

Three mutually exclusive health states were defined in the model: (i) progression free; (ii) progressed disease; and (iii) death. Patients enter the model after failure of prior crizotinib therapy. The cycle length adopted in the model corresponds to one month, with a half cycle correction applied at the beginning and end of the model cycles. A lifetime horizon of 10 years was adopted, with both costs and health outcomes (QALYs) discounted at an annual rate of 3.5%.

In the model, ceritinib is administered in the intervention arm and treatment is continued until disease progression. The base case comparator in this submission is BSC (no active treatment), and incremental outcomes (QALYs) and costs of ceritinib compared to this comparator are calculated as part of a cost-utility analysis. A number of scenario analyses are also conducted, including consideration of an alternative composite comparator for which 70% of patients are assumed to receive BSC (no active treatment) and 30% are assumed to receive active therapy (docetaxel) followed by BSC (no active treatment).

Clinical parameters

Clinical evidence on PFS and OS for ceritinib was sourced from ASCEND-2 and the subgroup of ASCEND-1 that matches the indication, and the data was pooled.

As both ASCEND-2 and ASCEND-1 are single-arm studies, a naïve indirect comparison is required to inform the cost-effectiveness analysis. Based on the findings of the clinical systematic literature review of studies relevant to the population of ALK+ NSCLC patients previously treated with crizotinib, no RCTs were identified to inform clinical inputs for the BSC (no active treatment) comparator. However, one retrospective study providing clinical efficacy data for the BSC (no active treatment) comparator was identified by this systematic literature review (Ou *et al.* 2014*)*. The retrospective analysis reported by Ou and colleagues, which considered a population of ALK+ NSCLC patients who have previously received crizotinib – a population that matches the decision problem of this submission – was used to inform OS for BSC in the model.[1] In order to address the limitations of a naïve indirect comparison, an extensive validation process was undertaken with a key oncologist based in the UK, who confirmed that the survival outcomes

experienced by patients receiving BSC in the Ou *et al.* study are likely to be experienced by any ALK+ NSCLC patient who does not receive active treatment. The Ou *et al.* study also provided OS estimates for patients receiving systemic chemotherapy (assumed to be docetaxel) followed by BSC for the scenario analysis exploring a composite comparator in which a proportion of patients receive active treatment (docetaxel) followed by BSC.

Given the lack of any appropriate studies providing PFS data for BSC (no active treatment) in the patient population relevant to this submission – that is patients with advanced ALK+ NSCLC previously treated with crizotinib – PFS for patients receiving BSC (no active treatment) was estimated using the Kaplan-Meier curve from the placebo arm in a phase III, randomised, double-blinded, placebo-controlled trial of erlotinib in NSCLC patients positive for the EGFR mutation.(12) The same source was used to inform the economic model for the PFS for patients receiving systemic chemotherapy (docetaxel) followed by BSC in the scenario analysis. Discussion with a leading oncologist in the treatment of ALK+ NSCLC patients in England and Wales confirmed that this is a reasonable approach.

PFS and OS data were incomplete and available survival data therefore required extrapolating in order to estimate PFS and OS benefits beyond observation. Extrapolation was based on parametric regression models in accordance with established criteria for extrapolating survival data. For each treatment arm, the use of a single regression curve was explored by fitting a variety of parametric curves to the OS data using exponential, Weibull, Gompertz, log-logistic, and log-normal functions. The best-fitting curves were selected based on multiple criteria including visual inspection, AIC/BIC, and internal and external validity, and the best-fitting curves were used as the base case survival models for the model.

Utility and cost parameters

Utilities for the cost-effectiveness evaluation in the base case were calculated by the use of mapping from the EORTC QLQ-C30 questionnaire to the EuroQoL EQ-5D for the progression free health state. For the progressive disease health state, utilities were based on Chouaid et al. (2013).(13)

When estimating monthly drug costs, the following costs were considered: unit drug costs, dosing, proportion of planned dose consumed, and drug administration costs. The base case input accounted for patients who may not take the full course of doses due to dose interruption or reduction associated with AEs, or non-compliance. The dose intensity for ceritinib ([redacted]) was based on the weighted average of the mean relative dose intesitises from the ASCEND-1 and ASCEND-2 trials.(11, 14) In the scenario analysis where 30% of patients are assumed to receive active therapy (docetaxel) for four cycles followed by BSC, the dose intensity for docetaxel was assumed to be 92.6% based on the PROFILE 1007 trial which compared crizotinib with intravenous chemotherapy (docetaxel or pemetrexed).(15)

Resource assumptions for routine medical management in the progression-free and post-progression disease states were derived from TA162 and TA258 and the unit costs from the PSSRU 2013-2014.(16, 17) For other types of resource use, unit costs were obtained from NHS reference costs 2013-2014.(18) The monthly frequencies of resource use were based on expert panel opinion reported in TA296.(19)

Adverse events (AEs) selected for inclusion in the model were grade 3/4 AEs affecting >5% of patients for any of the interventions in the analysis. Unit costs for AEs were obtained from NHS reference costs 2012-2013

Assumptions

The model assumes that the survival estimates from Ou *et al.* and Shepherd *et al.* are reflective of survival estimates on BSC (no active treatment) in the UK population of advanced ALK+ NSCLC patients previously treated with crizotinib. It also assumes that 10 years is a sufficient

length of time to capture all relevant costs and health outcomes and that adverse events only occur in the first month of treatment and last for 1 model cycle (one month).

Results

The base case results of the economic evaluation of ceritinib versus BSC (no active treatment are presented in Section 5.7. Ceritinib was found to be more costly (£59,155 vs. £7,203) but also more effective (1.08 QALY vs. 0.25 QALY) compared to BSC resulting in an incremental cost per QALY of £62,456. The results of the sensitivity analyses found the model to be robust to changes in key parameters.

Results for the scenario analysis in which a composite comparator was considered are also presented in Section 5.8.3.

Table 3: Cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)
BASE CASE							
BSC (no active treatment)	£7,203	0.42	0.25				
Ceritinib	£59,155	1.77	1.08	£51,952	1.35	0.83	£62,456 per QALY
SCENARIO							
30% on active therapy (docetaxel); 70% on BSC (no active treatment)	£8,564	0.50	0.29				
Ceritinib	£59,155	1.77	1.08	£50,591	1.27	0.79	£63,920 per QALY
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

Interpretation and conclusions of economic evidence

The results of this economic analysis demonstrate that the use of ceritinib in the treatment of adults with advanced ALK+ NSCLC previously treated with crizotinib not only considerably improves patients' quality of life (0.25 QALY for BSC vs 1.08 with ceritinib) but also prologs it (0.42 life years for BSC vs 1.77 life years for ceritinib) fulfilling end of life criteria and thereby providing valuable use of limited NHS resources.

The economic evaluation relies on very strong evidence and has many strengths which give confidence in the estimated modelled outputs for decision-making purposes. Firstly, effectiveness evidence (PFS and OS) for ceritinib was derived from large clinical trials designed specifically for advanced ALK-positive NSCLC with parametric survival curves used to extrapolate the data selected on the basis of a comprehensive assessment of goodness of fit, internal and external validations. Secondly the utility data for the progression free state was derived directly from the key ASCEND-2 trial using a mapping algorithm, thereby providing the

best source of QOL in this population. Finally, all model assumptions were validated and tested with clinical experts.

However, as with all economic evaluations, there are also has some weaknesses to the analysis presented in this submission. The main weakness of this analysis was the lack of an active-comparator RCT or efficacy data on comparators from a head-to-head study with ceritinib. The study by Ou *et al.* (2014) used to inform the naïve comparison in the cost-effectiveness model has limitations linked to the retrospective nature of the analysis. Another weakness, in common with TA296 and the modelling of crizotinib, was a lack of certainty around treatment duration for therapies used after progression with crizotinib, in terms of both trial-based data and clinical practice. Finally, the lack of trial-based utility values (for the progressive disease health state) as well as time-varying utility values generally, constrains the analysis to assuming generalisability of published data to the clinical trial data used, and to the UK general patient population. However, this is not uncommon in NICE appraisals of treatments in oncology.

Ceritinib is the only licensed treatment option for patients who progress on crizotinib. There are no other effective treatment options for these patients and ceritinib fulfills a significant unmet need in this setting. Ceritinib would represent a step-change in the current management of ALK+ NSCLC patients previously treated with crizotinib.

Ceritinib is an innovative targeted therapy and it was granted a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA).(20) A positive recommendation for ceritinib will provide patients and clinicians with a treatment option that is the only licensed targeted and effective therapy available in this setting.

2. The technology

2.1 *Description of the technology*

Brand name: Zykadia®

UK approved name: ceritinib

Therapeutic class: antineoplastic agent

Pharmacological class: tyrosine kinase inhibitor (TKI)

Mechanism of action:

Anaplastic lymphoma kinase positive non-small cell lung cancer (ALK+ NSCLC) patients possess an oncogenic variant of the ALK gene, most commonly as a result of a translocation between the gene for the ALK signalling protein and the gene for the EML4 signalling protein, though other fusion partners have been described.(21-24) This results in an EML4-ALK fusion protein that contains the N-terminal domain of the EML4 protein fused to the C-terminal protein kinase domain of ALK.(25)

The ALK protein is normally only activated by autophosphorylation resulting from dimerisation of the ALK protein upon ligand binding. The activated ALK protein in turn phosphorylates downstream signalling proteins involved in RAS and JAK/STAT signalling pathways, affecting cell growth and proliferation, decreasing cell apoptosis and promoting angiogenesis. In ALK+ NSCLC patients, the EML4-ALK fusion protein mediates ligand-independent dimerisation or oligomerisation of ALK, resulting in constitutive activity of the ALK tyrosine kinase.(26) This therefore appears to result in aberrant downstream signalling that can lead to over-proliferation of cells and development of tumours.

Ceritinib is an orally available, highly selective and potent second-generation ALK inhibitor. Ceritinib directly targets the ALK protein in an adenosine triphosphate (ATP)-competitive manner and acts as a tyrosine kinase inhibitor to inhibit autophosphorylation of ALK and ALK-mediated phosphorylation of downstream signalling proteins.(3) This results in inhibition of cell signaling that would otherwise promote cell proliferation and consequential development of tumours.

Structural differences in the binding of ceritinib to ALK protein, and greater affinity and specificity, compared to the binding of the first-generation ALK inhibitor crizotinib to ALK protein appear to provide a basis for the greater potency and specificity of ceritinib observed in pre-clinical studies. Ceritinib has also shown efficacy on crizotinib resistant mutations in preclinical models and clinical trials.(4, 5)

2.2 *Marketing authorisation/CE marking and health technology assessment*

European marketing authorisation

Ceritinib (Zykadia®) received marketing authorisation on 6th May 2015, for *the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.*

The Summary of Product Characteristics (SmPC) can be found in **Error! Reference source not found.**.

Anticipated launch date (UK)

The anticipated launch date of ceritinib is July 2015.

Non-EU regulatory approval

Ceritinib has been approved by the Food and Drug Administration (FDA) in the United States of America (USA) for the treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) who have progressed on, or are intolerant to, crizotinib. This indication was approved under the accelerated approval programme of the FDA based on tumour response rate and duration of response. Approval was granted on 29th April 2014.

In addition, ceritinib has been approved in the following jurisdictions:

- **Canada:** Therapeutic Product Directorate of Health Canada has approved the ceritinib New Drug Submission (NDS) under Notice of Compliance with Conditions (accelerated approval). The approved indication is as monotherapy for use in patients with ALK positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on, or who were intolerant to, crizotinib. The approved recommended dose is 750 mg taken orally once daily.

- **South Korea:** the Korean Food and Drug Administration (KFDA) approved ceritinib in January 2015 for the treatment of patients with ALK positive locally advanced or metastatic NSCLC who have received prior treatment with crizotinib.

- **Mexico:** the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) approved ceritinib in February 2015 for locally advanced or metastatic NSCLC that is ALK positive.

- **Ecuador**

- **Chile**

Health technology assessment

Ceritinib is not currently subject to any other heath technology assessment in the UK. It is anticipated that ceritinib will be submitted for assessment by the Scottish Medicines Consortium in Q3 2015.

2.3 *Administration and costs of the technology*

Table 4: Costs of the technology being appraised

	Cost
Pharmaceutical formulation	Ceritinib 150 mg hard capsules
Acquisition cost (excluding VAT) *	The list price is £4,923.45 for a 30 day supply, and is the price agreed with the Department of Health for 3 packs of 50 capsules each. This equates to a price of £0.22 per mg of ceritinib.
Method of administration	Oral, swallowed whole with water and on an empty stomach
Doses	750 mg
Dosing frequency	750 mg taken orally once daily at the same time each day As ceritinib is supplied in 150 mg capsules this corresponds to 5 capsules

	per day, taken at the same time.
Average length of a course of treatment	The summary of product characteristics states that treatment should continue for as long as benefit is observed. It also notes that treatment should be discontinued if dose reductions to 300 mg are still not tolerated. Based on this, the estimated average length of a course of treatment is taken as the median progression-free survival (PFS) observed in the clinical trials of ceritinib in the relevant patient population. Pooled median PFS across ASCEND-2 and the relevant population of ASCEND-1 was [redacted] (latest available data cut-offs: see Section 4.11.11).
Average cost of a course of treatment	Based on a median PFS of [redacted] and a monthly treatment cost of £4,995.25, the predicted average cost of a course of treatment is [redacted]. However, this figure may likely be lower given that reduced dose intensities were used across the two clinical trials of ceritinib in this indication.
Anticipated average interval between courses of treatments	Ceritinib should be used continuously unless temporary dose interruptions are required based on individual safety and tolerability. There is no anticipated interval between treatment courses.
Anticipated number of repeat courses of treatments	N/A – as above, ceritinib is anticipated to be administered continuously
Dose adjustments	Temporary dose interruption and/or dose reduction may be required based on individual patient safety and tolerability. If dose reduction is required due to an adverse drug reaction then this should be achieved by decrements of 150 mg daily. Approximately 54% of patients initiating treatment at 750 mg daily required at least one dose adjustment due to adverse reactions, with median time to first dose reduction of approximately 7 weeks. Full details of recommendations for dose interruption, reduction or discontinuation can be found in the Summary of Product Characteristics.
Anticipated care setting	Ceritinib treatment should be initiated and supervised by an experienced physician. It is anticipated that ceritinib treatment would be taken in the home care setting on a daily basis and managed in a secondary care outpatient setting.

Abbreviations: N/A, not applicable; PAS, patient access scheme; PFS, progression-free survival
Source: Summary of Product Characteristics(7), unless indicated otherwise

2.4 *Changes in service provision and management*

The indication under consideration in this submission is the treatment of adult patients with ALK positive (ALK+) advanced NSCLC previously treated with crizotinib. The patient population under consideration therefore represents a molecular subtype of the broader NSCLC patient population, and represents a later line of therapy.

Identification of the specific ALK+ patient population requires genetic testing to diagnose the ALK translocation. However, as described above, ceritinib is licensed only for use in patients previously treated with crizotinib. Diagnosis of the ALK+ genotype will therefore have already been performed on the patients eligible for treatment with ceritinib under the terms of this licence,

as this molecular subtyping is required in order to commence treatment with crizotinib. The current service provision for molecular subtyping in NSCLC is described in Section 3.1.4. There is no evidence that re-testing is required when moving from one ALK inhibitor to another. As such, introduction of ceritinib is not expected to result in any changes in service provision and management with regards to identification of the eligible patient population.

The main use of NHS resources associated with ceritinib is the requirement for regular physician visits in the hospital outpatient setting in order to continually monitor treatment outcomes. The SmPC for ceritinib recommends that patients are monitored with liver laboratory tests (including alanine transaminase (ALT), aspartate aminotransferase (AST) and total bilirubin) prior to the start of treatment, every 2 weeks for the first month of treatment and monthly thereafter. In addition, the SmPC recommends monitoring for fasting plasma glucose prior to the start of treatment and periodically thereafter as clinically indicated, and monitoring for pulmonary symptoms indicative of pneumonitis.

Currently, patients with advanced ALK+ NSCLC previously treated with crizotinib are expected to receive BSC (no active treatment). A full discussion of current treatment pathways is provided in Section 3.2. In current practice, patients in a progressive state of disease and receiving BSC are associated with costs and resource requirements related to medical management such as GP and outpatient visits, complete blood cell counts, serum chemistry, CT scans and X-rays, and palliative care. As such, the only additional monitoring requirements of note with the introduction of ceritinib are believed to be those relating to a requirement for liver laboratory tests, as described above. In addition, there is an expected increase in monitoring requirements for ceritinib compared to BSC resulting from the improved survival estimates for patients receiving ceritinib compared to those receiving BSC (see Section 4.13), thereby increasing the length of time for which patients require ongoing monitoring.

The additional liver function test monitoring requirements represent a pathology service already offered routinely on the NHS and are therefore not expected to be associated with any requirements for changes to the infrastructure of the NHS. The main resource use requirement of the NHS for treatment with ceritinib is staff time associated with the monitoring requirements.

As a scenario analysis within this submission, a composite comparator is considered in which a proportion of patients with advanced ALK+ NSCLC previously treated with crizotinib might be treated with active therapy (docetaxel) prior to BSC; please see Section 3.2 for a full discussion. For these patients, there will be an associated requirement for intravenous administration of systemic chemotherapy in a hospital setting. In contrast, ceritinib is an oral treatment that can therefore be self-administered by the patient in their own home. Introduction of orally administered ceritinib would therefore be expected to alleviate any current NHS resource burden of administering intravenous systemic chemotherapy in the hospital setting for patients eligible for ceritinib that might currently receive active treatment with docetaxel prior to BSC.

Ceritinib is not associated with any requirements for concomitant therapies and there are no particular therapies required to manage adverse reactions beyond normal standard of care. The SmPC of ceritinib provides details for the treatment and monitoring of adverse events based on evaluation of ceritinib across four clinical trials.(7) A summary of these details is provided below (please see Section 4.14 for full details of the safety profile of ceritinib):

- Gastro-intestinal events across four clinical studies of ceritinib were managed primarily with concomitant medicinal products including anti-emetic/anti-diarrhoeal medicines (ie. standards of care).

- Liver laboratory tests including ALT, AST and total bilirubin should be performed prior to treatment initiation, every 2 weeks for the first month and monthly thereafter (with more frequent testing if grade 2, 3 or 4 elevations are observed) in order to monitor for hepatotoxicity. It should be noted that events of hepatotoxicity were uncommon across the ceritinib clinical trials and that

events of grade 3 or grade 4 ALT elevations were manageable with dose interruption and/or dose reductions in the majority of cases.

- In addition, monitoring of fasting serum glucose is required prior to the start of ceritinib treatment and periodically thereafter as clinically indicated. Where indicated, anti-hyperglycaemic medicinal products may be administered or optimised.

Finally, clinician feedback suggests that adjuvant radiotherapy may be used for patients who progress on crizotinib. Where clinicians make use of this therapy, this would be performed regardless of whether the patient is being treated with ceritinib and hence does not constitute a concomitant medication requirement for the use of ceritinib and does not have any impact on the evaluation of the cost-effectiveness of ceritinib.

2.5 *Innovation*

Ceritinib presents a highly innovative treatment option with the potential to provide a number of health-related benefits that are not captured in the quality-adjusted life year (QALY) calculation presented in Section 5.1. The innovative nature of ceritinib has been recognised with the granting of a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA) for the treatment of adult patients with previously treated ALK+ NSCLC (a broader population than the current licence and the decision problem in this submission).(20)

Step-change in the management of ALK+ NSCLC patients previously treated with crizotinib

The introduction of ceritinib would represent a step-change in the current management of ALK+ NSCLC patients previously treated with crizotinib. This patient group represents a population with considerable unmet need, for which limited treatment options are available. These patients are highly likely to have been previously treated with either docetaxel, pemetrexed or both prior to initiation on crizotinib under the recommendations of current NICE clinical guideline 121 for lung cancer, with poor treatment outcomes on these therapies necessitating progression to a first-generation ALK inhibitor.(27) Response to crizotinib in this second line setting typically lasts for approximately 32 weeks (8 months), as measured by duration of response, and about one-third of patients with ALK+ NSCLC do not respond to crizotinib at all.(28) For these patients who progress on crizotinib, current treatment options are restricted to BSC, as defined by the NICE scope, in which patients receive no active treatment. Some patients who are considered fit enough might receive active therapy (docetaxel) prior to BSC, though it should be noted that many of these patients will have already been treated with this chemotherapy prior to treatment with an ALK+ inhibitor. Patients receiving BSC (no active treatment) after progression on crizotinib are associated with a very poor prognosis of approximately 2.2 months.(1)

Ceritinib would represent a step-change in the management of this condition by providing a treatment option that has demonstrated clinical benefits in terms of extension to life of approximately [redacted] for patients who progress on crizotinib (see below).(5, 11) Ceritinib would provide a novel, active treatment option for patients whose current options are limited to a passive treatment modality of BSC.

In addition, clinical expert opinion supports that ceritinib would also allow a sustainable and significant period of progression-free survival following disease progression on crizotinib. This is a result that has not been witnessed in the treatment of EGFR-positive patients, as once they experience disease progression on a given treatment, then patients do not normally experience a durable period of PFS on a different drug.

Ceritinib fulfils the end-of-life criteria

Given the information above, ceritinib fulfils the end of life criteria:

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

The only identified study presenting survival estimates for ALK+ NSCLC patients receiving BSC (no active treatment) following progression of disease on crizotinib has reported an estimate of median OS from the time of disease progression of only 2.2 months.(1) This indicates that the relevant patient population has a life expectancy under current clinical practice that is considerably below the 24 months stipulated under the end-of-life criteria. In this published study, some patients also received systemic chemotherapy prior to BSC, but the pooled estimate of OS when including these patients was still only 3.9 months. Even when considering OS estimates from this study that come from treatment strategies that do not reflect UK clinical practice or the decision problem as defined by the NICE scope (see Section 3.2), the estimates are well below the 24 months stipulated by the end-of-life criteria (5.4 months when considering only the group of patients treated with systemic chemotherapy followed by BSC; 8.9 months when considering the entire patient cohort, which includes patients who continued on crizotinib following disease progression).(1) Furthermore, the survival estimates from this study are based on a population of patients who have initially responded to crizotinib; within its licensed indication ceritinib is also eligible to be used in patients who have received crizotinib but have never experienced a response to this therapy, and who would be expected to have even shorter overall survival estimates.

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

Ceritinib has demonstrated median survival estimates of considerably greater than 3 months in patients with ALK+ NSCLC previously treated with crizotinib.

In a phase II clinical trial (ASCEND-2), median overall survival (OS) amongst 140 patients treated with ceritinib was 14.9 months (95% CI: 13.5, NE) and median progression-free survival (PFS) was 5.7 months (95% CI: 5.4, 7.6.(9) Survival estimates were similar in a phase I trial of ceritinib (ASCEND-1) in which 163 patients treated with ceritinib experienced a median OS of 16.7 months (95% CI: 14.8, NE) and median PFS of 6.9 months (95% CI: 5.6, 8.7).(10, 14) The pooled estimate of median OS across the ASCEND-2 and ASCEND-1 clinical trials was [redacted]; the pooled estimate of median PFS was [redacted].

When compared to an estimated median overall survival for treatment with BSC (no active treatment) of approximately 2.2 months (with an estimate of 3.9 months when also considering the use of systemic therapy), these results suggest that ceritinib offers an **extension to overall survival of approximately 10 months.(1)**

A published retrospective analysis of 73 patients treated with sequential crizotinib and ceritinib found that median combined PFS for sequential treatment was 17.4 months (95% CI: 15.5 – 19.4) and that the median PFS for patients treated with ceritinib in the post-crizotinib setting was 7.8 months (95% CI: 6.5 – 9.1).(29) A subgroup of patients in this study (n=32; 44%) received their crizotinib treatment in a second-line setting and this therefore represents a similar patient population to the PROFILE 1007 study of crizotinib. The combined median OS from the time of crizotinib initiation for sequential treatment with crizotinib and ceritinib for this patient subgroup was 30.3 months.

Given that median overall survival in the PROFILE 1007 study was 20.3 months, this indicates an approximate **10 month extension to life** for the post-crizotinib population when treated with ceritinib.(30)

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

There are expected to be approximately 120 patients eligible for ceritinib treatment each year in England and Wales (see Table 5), which represents a very small patient population.

Potency

Enzymatic and cell-based assays have demonstrated that ceritinib has a higher potency and greater specificity for the binding and inhibition of the ALK protein compared to crizotinib.

Ceritinib has demonstrated a 20 times greater target affinity for ALK than crizotinib in enzymatic assays (IC50 of 0.15 nM for ceritinib and 3 nM for crizotinib for ALK).(28, 31) In addition, the co-crystal structure of ceritinib bound to ALK appears to provide a structural basis for the effective inhibition of ALK in patients with crizotinib-resistant mutations, such as L1196M, G1269A, I1171T and S1206Y. (4)

Ceritinib therefore provides a treatment option in ALK+ NSCLC that provides a more potent therapy than previously received crizotinib. This extends the armamentarium available to physicians for treating a condition that is intrinsically linked to the activity of specific cellular signalling components, and introduces a treatment option with proven efficacy in ALK+ NSCLC patients previously treated with crizotinib but who harbour mutations conferring resistance to crizotinib therapy.

Recognition of the innovative nature of ceritinib by the MHRA

The innovative nature of ceritinib has been formally recognised through the granting of a PIM designation by the MHRA on 10th February 2015 for the treatment of adult patients with previously treated ALK+ NSCLC.(20)

This PIM designation highlights that the innovative nature of ceritinib has been formally recognised by a regulatory body. The PIM designation is part of the Early Access to Medicines scheme, which aims to grant earlier access to innovative treatments for patients with life-threatening and seriously debilitating conditions, and have an unmet need.

ALK+ NSCLC affects a younger population, many of whom are of working age

NSCLC patients with the ALK translocation tend to be younger in comparison to patients with non-ALK forms of NSCLC, with 255 patients in the crizotinib trials having a median age of 52 years.(26) Median age in the ASCEND-1 and ASCEND-2 trials of ceritinib was similarly 52 and 51 years, respectively.(5, 8) Therefore, many patients in the population under consideration in this submission would be expected to be of working age. A study of cancer in Europe found lung cancer to have the highest productivity losses among all cancers in 2009.(32) In addition, patients with brain metastases, which are a common presentation upon diagnosis of ALK+ NSCLC (see Section 3.1.6), have been shown to miss significantly more days of work and be associated with substantial productivity loss-related costs, albeit in a US study.(33) The detrimental impact of ALK+ NSCLC on societal productivity would therefore be expected to be considerable as a result of the lower average age of patients diagnosed with ALK+ NSCLC compared to lung cancer generally, and the frequency of brain metastases (see Section 3.1.2).

By improving lung symptoms, maintaining health-related quality of life (HRQoL) and providing positive outcomes for patients with brain metastases (see Section 4), ceritinib may help to reduce productivity loss that results from ALK+ NSCLC. This benefit is not captured in the QALY calculation presented in Section 5.1 and should be carefully considered.

Additionally, as NSCLC patients with the ALK translocation tend to be younger in comparison to patients with non-ALK forms of NSCLC, they are likely to have family and caring obligations and so their disease would therefore be expected have a considerable impact on family and dependents. This benefit is not captured in the QALY calculation presented in Section 5.1 and should also be carefully considered.

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

3.1 *Disease background*

3.1.1 Non-Small Cell Lung Cancer

The predominant cause of lung cancer is smoking, but lung cancer can also develop in people who have never smoked.(34) Lung cancer is the second most prevalent cancer type in the UK after breast cancer, with 34,269 cases diagnosed and referred to secondary care in England and Wales in 2013.(35) Of these cases, 3,704 were confirmed as having SCLC and 20,409 patients (59.6%) were confirmed as having NSCLC.(35)

NSCLC can be further sub-divided into three subtypes based on histology (squamous cell carcinoma, adenocarcinoma and large cell undifferentiated carcinoma).(36) NSCLC is also classified by stage; “advanced” disease usually refers to Stage IIIb/IV cancer, where the cancer has spread either locally to surrounding tissue or to distant regions of the body.

Disease progression is an important, but poorly defined clinical feature, which impacts upon overall survival, symptom burden, and treatment decisions.(37, 38) Progression is not rigorously defined in clinical practice, but in clinical trials the Response evaluation criteria in solid tumors (RECIST) provide a consistent tool for defining disease progression. Under the RECIST guidelines, NSCLC is classed as having “progressed”, when:(39)

- There is at least a 20% proportional increase and an absolute increase of at least 5 mm in the sum of diameters of target lesions, taking as reference the smallest sum on study, or
- There is the appearance of one or more new lesions

Disease progression is often a sign that the disease is not being adequately controlled on current therapy and therefore is often the point at which patients switch to a new treatment to try to regain control of their disease.

3.1.2 ALK+ molecular subtype of NSCLC

ALK was found to be an oncogenic driver of NSCLC in 2007, when it was found that people with a rearrangement of their ALK gene were more likely to develop NSCLC.(21) ALK is a receptor tyrosine kinase, which belongs to the insulin receptor superfamily, and is usually expressed in brain cells where it plays an important role in the development of the brain.(40) When the gene for ALK is rearranged in other cells in the body, fusion proteins can be formed and ALK-containing proteins are over-expressed in these cells.(40) Approximately 5% of stage IIIb/IV NSCLC cancer patients are ALK+.(41)

It has been observed that ALK+ patients are far more likely than ALK-negative NSCLC patients to never have smoked (or only smoked lightly), be of a younger age and have adenocarcinoma histology.(42-44) However, not all ALK+ patients will conform to these characteristics and therefore genetic characterisation of all NSCLC tumours with non-squamous histology is required.(45)

ALK-positivity also tends to be exclusive of other genetic mutations, so a single patient is unlikely to present with both ALK and EGFR mutations.(2, 46, 47) ALK+ tumours are also strongly associated with resistance to EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib.(42) Patients diagnosed with an EGFR mutation therefore represent a separate molecular subtype of NSCLC and are not relevant to this submission.

3.1.3 Estimation of the number of patients eligible for ceritinib treatment in England and Wales

The patient population in which ceritinib is licensed and considered in this submission is adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. As such, in order to be eligible for treatment with ceritinib, patients must have previously received treatment with crizotinib.

Second-line crizotinib treatment is funded by the CDF in England and there is no funding source in Wales, where crizotinib is available only through individual patient requests. We can assume that only around 2 patients in Wales are currently receiving crizotinib, and the number of new patients receiving crizotinib in England in a given year can be approximated as the number of notifications received by the CDF for crizotinib for that year. This data is available for the most recent financial year covering the period from April 2014 to March 2015. During this period there were 111 notifications to the CDF for crizotinib in 2014. As such in any given year we can assume that a total of 113 patients would be receiving crizotinib in England and Wales.

In order to estimate the patients that would be eligible for treatment with ceritinib, we have to consider those that have progressed on 2nd-line crizotinib treatment. In the PROFILE 1007 study of crizotinib, median progression-free survival on crizotinib was 7.7 months. The survival probability at this time point was 84%. Therefore in total 95 patients would be expected to survive following progression while on 2nd-line crizotinib treatment and of these it is anticipated that only 70% will be eligible for treatment with ceritinib based on feedback received from the clinical experts consulted (with the other 30% most likely treated with Best Supportive Care due to their poor prognosis). As such the total number of patients that would be receiving treatment with ceritinib in any given year in England and Wales was estimated at 66. Please see Table 5 for an outline of how the total population of patients eligible for ceritinib in England and Wales was calculated.

Table 5. Estimation of the number of patients eligible for ceritinib treatment in England and Wales

Population description	Estimated incident population in any given year	Assumption
Total patients receiving crizotinib	113	Based on CDF notifications for crizotinib covering the period from April 2014 to March 2015 and patients currently receiving crizotinib in Wales
Total patients progressed on crizotinib and still alive	95	84% of patients on crizotinib would be alive at progression and therefore be eligible for ceritinib. This is based on the survival probability at 7.7 months in the crizotinib arm of the PROFILE 1007 trial; 7.7 months was the median progression free survival on crizotinib.(28)
Patients eligible for treatment with ceritinib	66	Due to poor prognosis following progression on crizotinib it is estimated that only 70% of patients would be eligible for treatment with ceritinib

An alternative approach to calculating the eligible ALK+ NSCLC population was considered based on assumptions used previously in the TA296 submission for crizotinib. This derivation, resulting in an eligible patient population of 98 patients, has been presented **Error! Reference source not found.**.

3.1.4 Testing for ALK-positivity

The introduction of ceritinib following crizotinib will not require any additional testing to occur, as ALK-positivity must have already been ascertained prior to starting crizotinib. There is no

evidence that re-testing is required when moving from one ALK inhibitor to another. The Royal College of Pathologists (RCP) provides a suggested tissue pathway for NSCLC that encompasses testing for ALK positivity.(48) The RCP recommends that this mutation should be tested for via immunohistochemistry (IHC) followed by fluorescence *in situ* hybridisation (FISH) in NSCLC patients with evidence of adenocarcinoma or "not otherwise specified" NSCLC. In addition, ALK testing should be considered for NSCLC patients with evidence of squamous cell carcinoma or neuroendocrine differentiation if the patient is <50 years of age, a never/light smoker and/or their sample has signet ring morphology.

3.1.5 Prognosis and underlying course of ALK+ NSCLC

Delays in lung cancer diagnosis are a common problem that often results in diagnosis occurring in the latter stages of the disease. Common reasons include a low index of disease suspicion, which may be more prevalent in the ALK+ population due the relatively young patient population and tendency to be non-smokers.(42-44), (49) Late diagnosis at an advanced stage often leads to poor prognosis.(50) Cancer Research UK estimates that for patients with stage IIIb NSCLC the 5 year survival rate is 7-9% and that for patients with stage IV NSCLC the 5 year survival rate ranges between 2% and 13%.(50) Although it may seem illogical for the stage IIIb cancers to have a lower 5 year survival than some stage IV cancers, this is due to the fact that the staging looks only at the extent of the cancer, not at how fast the individual lesions grow or how well they respond to treatment.

Patients with ALK+ NSCLC have poor survival outcomes, with prognoses similar to, or possibly worse than, those of ALK-negative patients. ALK-positivity is therefore not a favourable prognostic factor in NSCLC. A study by Yang and colleagues of 300 adenocarcinoma NSCLC patients showed that the risk of experiencing lung cancer progression or recurrence within 5 years after diagnosis was more than two-fold greater in ALK+ patients compared to ALK-negative patients.(51)

Crizotinib represented the first licensed therapy specifically targeting the ALK fusion protein in ALK+ NSCLC and has demonstrated improvements to the prognosis of ALK+ NSCLC patients compared to chemotherapy.(30) However, approximately one-third of patients with ALK+ NSCLC fail to respond to crizotinib therapy and all crizotinib-treated patients will inevitably progress with a median OS less than 2 years in patients previously treated with chemotherapy.(28, 31)

In patients experiencing progression of disease on crizotinib, one study has reported that median overall survival from the time of disease progression was only 2.2 months for the patients who stopped crizotinib at progression and went on to receive BSC (no active treatment).(1) This is the most relevant available estimate for the final NICE scope and decision problem of this submission and for reflecting the current prognosis for the patient population that would be expected to be treated with ceritinib.

3.1.6 Clinical and economic burden of the disease

In addition to the poor survival outcomes associated with ALK+ NSCLC, the condition is also associated with a high symptomatic burden. Common symptoms reported among patients with NSCLC generally (not restricted to the ALK+ molecular subtype) include fatigue, lack of appetite and disease-related chest symptoms (cough, shortness of breath, pain, blood in sputum).(52-55) In addition to this physical burden, patients with NSCLC may suffer from psychological distress including worry/anxiety over their condition and depression.(52)

Diagnosis of ALK+ NSCLC is often late and upon initial diagnosis patients may often present with symptoms of bone metastatic disease, such as bone pain or fractures, in addition to their pulmonary symptoms.(51, 53) Furthermore, the brain is one of the most common sites of metastasis in ALK+ NSCLC patients and recent studies have reported that 30% – 50% of patients have brain metastasis at initial diagnosis of ALK+ disease and in one retrospective study

an additional 20% of patients developed brain metastases.(26, 56, 57) The symptomatic burden of brain metastasis consists of both constitutional symptoms such as fatigue, dyspnea, nausea, vomiting, headaches, seizures, pain and numbness and specific (focal) neurological symptoms that depend on the precise location of the tumour and may include alterations to sensation, motor weakness, visual disturbance and speech difficulties.(53, 58) In addition, it is a legal requirement in the UK to report diagnosis of brain metastases to the Driver and Vehicle Licensing Agency (DVLA) for consideration of suspension or withdrawal of a licence; this highlights the burden to patients of secondary brain tumours in ALK+ NSCLC. (59, 60)

In addition to the burden on patients clinically, ALK+ NSCLC also presents a substantial economic burden to society. Lung cancer as a broad indication was reported to have the highest economic burden of any cancer in the EU, accounting for 15% of the total burden of cancer in 2009.(61) A study from Oxford University evaluating the total economic costs of various forms of cancer in the UK specifically estimated the cost of lung cancer in the UK at £2.4 billion annually, far higher than any other form of cancer.(62) Although there are no UK estimates for advanced ALK+ NSCLC specifically, it is estimated that prevalence of NSCLC is more than 20,000. Given that approximately 13,600 of these NSCLC cases are stage IIIb/IV and an estimated 5% of stage IIIb/IV NSCLC cases are ALK+ NSCLC, the economic impact of this condition specifically is still considerable.(35, 41, 63)

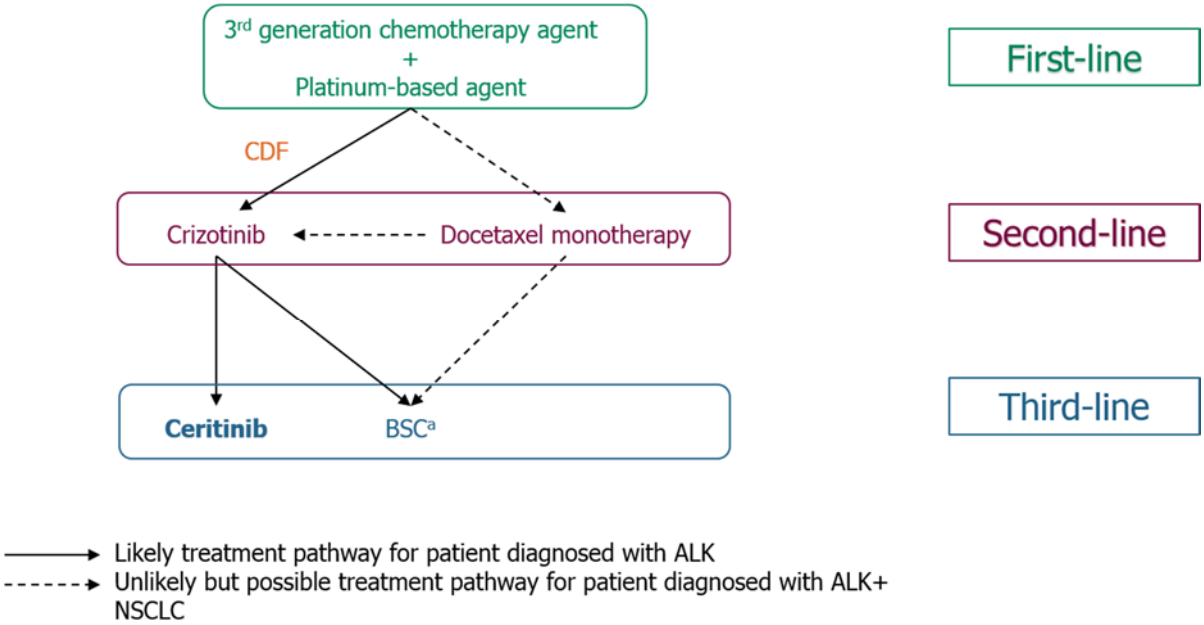
Advanced or metastatic NSCLC is associated with substantial direct healthcare costs resulting from requirements for hospital facilities, emergency rooms and outpatient department rooms to see patients and administer treatment such as intravenous chemotherapeutic agents.(64)

Beyond the direct healthcare costs, indirect healthcare costs may also be considerable. In particular, the fact that ALK+ NSCLC is, on average, diagnosed in patients who are still of working age means that there are potential substantial economic costs resulting from loss of productivity to society as well as a detrimental impact on family and dependents (see Section 2.5).

3.2 *Treatment pathway*

Our understanding of the current treatment pathway for ALK+ NSCLC based on consideration of NICE Clinical Guideline 121, discussion with expert clinicians and the proposed National Chemotherapy Algorithm is outlined in Figure 1 and discussed below.(65, 66)

Figure 1: Treatment pathway for ALK+ NSCLC



[a] BSC is considered to represents passive therapy aimed at symptom management and palliative care
Abbreviations: BSC: best supportive care; CDF: Cancer Drugs Fund, England only

Treatment options for early-stage NSCLC (Stage I and II) include surgery, radiotherapy, chemoradiotherapy, ablation and photodynamic therapies (NICE Treatment Pathways).(67) At stage III or IV NSCLC, NICE Clinical Guideline 121 recommends a combination of 3rd generation chemotherapy agents including docetaxel, gemcitabine, paclitaxel or vinorelbine, plus a platinum-based drug (carboplatin or cisplatin) as first-line chemotherapy options.(27) Pemetrexed in combination with cisplatin is also recommended as an option for first-line treatment if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.(68) Targeted first-line treatment options for NSCLC patients including afatinib, erlotinib and gefitinib are all recommended for patients who test positive for the EGFR tyrosine kinase mutation only and are therefore not relevant to the ALK+ population (see Section 3.1.2 above).

NICE recommends docetaxel monotherapy for second-line treatment of locally advanced or metastatic NSCLC when cancer has relapsed after previous chemotherapy. However it is unlikely that patients who have been sub-typed as having the ALK gene rearrangement would receive anything other than crizotinib, unless they do not have access to this medicine (see Equity and Equality – Section 3.4). Crizotinib for the second-line treatment of ALK-positive NSCLC is not recommended by NICE but is currently available in England through the Cancer Drugs Fund and hence is widely used in clinical practice.(19, 69)

Response to crizotinib in this second line setting typically lasts for approximately 32 weeks (8 months), as measured by duration of response, and approximately one-third of patients with ALK+ NSCLC do not respond to crizotinib at all.(28) Following disease progression on crizotinib, patients are currently faced with limited treatment options.

This lack of treatment options is reflected in the final NICE scope for this appraisal, which defines best supportive care (BSC) as the comparator to ceritinib in this submission. BSC represents passive therapy aimed at symptom management and palliative care ie. no active treatment, as noted in Figure 1. Clinical expert opinion has indicated that this is how the majority of patients who progress on crizotinib in clinical practice would be treated and supports that BSC (no active treatment) is the appropriate comparator to ceritinib in this submission, in alignment with the NICE final scope.

Prior to the use of BSC (no active treatment), some patients with advanced ALK+ NSCLC previously treated with crizotinib might receive active therapy in the form of systemic chemotherapy (docetaxel). With regards to the use of chemotherapy post-crizotinib, it should be

noted that a significant number of patients will have already been treated with chemotherapy (docetaxel or pemetrexed) in the first- and/or second-line of treatment for their ALK+ NSCLC. For some patients the use of docetaxel following progression on crizotinib would therefore represent a return to a treatment option that has previously been used without success and hence not be appropriate. Furthermore, given the toxic nature of chemotherapy, some patients will not be considered fit enough to undergo this treatment following progression on crizotinib.(70) Nonetheless, docetaxel treatment may be appropriate for some patients. Consideration of chemotherapy after treatment with crizotinib is supported by the proposed National Chemotherapy Algorithm; a form of guideline that specifies the acceptable ranges of regimen options for named steps on the patient pathway that is cancer site-specific.(66) Although only currently in draft form, the proposed algorithm is expected to be officially implemented in the near future, after the purdah period associated with the General Election 2015. This proposed algorithm reflects the treatment pathway according to what is currently actually commissioned and what is supported by evidence and therefore represents an additional source to provide understanding of current clinical practice. In addition to supportive care, this proposed National Chemotherapy Algorithm for NSCLC notes docetaxel as a potential treatment option. Based on this, the use of docetaxel followed by BSC in some patients who have been previously treated with crizotinib is explored as a scenario analysis within the economic evaluation in this submission (see Section 5.8.3).

3.3 *Comparators used in the submission*

The base case comparator to ceritinib in this submission is BSC (no active treatment). This is consistent both with the current treatment pathway for ALK+ NSCLC (Figure 1), supported by expert clinical opinion, and with the final NICE scope.

In addition, given that some patients may receive docetaxel prior to BSC (no active treatment) after progression on crizotinib, a scenario analysis is conducted in which a composite comparator of BSC (no active treatment) and docetaxel followed by BSC (no active treatment) is considered.

3.4 *Equity and Equality*

The Cancer Drugs Fund currently only covers provision of cancer therapies in England and therefore in Wales crizotinib is only available through individual patient request forms. Thus there are likely to be ALK+ NSCLC patients in Wales who are not being treated with crizotinib and will not therefore be able to access ceritinib, even if NICE positively recommends ceritinib for ALK+ NSCLC after crizotinib treatment.

4. Clinical effectiveness

Summary of Clinical Evidence

The clinical effectiveness of ceritinib in ALK+ NSCLC for patients who have previously received an ALK inhibitor has been established in two, open-label, single-arm trials: ASCEND-2 (n=140) and ASCEND-1 (n=163 in the relevant patient subgroup).

Response: overall response rate (ORR), time to response (TTR) and duration of response (DOR)

- **ORR by Investigator assessment (trial primary endpoint):** Ceritinib demonstrated a good ORR (defined as partial response [PR] and complete response [CR]) of 38.6% (95% CI: 30.5, 47.2) and 56.4% (95% CI: 48.5, 64.2) for ASCEND-2 (n=140) and ASCEND 1 (n=163), respectively.
  - Consistent results for ORR were seen using Blinded Independent Central Review Committee (BIRC) assessment as a secondary trial endpoint.
    - **TTR:** In ASCEND-2, patients were found to respond early to ceritinib, with the median time to response 1.8 months (95% CI: 1.6, 5.6) (based on Investigator assessment).
- **DOR:** A median duration of response of 9.7 months (95% CI 7.1, 11.1) and 8.25 months (95% CI 6.80, 9.69) based on Investigator assessment was reported for ASCEND-2 (n=54 patients with CR or PR) and ASCEND-1 (n=92 patients with CR or PR), respectively.

Progression free survival (PFS) and overall survival (OS)

- **PFS by Investigator assessment:** The median PFS for patients who received ceritinib was 5.7 months (95% CI: 5.4, 7.6) in ASCEND-2 and 6.93 months (95% CI: 5.55, 8.67) in ASCEND-1.
  - A pooled analysis of ASCEND-2 and ASCEND-1 resulted in a median PFS of [redacted]
- **OS:** The median overall survival (OS) for patients treated with ceritinib was 14.9 months (95% CI: 13.5, NE) in ASCEND-2 and 16.7 (95% CI: 14.8, NE) in ASCEND-1.
  - A pooled analysis of ASCEND-2 and ASCEND-1 resulted in a median OS of [redacted].

Comparative effectiveness: naïve indirect comparison

- The only available data identified for the relevant comparator of BSC (no active treatment) was from a retrospective analysis presenting OS of ALK+ NSCLC patients who have previously received crizotinib.(1)
- This study found median OS to be 2.2 months (95% CI: 1.1, 3.8) for patients who received BSC (no active treatment) in the post-crizotinib setting.
  - In addition, the study found median OS to be 5.4 months (95% CI: 3.8, 12.3) for patients who received systemic therapy and 3.9 months (95% CI: 2.7, 5.1) across both these patient groups.
  - Comparatively, the OS of ceritinib based on a pooled analysis of ASCEND-2 and ASCEND-1 was [redacted].

Safety

- Across both ASCEND-2 and ASCEND-1 ceritinib was associated with a low rate of AEs leading to discontinuation (7.9% and [redacted], respectively).
- The adverse event profile was consistent with that previously observed for ceritinib; the most commonly observed grade 3/4 AEs suspected to be related to the study drug included diarrhoea, vomiting, fatigue and increases in certain laboratory parameters.

Source: European Public Assessment Report, Summary of Product Characteristics, Mok *et al.* Felip *et al.*(6, 7, 9, 10)

4.1 *Identification and selection of relevant studies*

4.1.1 Identification of studies

A systematic literature review was conducted to identify all relevant published and unpublished randomised controlled trial (RCT) and non-RCT evidence relating to the efficacy of subsequent line therapies for advanced or metastatic NSCLC. Data from studies investigating the ALK+ NSCLC population specifically, or a non-ALK NSCLC population where at least two treatments of interest were administered, were extracted and used to inform evidence on clinical effectiveness. The systematic review was conducted according to the NICE guide to the methods of technology appraisal 2013 and therefore adhered to the Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care. The complete search strategy for this review is provided in **Error! Reference source not found.**.

4.1.2 Inclusion and exclusion criteria

The systematic review was conducted in two steps.

- Level 1 screening: All titles/abstracts for the records identified in the literature search were reviewed against the inclusion and exclusion criteria listed in Table 6.
- Level 2 screening: Full texts of studies that passed level 1 screening were retrieved and reviewed using the same inclusion/exclusion criteria (Table 6). Studies that satisfied this criteria were selected and included in the review.

Two researchers reviewed all citations independently in parallel, with any disagreements resolved by discussion or independent arbitration by a third reviewer.

Table 6: Eligibility criteria used in search strategies and study selection

		Eligibility Criteria
Inclusion criteria	**Population**	• Adults (≥18 years of age; also include if ≥80% population was adult) • Patients with advanced or metastatic (stage IIIB or IV) NSCLC If a study assessed a mixed population (e.g., early stage and advanced/late stage), we included the study if outcomes of interest were reported specifically for the population of interest (i.e., advanced or metastatic (stage IIIB or IV) NSCLC).
	Interventions	The intervention included at least one of the following drugs as subsequent-line treatment in the advanced/metastatic setting: • Crizotinib (monotherapy or combination therapy) • LDK378 (monotherapy or combination therapy) • Alectinib (monotherapy or combination therapy) • Docetaxel (monotherapy only) • Pemetrexed (monotherapy only) • Erlotinib (monotherapy or combination therapy) • Bevacizumab (monotherapy or combination therapy) • Best supportive care/ standard palliative care[a]
	Outcomes	At least one of the following outcomes was reported: • Response rate (RR) • Overall survival (OS) • Time to progression (TTP) • Time to treatment failure (TTF) • Progression-free survival (PFS)
	Study design	• Randomised controlled trials (RCTs) of any duration were eligible for inclusion; cross-over RCTs were included if data were presented at cross-over. • Non-RCT studies (e.g., long-term open-label follow-up studies) reporting the above outcomes were also eligible for inclusion

Exclusion criteria	**Population**	• Non-human study • Patients under 18 years old • 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)
	Interventions	• Studies did not include any of the treatments specified in the inclusion criteria • First-line treatments of study interventions in the advanced or metastatic setting were assessed
	Outcomes	Studies not providing sufficient data on clinical evidence listed in the inclusion criteria (i.e. not reporting RR, OS, TTP, TTF, PFS)
	Study design	• Duplicate publication of the same trial • Case reports • Commentaries and letters • Recommendations/ guidelines • Non-systematic reviews (i.e., narrative review article)
Publication type		Systematic reviews and meta-analyses were maintained during database search, but were excluded before level 1 screening. (Systematic reviews and meta-analyses were re-visited to identify or confirm selected studies.)
Language restrictions		Studies not in English were excluded from the review
Date restrictions		Electronic databases were searched from inception to 20th March 2015. Hand searching of congress proceedings was conducted for the most recent 4 years

[a] Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, palliative care, and symptom management.
Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progress free survival; RCT, randomised controlled trial; RR, response rate; TTF, time to treatment failure; TTP, time to progression

4.1.3 Study selection process

The electronic database search (**Error! Reference source not found.**, accessed 20th March 2015) identified 5166 records and conference searches identified 713 records; in total, 5245 records (4356 database abstracts, 889 conference abstracts) were screened after de-duplication of results. Of these, 4,497 records were excluded based on the level 1 screening of the title/abstract. On re-application of the review eligibility criteria to the remaining full-text papers (level 2), 270 studies were ultimately included in the review.

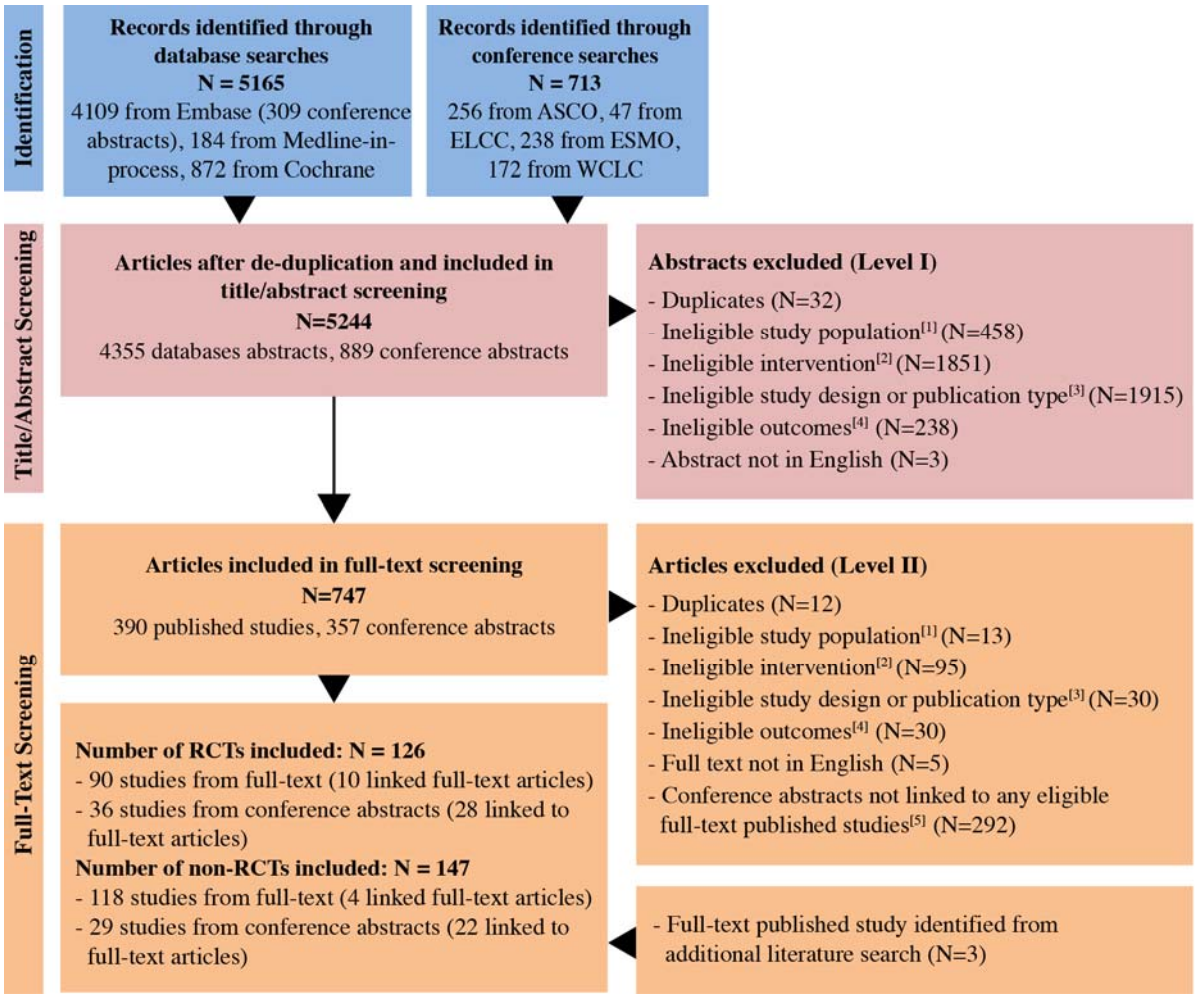
Three further studies were manually added on completion of the review as they were not originally captured by the database search terms. A summary of these studies is provided in Table 7 below.

Table 7: Justification for studies manually added to systematic review

	Explanation for not being captured by search terms
Gainor 2015(29)	Study was not indexed on OvidSP at the time of the search
Camidge 2012(71)	MeSH terms relating to the clinical trial design were developed in line with NICE guidance. However, the MeSH term under which this was indexed as a phase I trial was not captured by the search terms.
Lee 2013(72)	Study population did not specifically state advanced/ metastatic NSCLC, which was a requirement of the search terms

Therefore, a total of 126 included RCTs and 147 included non-RCTs included in the review met the systematic literature review eligibility and were considered for extraction. The PRISMA flow diagram for the study selection process for the clinical effectiveness evidence is shown in Figure 2.

Figure 2: PRISMA diagram for systematic literature review of clinical studies in subsequent lines of treat ment for advanced or metastatic NSCLC (Search Cut-off Date: 20th March, 2015)



Notes:

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NSCLC: Non-Small Cell Lung Cancer; ASCO: American Society for Clinical Oncology; ELCC: European Lung Cancer Conference; ESMO: European Society of Medical Oncology; WCLC; World Conference on Lung Cancer; RCT: Randomised Clinical Trial

[1] Study population of interest consisted of adults (at least 18 years old) with advanced or metastatic (stage IIIB or IV) NSCLC.
[2] Treatment interventions of interest consisted of subsequent lines of crizotinib, ceritinib, docetaxel (monotherapy only), pemetrexed (monotherapy only), erlotinib, bevacizumab, best supportive care/standard palliative care in advanced or metastatic settings.
[3] Study designs or publication types of interest consisted of the following:
-RCTs of any duration and cross-over RCTs if data were presented at cross-over;
-Non-RCT studies (e.g., long-term open-label follow-up studies) reporting the above treatment interventions of interest;
-Observational studies (e.g., cohort study, cross-sectional study, case-control study).
[4] Study outcomes of interest consisted of response rate, progress free survival, time to progression, time to treatment failure and overall survival rate.
[5] Studies published as abstracts or conference presentations were included if associated full-text articles were found and adequate data were presented. Eligible conference abstracts of anaplastic lymphoma kinase (ALK) rearranged NSCLC were all included regardless of availability of associated full-text articles.

The 126 identified RCTs and 147 identified non-RCTs corresponded to eligibility criteria that were broader than the decision problem presented in this submission, capturing all studies in patients with advanced or metastatic (stage IIIB or IV) NSCLC. This broad search strategy was performed in order to ensure that all potentially relevant articles were captured by the searching. In order to narrow the results of the systematic review to the decision problem – that is the ALK+ molecular subtype of patients who have been previously treated with an ALK inhibitor – 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

A complete list of all included studies following application of these criteria is provided in **Error! Reference source not found.**. Of these included studies, only two investigated the clinical efficacy and safety of ceritinib as a subsequent line therapy in ALK+ NSCLC patients, Gainor et al. 2015 and Shaw et al. 2014.(29, 73)

The internal Novartis database of the ceritinib clinical trial program was then additionally searched and cross-matched with these identified studies. Overall, this resulted in the identification of the studies listed in Table 8.

Table 8: Key studies from ceritinib clinical trial program

Study (Source)	Comparators	Patients (N)	RCT/non-RCT?	Identified publications from systematic review	Presented in submission
ASCEND-1 CLDK378X2101 (NCT01283516)	Single arm (oral ceritinib at 750 mg)	Adult patients with advanced ALK+ NSCLC (n=255)*	Non-RCT (phase I)	Shaw et al. 2014(74)	Yes (full presentation) – Study provides efficacy and safety data in the relevant patient population under consideration (See Section 4.11)
ASCEND-2 CLDK378A2201 (NCT01685060)	Single arm (oral ceritinib at 750 mg)	Adult patients with ALK+ NSCLC previously treatment with chemotherapy and crizotinib (n=140)	Non-RCT (phase II)	None	Yes (full presentation) – Study provides efficacy and safety data in the relevant patient population under consideration (See Section 4.11)
Gainor et al. 2015(29)	NA. Study presents a retrospective analysis of patients who have received crizotinib followed by ceritinib in ALK+ NSCLC	ALK-positive NSCLC patients who were previously treated with crizotinib, followed by ceritinib (n=73)	Non-RCT (real-world study)	Gainor et al. 2015(29)	Yes (limited presentation) – Study provides efficacy data in the relevant patient population under consideration. A limited presentation is given due to the limitations of the study design and the fact that the majority of patients (n=71) are enrolled in ASCEND-1 (See Section 4.12)
ASCEND-3 CLDK378A2203 (NCT01685138)	Single arm (oral ceritinib at 750 mg)	Crizotinib-naïve adult patients with ALK+ NSCLC (n=124)	Non-RCT (phase II)	None	Yes (limited presentation) – Although the crizotinib naïve patient population is not the population under consideration, a limited presentation of this study is given as it provides efficacy and safety evidence in the general ALK+ NSCLC population (See **Error! Reference source not found.**)
ASCEND-4 CLDK378A2301 (NCT01828099)	Chemotherapy (pemetrexed + cisplatin or pemetrexed + carboplatin) Oral ceritinib at 750 mg	Adult patients with ALK+ stage IIIB or IV non-squamous NSCLC who were previously untreated (n=348)	RCT (phase III)	None	No – Study is currently on-going and no results are available
ASCEND-5 CLDK378A2303 (NCT01828112)	Chemotherapy (pemetrexed or docetaxel) Oral ceritinib at 750 mg	Adult patients with ALK+ advanced NSCLC who have been treated previously with chemotherapy (platinum-doublet) and crizotinib(n=236)	RCT (phase III)	None	No – Study is currently on-going and no results are available

*Nine patients were non-NSCLC patients.
Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial
Source: as indicated

As highlighted in Table 8, no RCT evidence was identified for ceritinib in the relevant patient population of ALK$^+$ NSCLC patients who have been previously treated with an ALK inhibitor. Please see Section 4.11 for further details regarding the relevance of the studies presented in Table 8 of the submission.

4.2 *List of relevant randomised controlled trials*

No RCT evidence was identified. Please see Section 4.1 for further details.

4.3 *Summary of methodology of the relevant randomised controlled trials*

No RCT evidence was identified. Please see Section 4.1 for further details.

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

No RCT evidence was identified. Please see Section 4.1 for further details.

4.5 *Participant flow in the relevant randomised controlled trials*

No RCT evidence was identified. Please see Section 4.1 for further details.

4.6 *Quality assessment of the relevant randomised controlled trials*

No RCT evidence was identified. Please see Section 4.1 for further details.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

No RCT evidence was identified. Please see Section 4.1 for further details.

4.8 *Subgroup analysis*

No RCT evidence was identified. Please see Section 4.1 for further details.

4.9 *Meta-analysis*

No RCT evidence was identified. Please see Section 4.1 for further details.

4.10 *Indirect and mixed treatment comparisons*

Identification of relevant studies

The search strategy described in Section 4.1 also sought to identify clinical evidence for potential comparators to ceritinib relevant to the population of patients with ALK+ NSCLC.

Table 6 lists the therapies included in the search terms of the systematic literature review as potential therapies that may provide evidence in the population under consideration.

This search strategy identified one study assessing a relevant comparator in the patient population of interest (that is patients with ALK+ NSCLC previously treated with crizotinib), Ou *et al*. 2014.(1) A summary of this study is presented in Table 9.

Table 9: Summary of relevant comparator studies identified by clinical systematic review

Trial no. (acronym)	Study type	Data cut-off	Population	Primary objectives

Ou *et al*. 2014(1)	Retrospective analysis	2nd January 2012	Patients with advanced ALK-positive NSCLC enrolled in two ongoing multicentre, single-arm trials who developed RECIST-defined PD	To investigate the clinical benefits of continuing ALK inhibition with crizotinib beyond disease progression and to determine the characteristics associated with patients who experience clinical benefit.

Abbreviations: ALK, Anaplastic lymphoma kinase (ALK)-positive; NSCLC, non-small cell lung cancer; PD, progressive disease; RESIST, Response Evaluation Criteria In Solid Tumours
Source: as indicated

The Ou *et al.* study presents evidence in the post-crizotinib population of ALK+ NSCLC patients, considering patients who have received crizotinib as a 2nd-line therapy and exhibited progressive disease on crizotinib. This precisely matches the patient population under consideration for treatment with ceritinib in the decision problem presented in this submission.

Within the Ou *et al.* study, study participants fell into one of the following three treatment groups in the post-crizotinib setting, with overall survival estimates provided for each:

1. **Best supportive care only (no active treatment)**: these patients received no active treatment, reflective of how the majority of patients would be expected to be treated in the post-crizotinib setting in UK clinical practice and the base case comparator in this submission (see Section 3.2 and 3.3).

2. **Systemic therapy (ie. chemotherapy):** these patients received systemic chemotherapy (ie. active treatment). As described in Section 3.2, some patients may be treated in this manner in clinical practice and this is explored as a scenario analysis within this submission.

3. **Continued crizotinib:** although the focus of the Ou *et al.* study, continuation of crizotinib post progression is not considered reflective of UK clinical practice. Our understanding is that though some individual clinicians may elect to use this treatment strategy in isolated cases, this is not reflective of UK clinical practice from a clinical, funding or commissioning perspective:
   - Feedback received from a leading UK clinician strongly suggested that continuation on crizotinib is not standard practice.
   - Continuation on crizotinib is not consistent with the proposed National Chemotherapy Algorithm, a pathway that reflects current commissioning patterns and evidence consideration.(66)
   - The January 2015 CDF decision summary for crizotinib is quite clear in stipulating that retention of crizotinib in the CDF beyond April 2015 is based on an assumption of discontinuation of crizotinib on disease progression.(69) CDF funding for continued crizotinib beyond progression is therefore not available.

   As such, the continued crizotinib arm of this study will not be considered further in this submission.

Following the systematic literature review, the Ou *et al.* study was identified as the only study presenting evidence for a comparator treatment in the patient population of ALK+ NSCLC patients previously treated with crizotinib. Given the nature of the evidence base identified for ceritinib (Section 4.1), this study provides the basis of the assessment of the comparative effectiveness of ceritinib versus BSC in a naïve indirect comparison.

Further details regarding the Ou *et al.* study, including a comparison of the study population with the ceritinib clinical evidence base, and a naïve indirect comparison of the results of the evidence for ceritinib with that of the Ou *et al.* study, is presented in Section 4.13.

4.11 *Non-randomised and non-controlled evidence*

4.11.1 Identification of relevant studies

The methodology of the systematic literature review to identify all relevant non-RCT evidence is described in Section 4.1. As noted in Table 8, a total of 5 non-RCT studies were identified, of which only three have results available to present at this time (ASCEND-1, ASCEND-2, ASCEND-3).

ASCEND-3 recruited 124 crizotinib-naïve adult patients with ALK+ NSCLC. This patient population is outside the current marketing authorisation of ceritinib and the scope of this appraisal, which considers ceritinib within its currently licensed indication for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib. As such, results from the ASCEND-3 study are not considered relevant to present in the main body of this submission. However, ceritinib has recently been granted a Promising Innovative Medicine designation by the MHRA for the treatment of adult patients with previously-treated ALK+ NSCLC – a patient population for which the ASCEND-3 study provides evidence of clinical efficacy and safety.(20) In addition, although in a different position in the treatment pathway, the ASCEND-3 study does provide evidence of the efficacy and safety of ceritinib in ALK+ NSCLC patients broadly. As results are available from this study, these are provided in **Error! Reference source not found.** of the submission.

There are therefore two prospective, single-arm clinical trials assessing the safety and efficacy of ceritinib in ALK-positive advanced NSCLC adult patients previously treated with crizotinib and reporting results of direct relevance to this submission:

- ASCEND-2 (Study LDK378A2201): Phase II multicentre trial in ALK-positive NSCLC patients treated with ceritinib and previously treated with crizotinib

- ASCEND-1 (Study LDK378X2101): Phase I multicentre, open label dose-escalation and expansion trial in ALK-positive NSCLC patients treated with ceritinib and:
    - Previously treated with ALK inhibitor (n=163, treated subgroup)
    - ALK inhibitor naïve (n=83, treatment-naïve subgroup)

Results from the treatment-naïve subgroup of patients in ASCEND-1 will not be presented in this submission as this is outside of the licensed indication and decision problem of this submission (see **Error! Reference source not found.**).

An additional, a real-world retrospective analysis of ALK+ NSCLC patients treated with sequential crizotinib and ceritinib, conducted by Gainor et al. 2015, was also identified by the systematic literature review. This study is discussed briefly in 4.12.

Table 10 provides an overview of key details relating to the ASCEND-2, ASCEND-1 and Gainor *et al.* studies, including the data cut-off presented and the primary and secondary references used in the submission. Within this submission, efficacy and safety results are presented for the latest available data cut-off; results for the primary endpoint are additionally presented for the data cut-off on which the primary analysis of the trial was based.

Table 10: Summary of relevant non-RCTs presented in the main body of the submission

Trial no. (acronym)	Study type	Data cut-off	Population (n)	Primary objectives	Primary/ Secondary study ref.	Justification for inclusion
ASCEND-2 (Study LDK378A2201)	Phase II clinical trial	Latest data cut-off: 13th August 2014 (48 weeks) Primary analysis data cut-off: 26th February 2014 (24 weeks)	Chemotherapy and Crizotinib-treated ALK-positive, previously-treated, advanced NSCLC patients (n=140)	Demonstration of the anti-tumour activity of ceritinib	ASCEND-2 primary CSR and updated data cut-off CSR (8)	Presentation of clinical outcomes in the target population of ALK-positive NSCLC patients treated with ceritinib and previously treated with crizotinib.
ASCEND-1 (Study LDK378X2101)	Phase I clinical trial	Latest data cut-off: 14th April 2014 Primary analysis data cut-off: 2nd August 2013	Patients with locally advanced or metastatic ALK+ NSCLC that has progressed despite standard therapy (n=246; total trial population). Within this, the trial considered a population of patients previously treated with ALK+ inhibitor (n=162); this subgroup represents the population of relevance to this submission	To determine the MTD of ceritinib as a single agent when administered orally to adult patients with tumours characterized by genetic abnormalities in ALK	ASCEND-1 primary CSR and updated data cut-off CSR(5)	Presentation of clinical outcomes in the target population of ALK-positive NSCLC patients treated with ceritinib and previously treated with crizotinib.
Gainor et al.(29)	Retrospective analysis	June 2014	ALK-positive NSCLC patients who were previously treated with crizotinib, followed by ceritinib (n=73)	To determine the outcome of sequential treatment with crizotinib and ceritinib, with respect to PFS and OS.	Gainor et al.(29)	Presentation of clinical outcomes in the target population of ALK-positive NSCLC patients treated with ceritinib and previously treated with crizotinib.

Abbreviations: ALK, Anaplastic lymphoma kinase (ALK)-positive; CSR; Clinical Study Report; NSCLC, non-small cell lung cancer
Source: as indicated

4.11.2 Summary of methodology of non-randomised trials

ASCEND-2

ASCEND-2 was a single-arm, open-label, multicentre, phase II study of ceritinib, conducted in 140 adult patients with advanced ALK-positive NSCLC who had received 1-3 lines of cytotoxic chemotherapy and had progressed during therapy with crizotinib. A summary of the methodology of this trial is provided in Table 11.

Table 11: Summary of ASCEND-2 Methodology

Trial no. (acronym)	ASCEND-2 (LDK378A2201)
Location	Study centres: Canada (2), France (2), Germany (2), Hong Kong (2), Italy (6), Japan (9), South Korea (3), Netherlands (3), Singapore (1), Spain (4), United Kingdom (1), United States (16)
Design	A phase II multicentre, open label, single arm study. Subjects were screened for a period of up to 28 days, and if they met the entrance criteria, were assigned on Day 1 to 750 mg orally of ceritinib on a once-daily dosing schedule.
Duration of study	Subjects continued with the assigned study treatment until unacceptable toxicity, consent withdrawal at the discretion of the patient or Investigator, started a new anti-cancer therapy or died. The study began in 26th November 2012 and the collection date for the primary outcome measure reported in this submission was 13th August 2014.(11)
Intervention(s)	Ceritinib 750 mg oral (n=140), administered orally at the same time each day on a continuous dosing schedule. Treatment cycles in the trial were defined as 28-day periods.
Primary outcomes[a]	Demonstration of the anti-tumour activity of ceritinib as measured by overall response rate (ORR) by Investigator assessment as a primary end point Assessments of tumour response and progression were performed every eight weeks (every two cycles), starting from the first day of treatment with ceritinib.
Secondary outcomes[a]	Secondary outcomes of the study: • Duration of response (DOR)[b] • Disease control rate (DCR)[b] • Time to response (TTR)[b] • Overall intracranial response rate (OIRR)[b] • ORR by BIRC assessment • Progression free survival (PFS)[b] • Overall survival (OS) • Evaluation of the safety profile of ceritinib
Duration of follow-up	Survival: Following final tumour assessment, patients were contacted every 3 months until death. Safety: After discontinuation of study treatment patients were scheduled for an end of treatment visit within 7 days of the last dose. Patients who discontinued were followed up for adverse events until 30 days after the last dose of ceritinib.

[a]All tumour evaluations were performed according to RECIST version 1.1
[b]Outcomes were assessed by Investigator assessment and a Blinded Independent Review Committee (BIRC) (see Section 4.11.5)
Abbreviations: BIRC, Blinded Independent Review Committee; DOR, duration of response; DCR, disease control rate; NSCLC, non-small cell lung cancer; OIRR, overall intracranial response rate; ORR, overall response rate; OS, overall survival; PFS, progress free survival; RECIST, response evaluation criteria in solid tumours; TTR, time to response
Source: unless stated otherwise, primary CSR(8)

ASCEND-1

ASCEND-1 was a multicentre, phase I, open-label, dose-escalation and expansion study of ceritinib in patients with tumours characterised by genetic abnormalities in ALK, a summary of which is shown in Table 12.(5)

Table 12: Summary of ASCEND-1 Methodology

Trial no. (acronym)	ASCEND-1
Location	20 centres across 11 countries
Design	A phase I multicentre, open label, single arm, dose-escalation and expansion study. The dose-escalation phase enrolled patients with ALK+ tumours to determine the maximum tolerated dose (MTD)/ recommended dose (RD), safety, single and multiple-dose pharmacokinetics (PK), and anti-tumour activity of ceritinib. The dose-escalation phase was followed by an expansion phase wherein ALK+ patients were enrolled based on type of advanced tumour (predominantly NSCLC), and prior exposure to ALK inhibitors to further assess the safety, tolerability, PK, and anti-tumour activity of ceritinib in these patient populations at the RD. Subjects were enrolled in the expansion phase after the MTD had been estimated and continued to take 750 mg orally of ceritinib on a once-daily dosing schedule.
Duration of study	Patients continued treatment with ceritinib until the patient experienced unacceptable toxicity that precluded any further treatment, disease progression, and/or treatment was discontinued at the discretion of the investigator or by patient request. Patients who continued on treatment after disease progression discontinued study treatment once they were no longer deriving benefit as assessed by the investigator. End of study was defined as the time when all patients had discontinued ceritinib treatment, and all required safety follow-up (for AEs and SAEs for 28 days after the last dose of ceritinib) was completed or the patient had died, was lost to follow-up or withdrew their consent to further participate in the study. The study began in January 2011 and the collection date for the outcome measures reported in this submission was 14th April 2014.
Intervention(s)	**Expansion phase:** Ceritinib 750 mg oral (n=163 in the subgroup of patients treated with prior ALK+ inhibitor), administered orally at approximately the same time each day on a continuous dosing schedule. Treatment cycles in the trial were defined as 21-day periods.
Primary outcomes (including scoring methods and timings of assessments)[a]	**Dose-escalation phase:** To determine the maximum tolerated dose (MTD)/ recommended dose (RD) of ceritinib **Expansion phase:** Demonstration of the anti-tumour activity of ceritinib as measured by overall response rate (ORR)[a] and duration of response (DOR)[a]
Secondary outcomes[a]	**Expansion phase:** • Duration of response (DOR)[b] • Overall intracranial response rate (OIRR)[b] • Overall response rate (ORR)[b] • Progression free survival (PFS)[b] • Overall survival (OS) • Evaluation of the safety profile of ceritinib
Duration of follow-up	**Survival:** Survival information was collected every 3 months after the study evaluation unless the patient was lost to follow-up or withdrew consent to be followed for survival **Safety:** all patients were followed for adverse events (AEs) and serious adverse events (SAEs) for 28 days after the last dose of ceritinib.

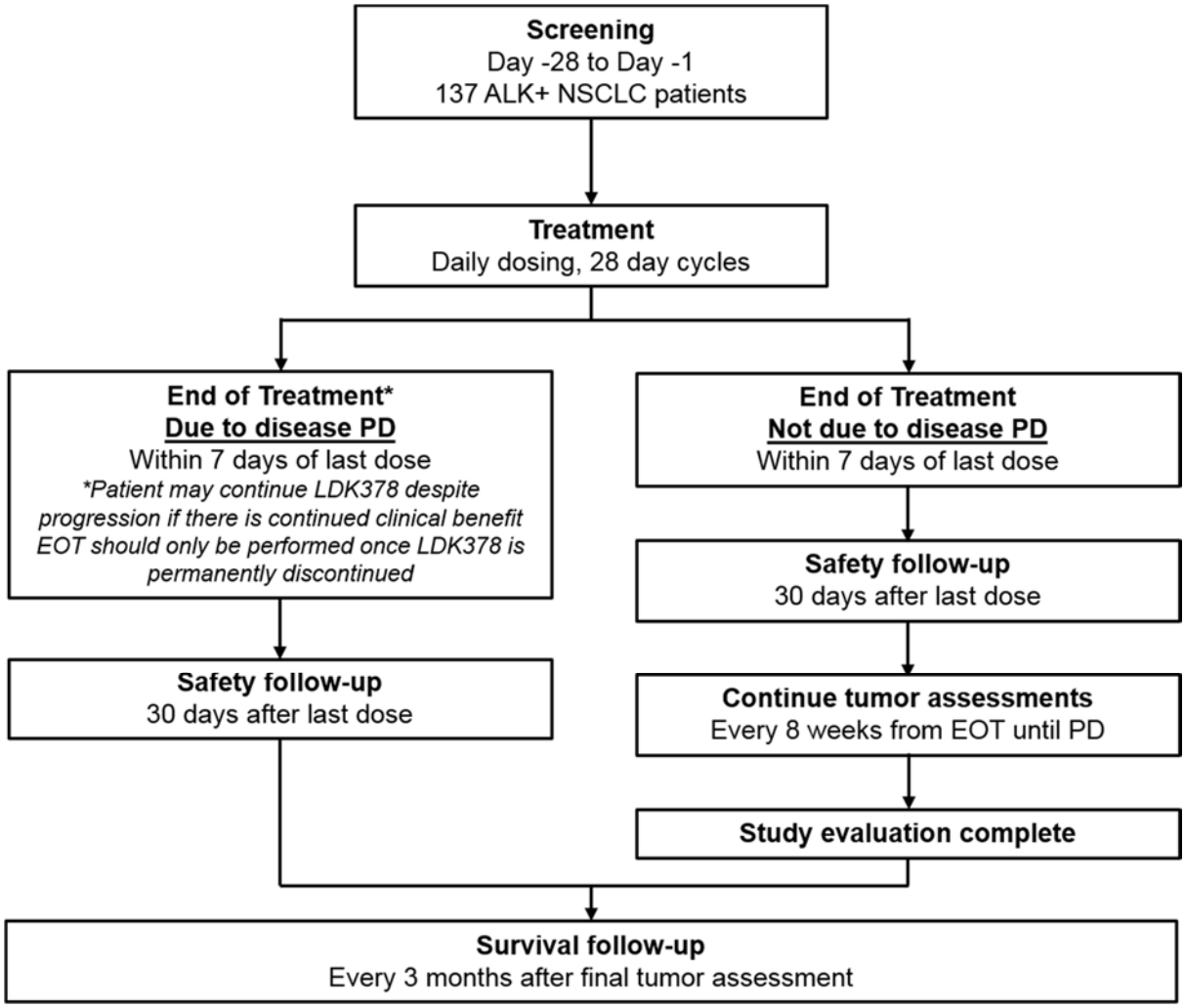
[a]All tumour evaluations were performed according to RECIST version 1.0
[b]Outcomes were assessed by Investigator assessment and a Blinded Independent Review Committee (BIRC) (see Section 4.11.5).
Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BIRC, Blinded Independent Review Committee; DOR, duration of response; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; OIRR, overall intracranial response rate; ORR, overall response rate; OS, overall survival; PFS, progress free survival; PK, pharmacokinetics; RD, recommended dose; RECIST, response evaluation criteria in solid tumours; SAE, serious adverse event
Source: unless stated otherwise, preliminary CSR(5)

4.11.3 Trial Structure

Diagrammatic representations of the trial structures of ASCEND-2 and ASCEND-1 are presented in Figure 3 and Figure 4, respectively.

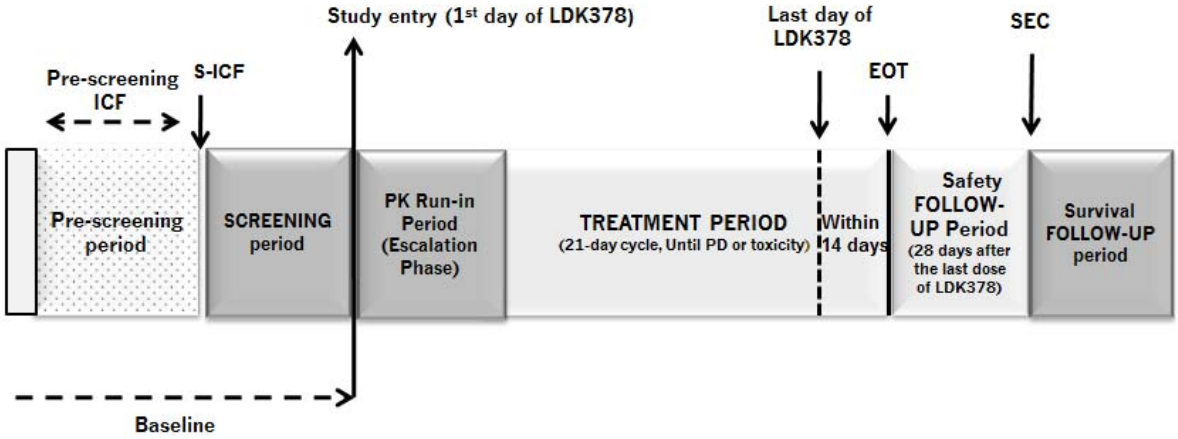
ASCEND-2

Figure 3: ASCEND-2 Study Design



ASCEND-1

Figure 4: ASCEND-1 Study Design



Pre-screening ICF: signature of the Pre-screening Informed Consent Form
S-ICF: signature of the Study Informed Consent Form
PD: progressive disease
EOT: end of treatment
SEC: study evaluation completion

As presented in Figure 4, the ASCEND-1 study consisted of an escalation phase which aimed to determine the maximum tolerated dose (MTD)/ recommended dose (RD), safety, single and multiple-dose pharmacokinetics (PK), and anti-tumour activity of ceritinib. This was followed by an expansion phase, which enrolled ALK+ patients based on type of advanced tumour (predominantly NSCLC), and prior exposure to ALK inhibitors to further assess the safety, tolerability, PK, and anti-tumour activity of ceritinib. In the expansion phase, patients were initiatied on 750 mg orally of ceritinib on a once-daily dosing schedule.

The expansion phase of this study represents the part of the study in which patients were treated with the licensed dose of ceritinib and hence this submission presents the results from this phase of the ASCEND-1 study only.

4.11.4 Eligibility criteria

Subjects were screened for a period of up to 28 days, and if they met the entrance criteria, were assigned on Day 1 to ceritinib 750 mg orally. The eligibility criteria for ASCEND-2 and ASCEND-1 are presented in Table 13.

Table 13: Inclusion and Exclusion Criteria

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
ASCEND-2	**I. Disease** • Histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC carrying an ALK rearrangement defined as 15% or more positive tumour cells as assessed by the FDA-approved Vysis ALK break-apart FISH test (Abbott Molecular Inc) using Vysis break-apart probes. • At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion was counted as a target lesion only if there was clear sign of progression since the irradiation. **II. Demography** • Age 18 years or older at the time of informed consent. • World Health Organization (WHO) performance status (PS) 0 to 2. • Life expectancy ≥ 12 weeks. **III. Organ function and laboratory results** • Patients with the following laboratory values at the screening visit: o Absolute neutrophil count ≥ 1.5×109/L o Platelets ≥ 75×109/L o Haemoglobin > 8 g/dL o Calculated creatinine clearance (using Cockcroft-Gault formula) > 30 mL/min o Total bilirubin < 1.5×ULN (Upper limit of normal), except for patients with Gilbert's syndrome, who were included only if total bilirubin < 3.0×ULN or	**I. Medical History** • Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within the two weeks prior to study entry to manage CNS symptoms. • History of carcinomatous meningitis. • Presence or history of a malignant disease other than NSCLC that was diagnosed and/or required therapy within the past three years. Exceptions to this exclusion include completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type. • Clinically significant, uncontrolled heart disease, such as: o Unstable angina within six months prior to screening o Myocardial infarction within six months prior to screening o History of documented congestive heart failure (New York Heart Association functional classification III-IV) o Uncontrolled hypertension defined by a Systolic Blood Pressure ≥ 160 mm Hg and/or o Diastolic Blood Pressure ≥ 100 mm Hg, with or without anti-hypertensive medication. o Initiation or adjustment of antihypertensive medications was allowed prior to screening o Ventricular arrhythmias o Supraventricular and nodal arrhythmias not controlled with medication o Other cardiac arrhythmia not controlled with medication o Corrected QT (QTc) > 470 ms using Fridericia correction (QTcF)

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	direct bilirubin < 1.5×ULN o Aspartate transaminase (AST) < 3×ULN, except for patients with liver metastasis, who were included only if AST < 5×ULN o Alanine transaminase (ALT) < 3×ULN, except for patients with liver metastasis, who were included only if ALT < 5×ULN o Patients having the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements during screening: ▪ Potassium ▪ Magnesium ▪ Phosphorus ▪ Total calcium (corrected for serum albumin) **IV. Prior treatment** • Patients with stage IIIB or IV NSCLC at the time of study entry that had progressed during therapy with crizotinib or within 30 days of the last dose, regardless of whether the patient had previously shown tumour regression or not: o Crizotinib was the last prior systemic antineoplastic therapy received by the patient prior to study entry (radiotherapy is not considered a systemic antineoplastic therapy) o If a patient had received a first treatment with crizotinib prior to cytotoxic chemotherapy and then received a second regimen of crizotinib after cytotoxic chemotherapy, the patient was allowed to enter the study, but the patient should have progressed on the most recent regimen of crizotinib (or within 30 days of last dose) o Patients had received their last dose of crizotinib ≥ one week prior to the first dose of ceritinib and	on the screening electrocardiogram (ECG, as mean of triplicate) study drug. o Systemic anti-cancer therapy given after the last dose of crizotinib and prior to starting study drug. • Impairment of gastrointestinal (GI) function or GI disease that might significantly alter the absorption of ceritinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, or malabsorption syndrome). • Other severe, acute, or chronic medical or psychiatric conditions including uncontrolled diabetes mellitus or laboratory abnormalities that in the opinion of the Investigator might increase the risk associated with study participation, or that may interfere with the interpretation of study results. • History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention. **II. Prior therapy** • Prior therapy with other ALK inhibitor investigational agents with the exception of crizotinib. • Thoracic radiotherapy to lung fields ≤ four weeks prior to starting the study treatment or patients who had not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ two weeks prior to starting the study treatment or patients who had not recovered from radiotherapy related toxicities. Palliative radiotherapy for bone lesions ≤ two weeks prior to starting study treatment was allowed. • Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within four weeks prior (two weeks for resection of brain metastases) to starting study drug or who had not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) the study ≥ one week after the procedure. **III. Current medications** • Patients treated with medications that met one of the following

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	recovered from crizotinib toxicities • Patients who had received cytotoxic chemotherapy to treat their stage IIIB or IV NSCLC: o All patients who had received at least one and a maximum of three prior lines of cytotoxic chemotherapy o Prior cytotoxic chemotherapy was to include a platinum doublet o Prior erlotinib or gefitinib did not count as a line of cytotoxic chemotherapy • Neoadjuvant or adjuvant cytotoxic chemotherapy for the curative treatment of NSCLC was counted as one prior line of treatment if relapse occurred within 12 months from the end of the cytotoxic chemotherapy. • Patients had to have recovered from all toxicities related to prior anticancer therapies to grade ≤ 2 (Common terminology criteria for adverse events [CTCAE] v 4.03). However, patients with persistent grade 2 nausea/vomiting and/or grade 2 diarrhoea despite optimal supportive therapy were not allowed to participate in the study. Patients with any grade of alopecia were allowed to enter the study. **V. Informed consent** • Written informed consent for the main study was obtained prior to any screening procedures. If consent could not be expressed in writing, it was formally documented and witnessed, ideally via an independent trusted witness. **VI. Availability of tumour sample** • Patients had a tumour tissue sample available, as an archival sample (collected either at the time of diagnosis of NSCLC or any time since) or as a new biopsy.	criteria and that could not be discontinued at least one week prior to the start of treatment with ceritinib and for the duration of the study: o Strong inhibitors or strong inducers of CYP3A4/5 o Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, CYP2C8 and/or CYP2C9 o Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes • Patients treated with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants at the time of screening. • Patients who received unstable or increasing doses of corticosteroids. If patients were on corticosteroids for endocrine deficiencies or tumour-associated symptoms other than CNS related, dose was to be stabilized (or decreasing) for at least five days before first dose of study treatment. • Patients treated with any enzyme-inducing anticonvulsant that could not be discontinued at least one week before first dose of study treatment, and for the duration of the study. Investigational agents within four weeks or ≤ 10×half-life of the agent (whichever was longer) before first dose of study treatment. **IV. Pregnancy statement and contraception requirements** • Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective contraception during the study and for 30 days after stopping treatment. • Sexually active males had to use a condom during intercourse while taking the drug and for three months after stopping ceritinib treatment and should not father a child in this period. **V. Others** • Patients with known hypersensitivity to any of the excipients of ceritinib (microcrystalline cellulose, mannitol, crospovidone, colloidal

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		silicon dioxide and magnesium stearate).
ASCEND-1	**I. Disease** • Patients diagnosed with a locally advanced or metastatic malignancy that has progressed despite standard therapy, or for which no effective standard therapy exists. Only patients with tumours characterized by genetic abnormalities in ALK were enrolled. For NSCLC, an ALK translocation must be detected by FISH in ≥ 15% of tumour cells. In patients with diseases other than NSCLC, ALK translocation is not required and overexpression of ALK protein may be considered indicative of a genetic abnormality in ALK. • Measurable disease:[a] o Presence of at least one measurable lesion as determined by modified RECIST version 1.0. o Note: Lesions in previously irradiated areas were not considered measurable, unless clear progression has been observed since the radiotherapy. **II. Demography** • Age ≥ 18 years. • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. • Life expectancy ≥ 12 weeks. **III. Organ function and laboratory results** • Patients had the following laboratory values (obtained within 14 days of enrollment): o Absolute neutrophil count (ANC) ≥ 1.5 x 109/L. o Hemoglobin (Hgb) ≥ 9 g/dL (≥ 90 g/L). o Platelets ≥ 100 x 109/L. o Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN), except for patients with Gilbert's syndrome who may be included if total bilirubin ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN.	**I. Medical History** • Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids to control their CNS disease. If a patient required steroids for management of CNS symptoms, the steroid dose had to be stable for the two weeks preceding study entry. Note: Patients with controlled CNS metastases, or asymptomatic CNS metastases that did not require local antineoplastic therapy, such as radiotherapy or surgery, participated in this study. • Patients with unresolved nausea, vomiting or diarrhoea > CTCAE grade 1. • Impairment of gastrointestinal (GI) function or GI disease that significantly altered the absorption of ceritinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, or small bowel resection). • History of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease. • Acute or chronic liver disease. Evidence of active viral hepatitis, including Hepatitis A, B or C (testing for viral hepatitis was not mandatory). • Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing was not mandatory). • Patients with a prior or current history of a second malignancy (except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin, or any other curatively treated malignancy that had not been treated or recurred in the prior 3 years). • Clinically significant cardiac disease including congestive heart failure (New York Heart Association Class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy; or clinically uncontrolled hypertension (systolic blood pressure [SBP] > 140 mmHg or diastolic blood pressure [DBP] > 90 mmHg). Impaired cardiac function or clinically significant cardiac diseases, including

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	o Aspartate aminotransferase (AST) and ALT ≤ 2.5 x ULN, except for patients with tumour involvement of the liver who had ALT and AST ≤ 5 x ULN. o Calculated creatinine clearance (CrCL) ≥ 50 mL/min (≥ 0.835 mL/s) (Cockcroft-Gault formula). o Serum amylase ≤ ULN (the patient was enrolled if amylase > ULN but there was no evidence of pancreatic disease). o Serum lipase ≤ ULN (the patient was enrolled if lipase > ULN but there was no evidence of pancreatic disease). o Fasting plasma glucose ≤ 200 mg/dL (≤ 11.1 mmol/L). **IV. Prior treatment[ab]** • Patients with NSCLC that had progressed during treatment with a prior ALK inhibitor or within 2 weeks of the last dose of a prior ALK inhibitor, and the first dose of ceritinib was expected to be ≤ 60 days since the last dose of the prior ALK inhibitor. **OR** • Patients with NSCLC that had progressed since treatment with prior ALK inhibitor, but that need not have been the last prior therapy, and they did not meet the previous criteria. **V. Informed consent** • Patients gave written informed consent to participate in this study. **VI. Availability of tumour sample** • Tumour samples collected in this study could be used for two purposes: o To confirm ALK status of patients	any one of the following: o Complete left bundle branch block o Obligated use of a cardiac pacemaker o Congenital long QT syndrome o History or presence of ventricular tachyarrhythmia o Presence of unstable atrial fibrillation (ventricular response > 100 beats per minute [bpm]) o Clinically significant resting bradycardia (< 50 bpm) o Corrected QT interval using Frederica formula (QTcF) > 450 ms for males and > 470 ms for females at screening electrocardiogram (ECG) o PR > 240 ms o QRS > 110 ms o Right bundle branch block + left anterior hemiblock (bifascicular block) o Angina pectoris < 3 months prior to starting study drug o Acute myocardial infarction < 3 months prior to starting study drug • Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromised compliance with the protocol. **II. Prior therapy** • Patients treated with chemotherapy or biologic therapy or other investigational agent < 2 weeks prior to starting study drug for compounds with a half-life ≤ 3 days, and < 4 weeks prior to starting study drug for compounds with a prolonged half-life. - Note: Patients whose immediate prior treatment was crizotinib could start treatment with ceritinib one week after the last dose of crizotinib. • Unresolved toxicity greater than CTCAE grade 1 from previous anti-cancer therapy or radiotherapy (excluding neurotoxicity, alopecia, ototoxicity, lymphopenia), or incomplete recovery from previous surgery, unless agreed by Novartis and the Principal Investigator and was documented.

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	o For exploratory biomarker assessment. • For ALK testing: o If an archival tumour sample was available, it was planned to be collected during the pre-screening period. In patients who were previously treated with an ALK inhibitor, whenever possible the patient's archived tumour block/slide were obtained after disease progression following the prior ALK inhibitor therapy. o For patients without an archival tumour sample or documented evidence of ALK abnormalities, a fresh biopsy was collected for ALK testing. • For biomarker assessment: o At baseline: If the tumour sample collected for ALK testing was sufficient, it was also used for biomarker assessments. o If not, a fresh tumour biopsy (core needle or surgical) for biomarker assessment was collected, if feasible (ideally prior to start of treatment with ceritinib, however the timing of the biopsy could be at the discretion of the Investigator).	• Patients who received radiotherapy to a large volume (including whole brain radiotherapy) < 2 weeks prior to starting study drug, and patients who had received radiotherapy to a small volume (including stereotactic radiotherapy to the CNS) < 1 week prior to starting study drug. • Patients who had underwent major surgery < 2 weeks prior to starting study drug or who had not recovered from the surgical procedure. **III. Current medications** • CYP3A4/5: • Patients treated with medications that were known to be strong inhibitors or inducers of CYP3A4/5 that could not be discontinued at least a week prior to start of treatment with ceritinib and for the duration of the study. • Patients receiving medications that were mainly metabolized by CYP3A4/5 and had low therapeutic index that could not be discontinued at least a week prior to start of treatment with ceritinib, and for the duration of the study. • CYP2C9: patients receiving warfarin and phenytoin that could not be discontinued at least a week prior to start of treatment with ceritinib and for the duration of the study. • Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes. • Anticoagulants: Patients receiving coumarin-type anticoagulants who could not discontinue at least a week prior to start of treatment and for the duration of the study. Treatment with therapeutic doses of coumarin-type anticoagulants for line patency (maximum daily dose of 2 mg) was permitted. Low molecular weight heparin was permitted. • Patients using illegal drugs. • Patients receiving concurrent investigational drugs, radiotherapy or chemotherapy.

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		IV. Pregnancy statement and contraception requirements • Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. • Women of child-bearing potential, defined as women physiologically capable of becoming pregnant, unless they were using effective methods of contraception during dosing of study treatment through the study completion visit, 28 days after the last dose of study drug. • Sexually active males had to use a condom during intercourse while taking the drug and for 28 days after the last dose of study drug, and could not father a child in this period. A condom was required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. **V. Others** • Patients unwilling or unable to comply with the protocol (including patients unable to swallow multiple capsules).

[a] Criteria refers specifically to patients in the expansion phase.
[b] Criteria refers specifically to patients of interest who had been treated with a prior ALK inhibitor (n=163). All of these patients had received crizotinib, in addition five of these patients were also treated with another ALK inhibitor, CH5424802, as the last prior ALK inhibitor.
Abbreviations: ALK, Anaplastic lymphoma kinase; CSR; Clinical Study Report; CTCAE, Common terminology criteria for adverse events; DBP, diastolic blood pressure ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; RECIST, response evaluation criteria in solid tumours; SBP, systolic blood pressure; ULN, upper limit of normal
Source: Preliminary CSRs(5, 8)

4.11.5 Outcomes

Commonly used outcome measures across both trials and the corresponding definitions are presented in Table 14. Efficacy outcomes were estimated based on Investigator assessment. A Blinded Independent Review Committee (BIRC) also evaluated response related endpoints and progression-free survival to off-set any potential investigator-led bias.

Table 14: Definitions of Efficacy Endpoints

Endpoint	Definition
Time to event outcomes	
Overall survival (OS)	Time from first treatment to death due to any cause
Progression free survival (PFS)	Time from treatment to the date of disease progression or death
Time to progression (TTP)	Time from treatment to the date of disease progression
Time to tumour response (TTR)	Time from treatment to CR or PR
Best response	
Objective/Overall response rate (ORR)	Percentage of patients with complete or partial response to treatment
Disease control rate (DCR) [ASCEND-2 only]	Proportion of patients with BOR of CR, PR, or SD
Complete response (CR)	Disappearance of all known lesion(s); confirmed at 4 weeks
Partial response (PR)	At least 30% decrease; confirmed at 4 weeks
Stable disease (SD)	Neither PR nor PD criteria met
Progressive disease (PD)	≥20% increase; no CR, PR or SD documented before increased disease, or new lesion(s)

Abbreviations: BOR, best overall response; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease; ORR, overall response rate; OS, overall survival; PFS, progress free survival; TTP; time to progression; TTR, time to response
Source: Preliminary CSRs(5, 8)

ASCEND-2

A summary of the primary and secondary outcomes and measures for ASCEND-2 is presented in Table 15.

Table 15: Primary and Secondary Outcomes of ASCEND-2

Outcome(s) and measures	Reliability/validity/current use in clinical practice
Primary outcome(s) and measures	
Overall response rate (ORR)	Overall response rate is a highly important outcome for patients in clinical practice. It has quality of life implications and is related to overall survival. Guidelines detailing a standardised approach to solid tumour measurement in the form of the RECIST criteria have recently been updated
Secondary outcome(s) and measures	
Duration of response (DOR)*	Duration of response is a standard clinical endpoint in the evaluation of cancer treatments.
Disease control rate (DCR)*	The control of disease is a vital outcome for new therapies.
Time to Response (TTR)*	The time between taking the drug and onset of a clinical response is an important outcome and a standard clinical endpoint.
Overall intracranial response rate (OIRR)*	Overall response rate is a highly important outcome for patients in clinical practice. It has quality of life implications and is related to overall survival.

Outcome(s) and measures	Reliability/validity/current use in clinical practice
Overall response rate (ORR)*	Overall response rate is a highly important outcome for patients in clinical practice. It has quality of life implications and is related to overall survival. Guidelines detailing a standardised approach to solid tumour measurement in the form of the RECIST criteria have recently been updated.
Overall survival (OS)	Extension of life is arguably the most important outcome for a patient in clinical practice.
Progression-free survival (PFS)*	Progression free survival is a highly important outcome for patients in clinical practice. Disease progression has quality of life implications and is related to overall survival. Guidelines detailing a standardised approach to solid tumour measurement in the form of the RECIST criteria have recently been updated.
To evaluate the safety profile of ceritinib	Adverse events would be closely monitored in clinical practice

*Outcomes were assessed by Investigator assessment (based on RECIST version 1.1) and a Blinded Independent Review Committee (BIRC) (see Section 4.11.5)
Abbreviations: DOR, duration of response; DCR, disease control rate; OIRR, overall intracranial response rate; ORR, overall response rate; OS, overall survival; PFS, progress free survival; RECIST, response evaluation criteria in solid tumours; TTR, time to response
Source: Preliminary CSR(8)

ASCEND-1

A summary of the primary and secondary outcomes and measures for ASCEND-1 is presented in Table 16.

Table 16: Primary and Secondary Outcomes of ASCEND-1

Outcome(s) and measures	Reliability/validity/current use in clinical practice
Primary outcome(s) and measures	
Overall response rate (ORR)* and duration of response (DOR)*	Overall response rate is a highly important outcome for patients in clinical practice. It has quality of life implications and is related to overall survival. Guidelines detailing a standardised approach to solid tumour measurement in the form of the RECIST criteria have recently been updated Duration of response is a standard clinical endpoint in the evaluation of cancer treatments.
Secondary outcome(s) and measures	
Duration of response (DOR)*	Duration of response is a standard clinical endpoint in the evaluation of cancer treatments.
Overall intracranial response rate (OIRR)*	Overall response rate is a highly important outcome for patients in clinical practice. It has quality of life implications and is related to overall survival.
Overall response rate (ORR)*	Overall response rate is a highly important outcome for patients in clinical practice. It has quality of life implications and is related to overall survival. Guidelines detailing a standardised approach to solid tumour measurement in the form of the RECIST criteria have recently been updated.
Overall survival (OS)	Extension of life is arguably the most important outcome for a patient in clinical practice.
Progression-free survival (PFS)*	Progression free survival is a highly important outcome for patients in clinical practice. Disease progression has quality of life implications and is related to overall survival. Guidelines detailing a standardised approach to solid tumour measurement in the form of the RECIST criteria have recently been updated.

Outcome(s) and measures	Reliability/validity/current use in clinical practice
To evaluate the safety profile of ceritinib	Adverse events would be closely monitored in clinical practice

*Outcomes were assessed by Investigator assessment (based on RECIST version 1.0) and a Blinded Independent Review Committee (BIRC) (see Section 4.11.5)
Abbreviations: DOR, duration of response; OIRR, overall intracranial response rate; ORR, overall response rate; OS, overall survival; PFS, progress free survival; RECIST, Response Evaluation Criteria In Solid Tumours
Source: Preliminary CSR(5)

4.11.6 Statistical analysis and definition of study groups in the relevant studies

Table 17: Summary of Statistical Analyses in ASCEND-2

	ASCEND-2	ASCEND-1
Hypothesis objective	**Null hypothesis:** The overall response rate will be less than or equal to 25% in those treated with ceritinib. **Alternative hypothesis:** The overall response rate will be greater than 25% in those treated with ceritinib	NR
Statistical analysis	**Primary endpoint:** ORR, as assessed by the Investigator per RECIST 1.1, was estimated and the exact 95% CI was provided.	ORR, as assessed by the Investigator per RECIST version 1.0, was estimated and 95% CIs based on the exact binomial distribution were presented. DOR, as assessed by the Investigator per RECIST version 1.0, was described using Kaplan-Meier methods and included estimated median (in months) with 95% CI, 25th and 75th percentiles.
Sample size, power calculation	A total sample size of 140. The study targeted an ORR of 38%. A response rate of 25% or less was considered as insufficient level of activity for the proposed patient population. Therefore, H_0: ORR ≤ 25% was tested vs. H_1: ORR > 25% using a one-sided test with α=0.025 based on the exact binomial distribution. The null hypothesis was to be rejected and the study declared positive based on the probability of obtaining the observed ORR under a binomial distribution with underlying parameter p0=0.25. Based on 137 patients required to test the null hypothesis, if 45 or more responses were observed (observed ORR of 32.8%), H_0 was to be rejected at a one-sided α=0.025.	During the expansion phase, up to 310 patients were enrolled, with at least 25 and up to 100 patients in each of the NSCLC arms (Arms 1A, 1B and 2), and approximately 10 patients in Arm 3. In Arms 1A and 1B, given a sample size of 25 patients per arm, if 7 responses were seen (observed ORR of 28%), the posterior probability that the true ORR being <10% was 1% and being ≥25% was 59%, with 95% credible interval of (12.6%, 45.7%). Given a sample size of 100 patients per arm, if 25 responses were seen (observed ORR of 25%), the 95% credible interval was (17.0%, 33.7%). In general, for any sample size of 25 or greater ceritinib demonstrated preliminary evidence of clinically relevant antitumour activity if the lower bound of the 95% credible interval was greater than 10% at the MTD/RDE within that arm.
Data management, patient withdrawals	Confirmed PR or CR reported prior to any additional anticancer therapy was considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response. Patients with a best overall response (BOR) of 'Unknown' per RECIST 1.1 were considered as non-responders when estimating ORR. Patients who had disease progression and continued to receive study drug after progression qualified for PD at the time of progression and were counted as PD in the derivation of ORR and any other efficacy endpoints.	Confirmed PR or CR reported prior to any additional anticancer therapy was considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response. Patients who were of unknown clinical response were treated as non-responders when estimating ORR. Patients who had PD and continued to receive study drug after progression qualified for PD at the time of progression and were counted as PD in the derivation of ORR and other efficacy endpoints. If a patient did not have an event, DOR was censored at the date of last adequate tumour assessment.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; MTD, maximum tolerated dose; NR, not reported; NSCLC, non-small celllung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; RDE, recommended dose for expansion
Source: ASCEND-2 preliminary CSR(8) and ASCEND-1 protocol(75)

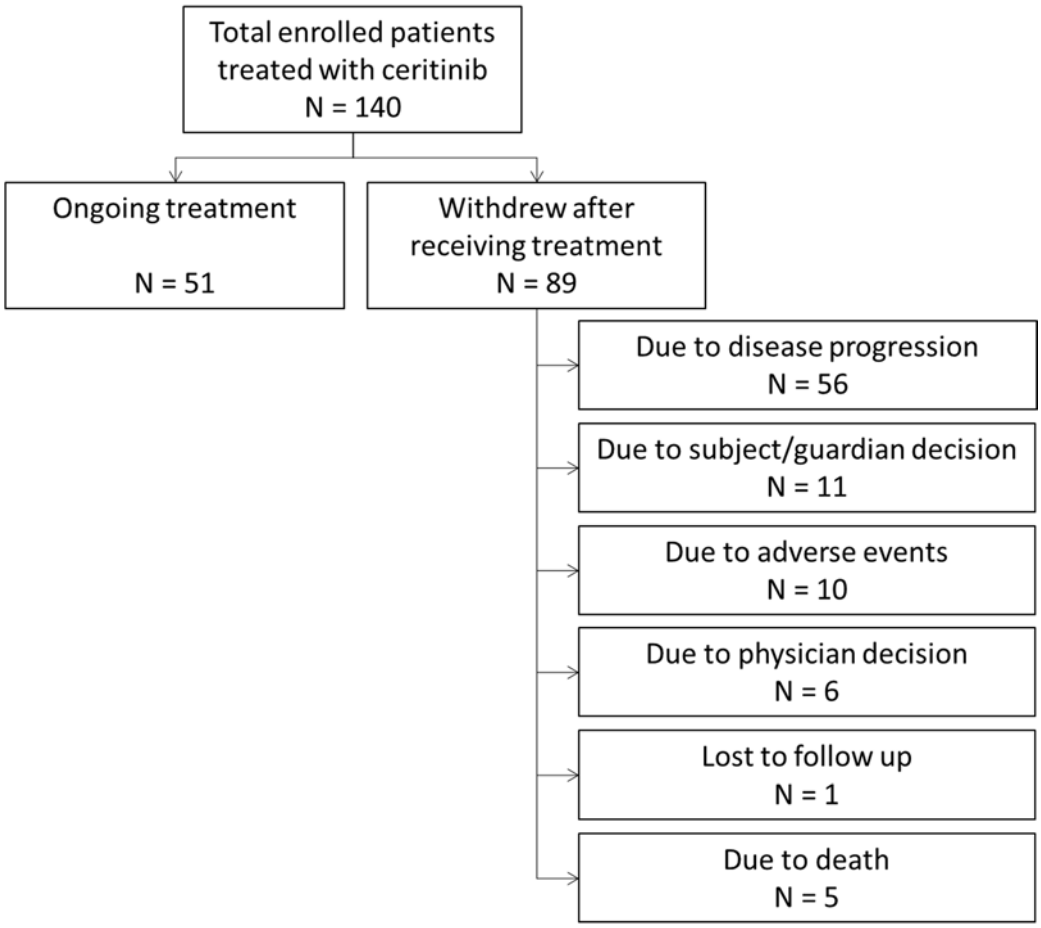
4.11.7 Study Participants

Participant flow in the non-randomised trials

ASCEND-2

Patient flow in the ASCEND-2 clinical trials is presented in Figure 5. This description represents the status of all patients enrolled up to the updated cut-off date of the 14th August 2014.

Figure 5: Patient flow in ASCEND-2



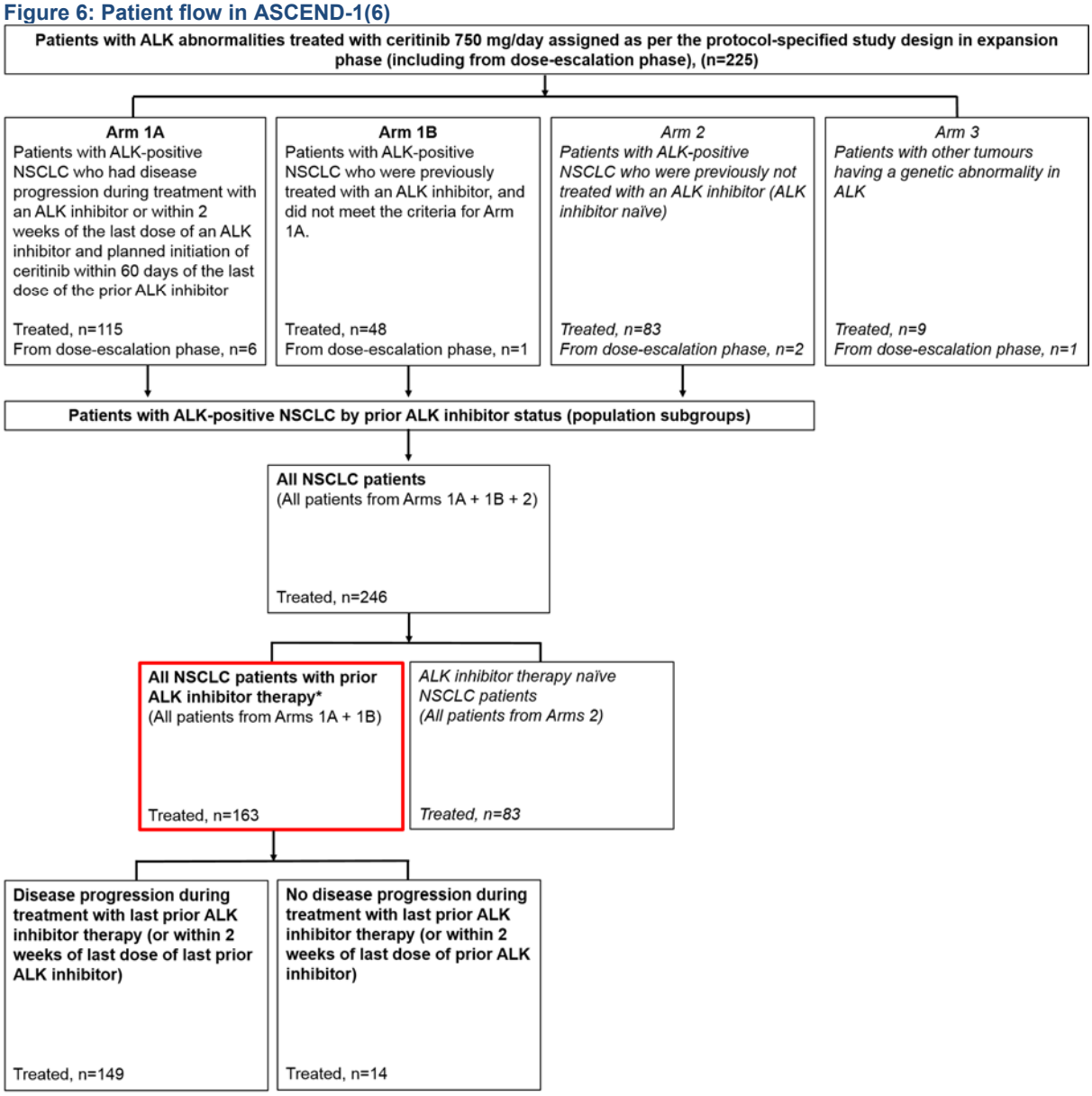
ASCEND-1

Patients enrolled in ASCEND-1 were split into subgroups dependent on their disease status and prior ALK inhibitor status. The eligibility criteria of the trial were broader than the population of interest to this submission, including ALK+ inhibitor naïve patients as well as patients previously treated with an ALK+ inhibitor.

The entire patient population, as well as the specific subgroup of interest in this submission – patients previously treated with an ALK+ inhibitor (n=163) - is shown in Figure 6. Within the main body of this submission results are only presented for this subgroup of patients, as this matches the decision problem under consideration in the submission. The patient flow and current status of this subgroup is shown in Figure 7.

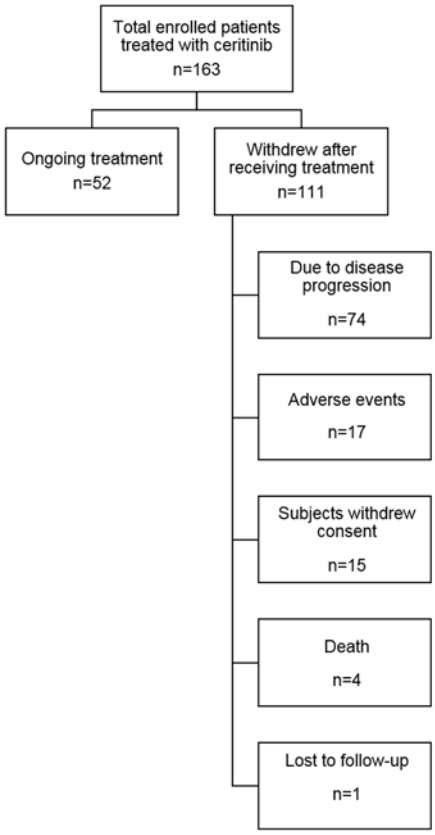
Results for the subgroup of ALK+ inhibitor naïve patients (n=83) and the study population as a whole (n=246) are presented in **Error! Reference source not found.**.

Figure 6: Patient flow in ASCEND-1(6)



* Patients of interest are outlined in red.

Figure 7: Patient flow in ASCEND-1 expansion phase(10)



4.11.8 Baseline characteristics

The key baseline characteristics of the patients enrolled in ASCEND-2 and the treated subgroup population of ASCEND-1 are presented in Table 18. The key demographic characteristics between the studies were similar in terms of age, sex and race; however, there were slight differences in the severity of disease between the two studies. Specifically, ASCEND-1 was associated with a lower proportion of patients classified as fully active by the ECOG performance rating (ie. ECOG equal to 0; 23.3% versus 30.0%) and both the Investigator assessment and the BIRC assessment concluded that the median burden of the disease was greater in this trial (Table 18).(9-11, 14) However, patients in ASCEND-2 were more likely to have received a higher number of prior treatments.

Table 18: A Summary of the Baseline Characteristics of Patients Included in ASCEND-2 and ASCEND-1

	ASCEND-2 (n=140)	ASCEND-1 (n=163)
Age (years):		
Mean (SD)	51.2 (11.62)	51.5 (11.63)
Median, (Min, Max)	51 (29 – 80)	52 (24-80)
Category (years) [n (%)]		
<65	122 (87.1)	141 (86.5)
≥65	18 (12.9)	22 (13.5)
Sex [n (%)]		
Male	70 (50.0)	75 (46.0)
Female	70 (50.0)	88 (54.0)
Race [n (%)]		
Caucasian	84 (60.0)	108 (66.3)
Asian	53 (37.9)	47 (28.8)
Other	3 (2.1)	8 (4.9)
Ethnicity [n (%)][1]		
Hispanic or Latino	[redacted]	16 (9.8)
East Asian	[redacted]	NR
Southeast Asian	[redacted]	NR
South Asian	[redacted]	NR

	ASCEND-2 (n=140)	ASCEND-1 (n=163)
West Asian	[redacted]	NR
Other	[redacted]	NR
Unknown	[redacted]	NR
Not Reported	[redacted]	NR
ECOG Performance Status (WHO) [n (%)]		
0	42 (30.0)	38 (23.3)
1	78 (55.7)	104 (63.8)
≥2	20 (14.3)	21 (12.9)
Smoking status [(n (%)]		
Never smoker	NR	109 (66.9)
Ex-smoker	NR	49 (30.1)
Current smoker	NR	5 (3.1)
Disease Burden (SOD at Baseline for Target Lesions Based on Investigator assessment) (cm)		
N	140	163
Mean (SD)	6.7 (6.21)	9.2 (6.80)
Median	4.3	8.0
Minimum – Maximum	1.0 – 38.0	1.0-42.4
Disease Burden (SOD at Baseline for Target Lesions based on BIRC assessment) (cm)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum - Maximum	[redacted]	[redacted]
Histological classification [(n (%)][2]		
Adenocarcinoma	129 (92.1)	152 (93.3)
Adenosquamous cell carcinoma	[redacted]	[redacted]
Bronchioalveolar carcinoma	[redacted]	[redacted]
Mucinus adenocarcinoma	[redacted]	[redacted]
Papillary serous	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]
Undifferentiated carcinoma	[redacted]	[redacted]
Large cell carcinoma	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Time Since Initial Diagnosis of Primary Site (months)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum – Maximum	[redacted]	[redacted]
Time from Initial Diagnosis of Primary Site to First Dose of Study Drug (months)		
N	[redacted]	163
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	21.2
Minimum – Maximum	[redacted]	2.4 – 174.2
Time from Initial Diagnosis to First Recurrence/Progression (months)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum – Maximum	[redacted]	[redacted]
Number of prior regimens* [n (%)]:		
1	0 (0.0)	26 (16.0)
2	61 (43.6)	45 (27.6)
3	50 (35.7)	35 (21.5)
>3	29 (20.7)	57 (35.0)

[1] Ethnicity [n (%)] in ASCEND-1 reported as Hispanic/Latino: 16 (9.8); Chinese: 12 (7.4); Indian (Indian subcontinent): 3 (1.8); mixed ethnicity: 1 (0.6) and other: 131 (80.4)(6). [redacted]. Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, not reported; SOD, sum of longest diameter; WHO, World Health Organisation
Source: Published posters, preliminary CSRs and updated results(5, 8-11, 14)

4.11.9 Critical appraisal

Critical appraisals of ASCEND-2 and ASCEND-1 were performed as per the NICE guidelines in adherence to the Centre for Reviews and Dissemination (CRD); please see **Error! Reference**

source not found..(76) Differences between the Investigator assessment and BIRC assessment are discussed in Section 4.11.5.

4.11.10 Clinical Effectiveness

Summary of results

A summary of the key results reported across ASCEND-2 and ASCEND-1 is reported in Table 19. The results were similar across both trials with ceritinib. Full results from these studies can be found below.

Table 19: Summary of key efficacy outcomes in ASCEND-2 and ASCEND-1

	ASCEND-2 Investigator Assessment Ceritinib 750 mg (n=140)(9)	ASCEND-2 BIRC Assessment Ceritinib 750 mg (n=140)(9, 11)	ASCEND-1 Investigator Assessment Ceritinib 750 mg (n=163)(6, 7, 10)	ASCEND-1 BIRC Assessment Ceritinib 750 mg (n=163)(7)
Data cut-off	**13th August 2014**		**14th April 2014**	
ORR – n (%) [95% CI]	54 (38.6) [30.5, 47.2]	50 (35.7) [27.8, 44.2]	92 (56.4) [48.5, 64.2]	75 (46.0) [38.2, 54.0]
DCR – n (%) [95% CI]	108 (77.1) [69.3, 83.8]	88 (62.9) [54.3, 70.9]	NR	NR
DOR[a] – Median (Min-Max), months	9.7 [7.1, 11.1]	9.7 [5.6, 12.9]	8.25 [6.80, 9.69]	8.8 [6.0, 13.1]
TTR – Median [95% CI], months	1.8 (1.6 – 5.6)	[redacted]	NR	NR
PFS – Median [95% CI],months	5.7 [5.4, 7.6]	7.2 [5.4, 9.0]	6.93 [5.55, 8.67]	7.0 [5.7, 8.6]
OS – Median [95% CI], months	14.9 [13.5, NE]	NA	16.7 [14.8, NE]	NA

[a]Patient populations for DOR outcome are based on those who achieved CR and PR
Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, non-estimable; NR, not reported; ORR, overall response rate; PR, partial response; TTR, time to response; PFS, progression-free survival; OS, overall survival
Source: as indicated

ASCEND-2

Response rates

The primary efficacy endpoint of the ASCEND-2 trial was ORR. In the ASCEND-2 trial, among the 140 patients treated with ceritinib the ORR was 38.6% (95% CI: 30.5, 47.2) based on Investigator assessment.(9) The assessment of response by the BIRC was consistent with the results obtained by the Investigator assessment (

Table 20).

The results for ORR at the 13th August data cut-off (48 weeks) were seen to be consistent with those at the primary analysis cut-off date of 26th February 2014 (24 weeks).

Patients were found to respond early to ceritinib, with the median time to response 1.8 months (95% CI: 1.6, 5.6).(9)

Table 20: Comparison of Investigator versus BIRC Assessment of Response to Treatment. Data cut-off 13th August 2014.

	ASCEND-2 Investigator Assessment	ASCEND-2 BIRC Assessment

	Ceritinib 750 mg (n=140)	Ceritinib 750 mg (n=140)
Best overall response, n (%)		
Complete response (CR)	4 (2.9)	0
Partial response (PR)	50 (35.7)	50 (35.7)
Stable disease (SD)	54 (38.6)	38 (27.1)
Progressive disease (PD)	19 (13.6)	15 (10.7)
Non-CR/Non-PD	NR	22 (15.7)
Unknown	13 (9.3)	15 (10.7)
ORR (CR + PR), n (%) [95% CI][a]	54 (38.6), [30.5, 47.2]	50 (35.7) , [27.8, 44.2)]
DCR (CR + PR + SD), n (%) [95% CI]	108 (77.1), [69.3, 83.8]	88 (62.9), [54.3, 70.9]

[a] Exact binomial 95% CI; p-value < 0.001 associated with exact test of H0: ORR <= 25% vs. H1: ORR >25% based on exact binomial distribution indicates statistical significance (one-sided) at the 0.025 level.
Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease
Source: Mok *et al.* 2015(9)

The disease control rate (DCR) was 77.1% (95% CI: 69.3, 83.8) based on Investigator assessment, compared to 62.9% (95% CI: 54.3, 70.9) based on BIRC assessment.(9) The slightly lower value observed in the BIRC assessment primarily results from the reduced classification of patients with SD (n=38 compared to n=54 in the BIRC and Investigator assessments, respectively). Additionally, a greater number of patients were classified as having a progressive disease in the Investigator assessment (n=19), compared to the BIRC assessment (n=15).

Duration of response

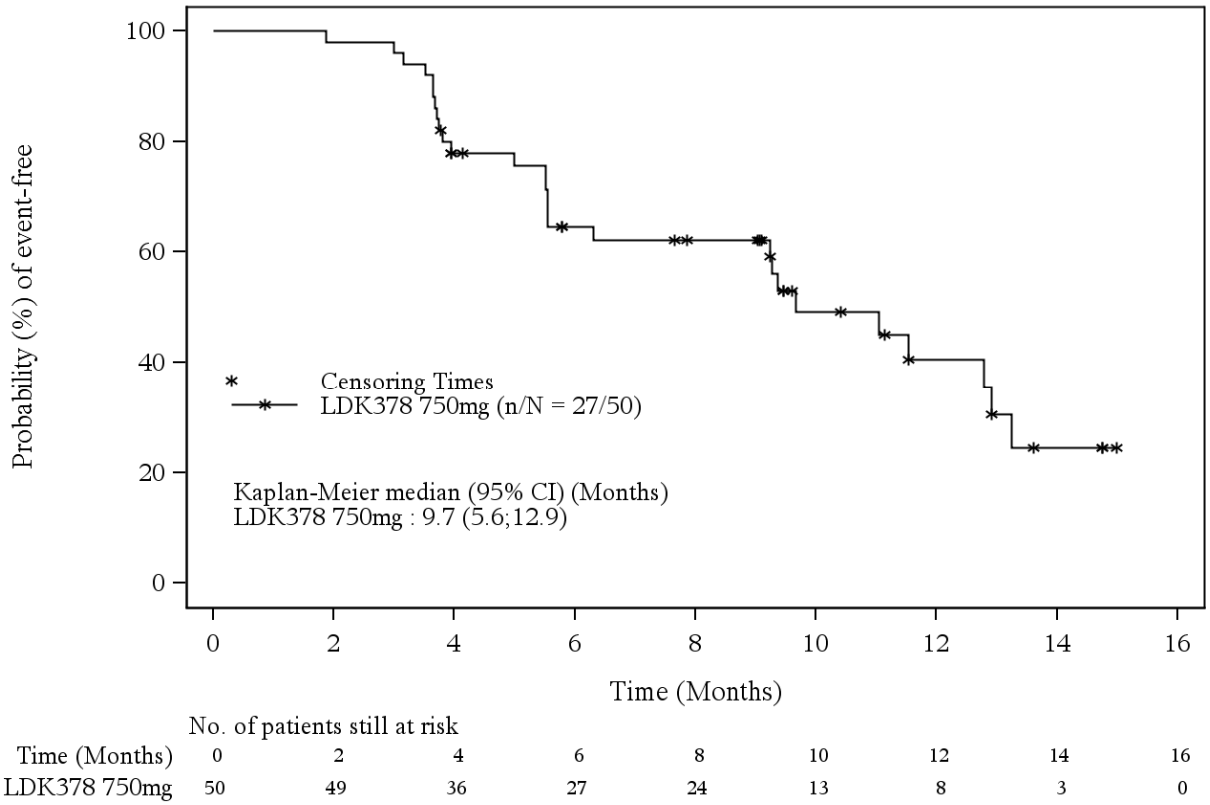
The estimated median Investigator-assessed duration of response (DOR) for patients with a confirmed CR or PR was 9.7 months (95% CI: 7.1, 11.1) (Table 21).(9) The assessment of response by the BIRC was consistent with the results obtained by the Investigator assessment. The Kaplan-Meier plot for DOR based on the BIRC assessment is presented in Figure 8.

Table 21: Comparison of Investigator versus BIRC Assessment of Duration of Response (DOR). Data cut-off 13th August 2014.

	ASCEND-2 Investigator Assessment Ceritinib 750 mg (n=54)	ASCEND-2 BIRC Assessment Ceritinib 750 mg (n=50)
Median DOR (months), [95% CI]	9.7, [7.1, 11.1]	9.7, [5.6, 12.9]
12-month DOR Rate (%) [95% CI]	[redacted]	[redacted]

n: Total number of patients with confirmed CR/PR.
Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; DOR, duration of response;
Source: Mok *et al.*(9) ASCEND-2 updated results (cut-off August 2014)(11)

Figure 8: Kaplan-Meier Plot of Duration of Response for Patients in ASCEND-2 based on BIRC assessment. Data cut-off 13th August 2014.



Source: ASCEND-2 updated results (cut-off August 2014), Mok *et al.*(9, 11)

Progression free survival

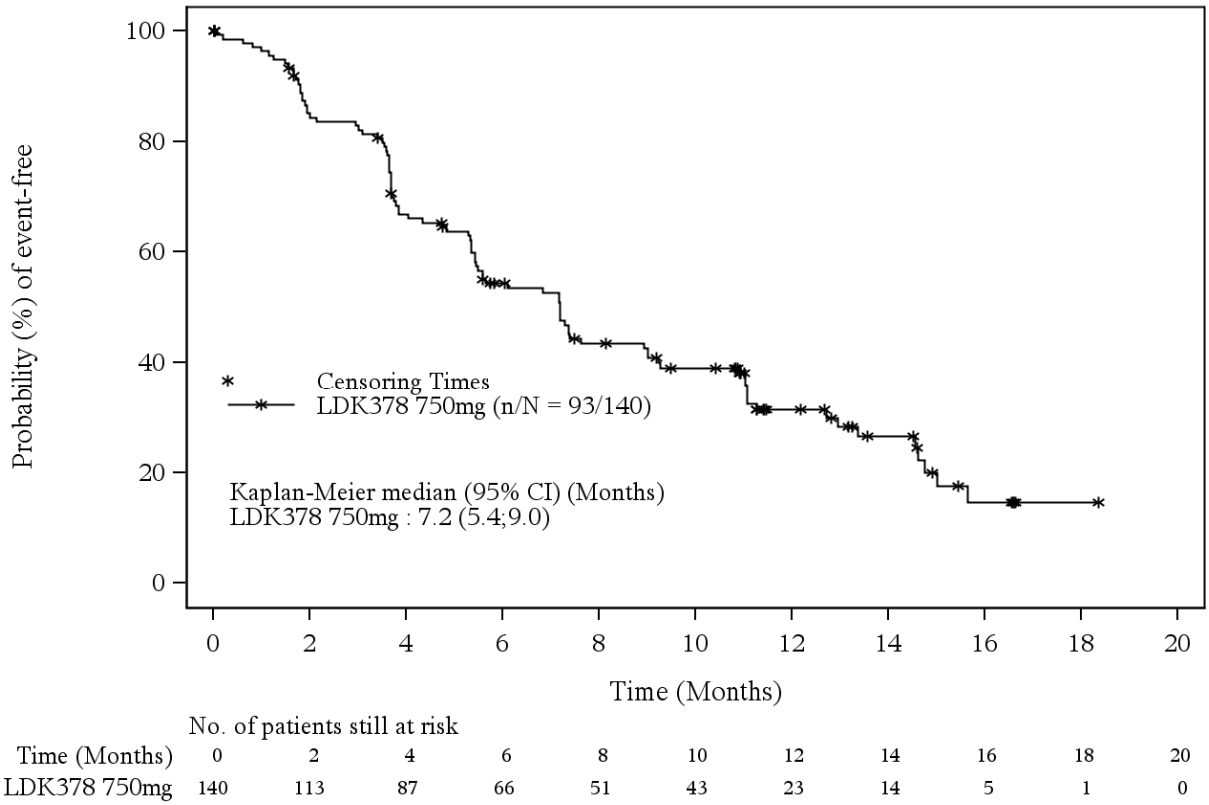
In ASCEND-2, the median PFS was 5.7 months (95% CI: 5.4, 7.6).(9) The assessment of response by the BIRC was consistent with the results obtained by the Investigator assessment, as seen in Table 22 . A Kaplan-Meier plot of PFS is shown in Figure 9.

Table 22: Comparison of Investigator versus BIRC assessment of Progression Free Survival (PFS). Data cut-off 13th August 2014.

	ASCEND-2 Investigator Assessment Ceritinib 750 mg (n=140)	ASCEND-2 BIRC Assessment Ceritinib 750 mg (n=140)
No. of events	[redacted]	93 [redacted]
No. of patients censored	[redacted]	[redacted]
Median PFS (month) [95% CI]	5.7 [5.4, 7.6]	7.2 [5.4, 9.0]
PFS rate at 12 months (%) [95% CI]	[redacted]	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; PFS, progression free survival
Source: Mok *et al.*(9) ASCEND-2 updated results (cut-off August 2014)(11)

Figure 9: Kaplan-Meier Plot of Progression Free Survival for Patients in ASCEND-2 based on BIRC assessment. Data cut-off 13th August 2014.



Source: ASCEND-2 updated results (cut-off August 2014), Mok *et al.*(9, 11)

Overall survival

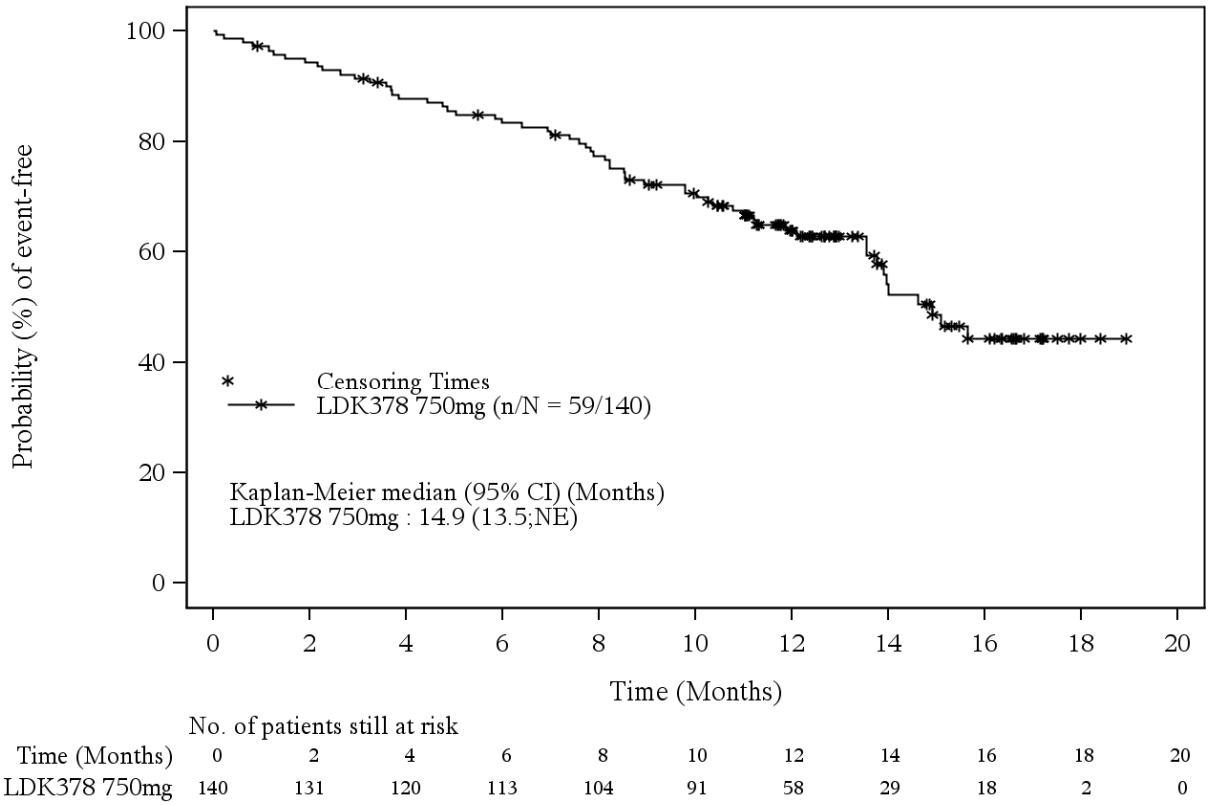
In ASCEND-2, the median OS was 14.9 months (95% CI: 13.5, NE) as shown in Table 23.(9) A Kaplan Meier curve representing OS is shown in Figure 10.

Table 23: Overall Survival in ASCEND-2. Data cut-off 13th August 2014.

	ASCEND-2 Ceritinib 750 mg (n=140)
No. of deaths, n (%)	59 ([redacted])
No. patients censored	81 (57.9)
Percentiles (% [95% CI])	
25th percentile (month)	[redacted]
Median (month)	14.9 (13.5, NE)
75th percentile (month)	[redacted]
12-month survival rate (% [95% CI])	
12 months	[redacted]

Abbreviations: CI, confidence interval; NE, non-estimable
Source: Mok *et al.*(9) ASCEND-2 updated results (cut-off August 2014)(11)

Figure 10: Kaplan-Meier Plot of Overall Survival for Patients in ASCEND-2. Data cut-off 13th August 2014.



Source: ASCEND-2 updated results (cut-off August 2014), Mok *et al.*(9, 11)

ASCEND-1

Response rates

In the ASCEND-1 trial, among the 163 patients treated with ceritinib after a prior ALK-inhibitor, the ORR was 56.4% (95% CI: 48.5, 64.2) based on Investigator assessment (Table 24).(10) The assessment of response by the BIRC was consistent with the results obtained by the Investigator assessment.

Table 24: Comparison of Investigator versus BIRC Assessment of Overall Response Rate (ORR). Data cut-off 14th April 2014.

	ASCEND-1 Investigator Assessment Ceritinib 750 mg (n=163)[a]	ASCEND-1 BIRC Assessment Ceritinib 750 mg (n=163)[b]
Best overall response, n (%)[c]		
Complete response (CR)	3 (1.8)	[redacted]
Partial response (PR)	89 (54.6)	[redacted]
Stable disease (SD)	29 (17.8)	[redacted]
Progressive disease (PD)	16 (9.8)	[redacted]
Unknown	26 (16.0)	[redacted]
Overall response rate (ORR) (CR or PR), n (%) [95% CI][d]	92 (56.4), [48.5, 64.2]	75 (46.0), [38.2, 54.0]

[a] Patients with prior ALK inhibitor. Best overall response is based on Investigator's assessment of disease status using RECIST 1.0 criteria.
[b] Patients with prior ALK inhibitor. Best overall response is based on BIRC assessment of disease status using RECIST 1.0 criteria
[c] CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met.
[d] Exact binomial 95% Confidence Interval
Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease
Source: Felipe *et al.*(10) ASCEND-1 updated results (cut-off April 2014)(14)

Duration of response

The estimated median Investigator-assessed duration of response (DOR) for patients with a confirmed CR or PR was 8.25 months (95% CI: 6.80, 9.69) (Table 25).(10) The assessment of response by the BIRC was consistent with the results obtained by the Investigator assessment. The Kaplan-Meier plot for DOR based on the BIRC assessment is presented in Figure 11.

Table 25: Comparison of Investigator versus BIRC Assessment of Duration of Response (DOR). Data cut-off 14th April 2014.

	ASCEND-1 Investigator Assessment Ceritinib 750 mg (n=92)	ASCEND-1 BIRC Assessment Ceritinib 750 mg (n=75)
No. of events	[redacted]	[redacted]
Progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
No. of censored	[redacted]	[redacted]
Median DOR (months), [95% CI]	8.25 [6.80, 9.69]	8.8 [6.0, 13.1]
12-month DOR Rate (%) [95% CI]	[redacted]	[redacted]

N: Total number of patients included in the analysis.
Median DOR with 95% CIs is calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; DOR, duration of response
Source: ASCEND-1 updated results (cut-off April 2014)(14), Summary of Product Characteristics(7), European Public Assessment Report(6)

Figure 11: Kaplan-Meier Plot of Duration of Response for Patients in ASCEND-1 based on BIRC assessment. Data cut-off 14th April 2014.

[redacted]

Source: ASCEND-1 statistical outputs (cut-off April 2014)(77)

Progression free survival

In ASCEND-1, the median PFS was 6.93 months (95% CI: 5.55, 8.67).(10) The assessment of response by the BIRC was consistent with the results obtained by the Investigator assessment, as seen in Table 26. The Kaplan-Meier plot for DOR based on the BIRC assessment is presented in shown in Figure 12.

Table 26: Comparison of Investigator versus BIRC assessment of Progression Free Survival (PFS). Data cut-off 14th April 2014.

	ASCEND-1 Investigator Assessment Ceritinib 750 mg (n=163)	ASCEND-1 BIRC Assessment Ceritinib 750 mg (n=163)
No. of events	113 (69.3%)	[redacted]
Progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
No. of censored	50 (30.7%)	[redacted]
Median PFS (month) [95% CI]	6.93 [5.55, 8.67]	7.0 [5.7, 8.6]
PFS rate at 12 months (%) [95% CI]	27.2 [19.8, 35.1]	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; PFS, progression free survival
Source: Felipe *et al.*(10) ASCEND-1 updated results (cut-off April 2014)(14) Summary of Product Characteristics(7)

Figure 12: Kaplan-Meier Plot of Progression Free Survival for Patients in ASCEND-1 based on BIRC assessment. Data cut-off 14th April 2014.

[redacted]

Source: ASCEND-1 statistical outputs (cut-off April 2014)(77)

Overall survival

In ASCEND-1, the median OS was 16.7 months (95% CI: 14.8, NE) as shown in Table 27. A Kaplan Meier curve representing OS is shown in Figure 13.

Table 27: Overall Survival in ASCEND-1. Data cut-off 14th April 2014.

	ASCEND-1

	Ceritinib 750 mg (n=163)
No. of deaths, n (%)	63 (38.7)
No. patients censored	100 (61.3)
Percentiles (% [95% CI])	
25th percentile (month)	[redacted]
Median (month)	16.7 (14.8, NE)
75th percentile (month)	[redacted]
12-month survival rate (% [95% CI])	
12 months	67.2 (58.9, 74.1)

Abbreviations: CI, confidence interval; NE, non-estimable
Source: ASCEND-1 updated results (cut-off April 2014)(14), European Public Assessment Report(6)

Figure 13: Kaplan-Meier Plot of Overall Survival for Patients in ASCEND-1. Data cut-off 14th April 2014.

[redacted]

Source: ASCEND-1 updated results (cut-off April 2014)(14)

4.11.11 Pooled Efficacy data (ASCEND-2 and ASCEND-1)

The baseline characteristics of the ASCEND-2 and ASCEND-1 clinical trials are sufficiently similar to permit a pooled analysis of results (see Section 4.11.8). A pooled analysis of the clinical endpoints informing the cost-effectiveness economic model is presented below. Pooled results are sourced from ASCEND-2 updated results (cut-off August 2014) and ASCEND-1 statistical outputs (cut-off April 2014).(11, 14)

Table 28: Median PFS/OS in the pooled cohort (ASCEND 1 and 2)

	Pooled results BIRC assessment ASCEND-2 and ASCEND-1 (n=303)
PFS – Median [95% CI],months	[redacted]
OS – Median [95% CI], months	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; PFS, progression free survival; OS, overall survival
Source: see above

4.12 *Additional real-world evidence*

As reported in Section 4.11, an additional real-world retrospective analysis of ALK+ NSCLC patients treated with sequential crizotinib and ceritinib was also identified by the systematic literature review. Conducted by Gainor et al., the study aimed to determine the outcome of

sequential treatment with crizotinib and ceritinib, with respect to PFS and OS outcomes. A brief overview of the trial methodology and a summary of the key results are presented below.

4.12.1 Study Overview

In this retrospective review, 73 ALK-positive NSCLC patients who were previously treated with crizotinib, followed by ceritinib, were identified across four institutions. All patients were treated with sequential crizotinib and ceritinib between 2008 and 2014, and received ceritinib either as part of a clinical trial (n=71; NCT01283516) or on a compassionate use basis (n=2).

Medical records were reviewed to determine OS and PFS on crizotinib and ceritinib (data were updated as of June 2014).The Kaplan-Meier method was used to estimate all PFS and OS endpoints, and the log-rank test was used to compare differences between groups.

4.12.2 Results

Among 73 ALK-positive patients, the median PFS on crizotinib was 8.2 months [95% CI: 7.4, 10.6]. The median interval from crizotinib discontinuation to initiation of ceritinib was 25 days (range 1–694) and the median PFS on ceritinib was 7.8 months [95% CI: 6.5–9.1]. This was similar for patients who received no interval therapies between crizotinib and ceritinib (n=53, 7.8 months [95% CI: 5.4, 9.8]). The median combined PFS for sequential treatment with crizotinib and ceritinib was 17.4 months (95% CI: 15.5, 19.4).

Among 23 patients who underwent post-crizotinib/pre-ceritinib biopsies, there was no difference in PFS on ceritinib between patients with or without *ALK* resistance mutations (median PFS 5.8 versus 6.5 months, respectively; p=0.510).

In the overall study population, median OS from the date of diagnosis was 49.4 months (35.5–63.1). Among 25 ALK-positive patients with brain metastases identified prior to initiation of crizotinib, the median OS was 42.2 months (95% CI: 26.4-51.2). Thirty-two (44%) patients received crizotinib in the second-line setting – therefore directly reflecting the treatment pathway outlined in this submission – and the median OS from the time of crizotinib initiation for patients treated with ceritinib in this subset of patients was 30.3 months (95% CI: 18.0-43.8 months).

4.12.3 Summary

Gainor et al. demonstrated that ceritinib had significant anti-tumour activity in ALK-positive NSCLC, even when crizotinib immediately precedes treatment (median combined PFS of 17.4 months). Furthermore, the treatment effect was retained in patients who developed ALK resistance mutations on crizotinib. The combined overall survival in line with the treatment indication under review was 30.3 months.(29)

The crizotinib PROFILE 1007 trial reported median OS on crizotinib to be 20.3 months. Therefore, this evidence from the Gainor *et al.* study is suggestive of an approximately 10 month extension to life when ceritinib is used sequentially to crizotinib.(30)

4.13 *Naïve indirect comparison*

As described in Section 4.10, the only identified study providing evidence of clinical effectiveness of a relevant comparator to ceritinib in the population of patients with advanced ALK+ NSCLC previously treated with crizotinib is the Ou *et al.* study. This study evaluated patients receiving BSC (no active treatment), of relevance to the decision problem outlined in this submission. In addition, this study also evaluated patients receiving systemic chemotherapy, of relevance to a scenario analysis presented in Section 5.8.3. Details of the Ou *et al.* study are provided below.

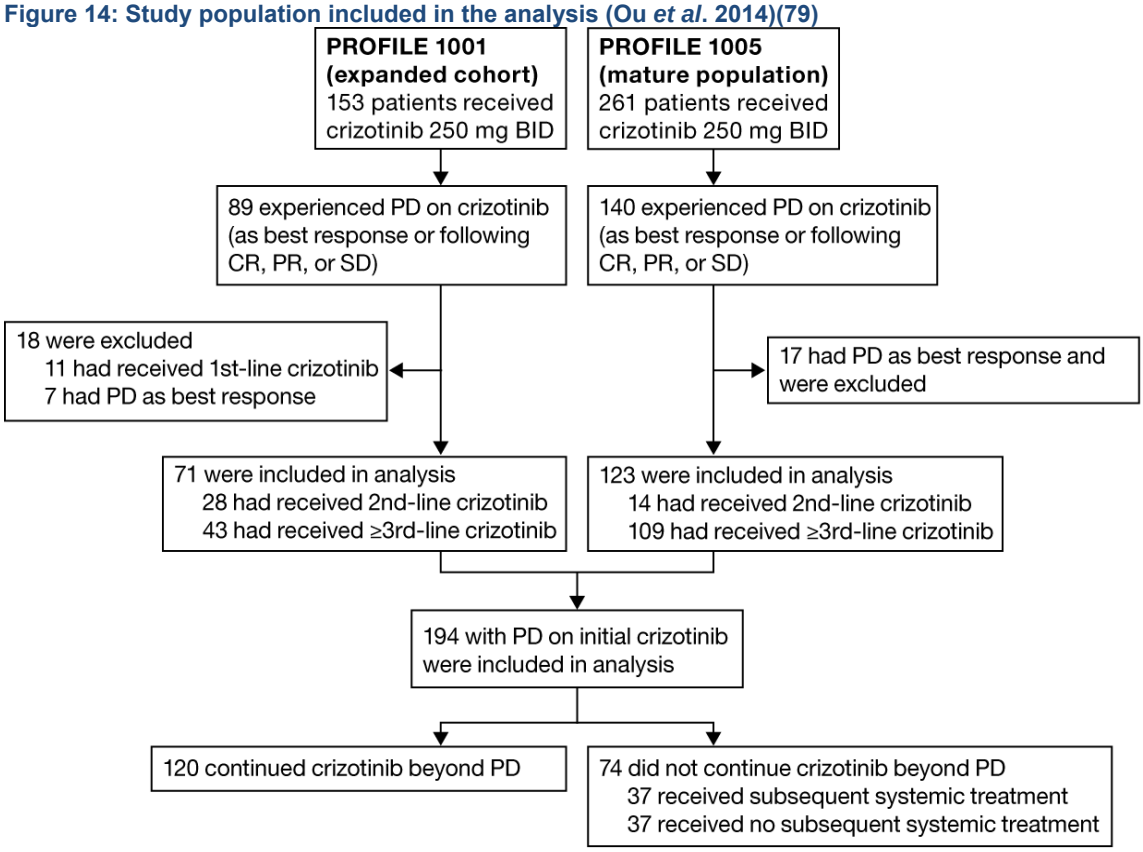
4.13.1 Participants and methodology

Patients with advanced ALK-positive NSCLC enrolled in either PROFILE 1001 expansion cohort or PROFILE 1005 (and treated by 1st February 2011 in the latter study) were included in this analysis. The methodology of both trials and the key inclusion and exclusion criteria for PROFILE 1001 and PROFILE 1005 have been previously described.(78)

Although the trials were similar, a major difference between the two was that patients in PROFILE 1005 must have failed at least one line of treatment, while patients in PROFILE 1001 could have been treatment-naïve. However, patients who had received crizotinib as first-line treatment in PROFILE 1001 were excluded from the retrospective analysis by Ou *et al.* to ensure that comparable populations of patients from the two trials were analysed. The Ou *et al.* publication also notes that patients from either study whose best overall response to initial crizotinib treatment was progressive disease (PD) were also excluded from the analysis by Ou *et al*. in order to avoid introducing bias into the analysis.

The study population included in the analysis is described below (Figure 14). Baseline characteristics of the patient population of PROFILE 1001 and PROFILE 1005 are included in **Error! Reference source not found.**.

Figure 14: Study population included in the analysis (Ou *et al*. 2014)(79)



Abbreviations: BID, twice daily; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease

Figure 14 shows how the 194 patients included in the retrospective analysis were split between three different post-progressive disease treatment strategies, as follows:

- 37 patients received BSC (no active treatment).
- 37 patients received systemic therapy
- 120 patients continued on crizotinib post disease progression (not considered further in this submission)

Baseline characteristics and results of the BSC (no active treatment) and systemic therapy arms are reported in this submission.

4.13.2 Outcomes

The key measure of clinical efficacy in the post-crizotinib population was overall survival (OS). The Kaplan−Meier method was used to estimate OS endpoints and two-sided 95% confidence intervals (CIs) were determined using the Brookmeyer–Crowley method.

4.13.3 Baseline characteristics

The baseline characteristics of patients included in the analysis are presented in Table 29 below. The study publication only provides baseline characteristics for patients who did not continue crizotinib and therefore received either BSC or systemic therapy (n=74) together. The Ou *et al.* publication does not provide baseline characteristics for the group of patients receiving BSC (n=37) and the group of patients receiving systemic therapy (n=37) separately.

Table 29: Baseline characteristics of patients included in the analysis

Characteristic	Did not continue CBPD, n (%) (n=74)
Age (years)	
Mean (median)	52 (54)
Range	28–78
Age category	
< 65 years	68 (92)
≥ 65 years	6 (8)
Sex	
Male	35 (47)
Female	39 (53)
Ethnicity	
White	34 (46)
Asian	34 (46)
African-American	5 (7)
Other	1 (1)
Clinical trial	
PROFILE 1001	23 (31)
PROFILE 1002	51 (69)
Smoking history	
Never-smoker	53 (72)
Former-smoker	19 (26)
Current smoker	2 (3)
ECOG PS at baseline	
0	14 (19)
1	48 (65)
2	11 (15)
3	1 (1)
ECOG PS at disease progression	
0	18 (24)
1	43 (58)
2	8 (11)
≥3	2 (3)
Missing	3 (4)
Histology	
Adenocarcinoma	71 (96)
Other	3 (4)
Prior lines of therapy (for advanced/metastatic disease)	
1	15 (20)
≥2	59 (80)
Prior platinum-based therapy	
Yes	72 (97)
No	2 (3)

Abbreviations: CBPD, crizotinib beyond progressive disease; ECOG PS, Eastern Cooperative Oncology Group performance status

Source: Ou *et al.* (2014)(1)

Selected baseline characteristics from the study population describe above have been compared with the ASCEND-2 and ASCEND-1 trials which present the key clinical evidence on ceritinib (Section 4.11) (Table 30).

Table 30: Comparison of selected baseline characteristics of Ou *et al*. 2014 and the ceritinib clinical evidence (ASCEND-2 and ASCEND-1)

	Ou *et al*. 2014(1) Did not continue CBPD, (n=74)	ASCEND-2 (n=140)(6, 9)	ASCEND-1(5) (n=163)(6, 10)
Cancer Type	ALK+ NSCLC	ALK+ NSCLC	ALK+ NSCLC
Male sex n, (%)	35 (47)	70 (50.0)	75 (46.0)
Mean Age (range)	52.0 (28–78)	51.2 (29–80)	51.5 (24-80)
ECOG performance status, grade			
0	14 (19)	42 (30.0)	38 (23.3)
1	48 (65)	78 (55.7)	104 (63.8)
2+	12 (16)	20 (14.3)	21 (12.9)
Smoking history			
Never-smoker	53 (72)	NR	109 (66.9)
Former-smoker	19 (26)	NR	49 (30.1)
Current smoker	2 (3)	NR	5 (3.1)
Prior lines of therapy (for advanced/ metastatic disease)			
1	15 (20)	0 (0)	26 (16.0)
≥2	59 (80)	140 (100.0)	137 (84.0)

Abbreviations: ALK, Anaplastic lymphoma kinase; CBPD, crizotinib beyond progressive disease; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; NR, not reported
Source: as indicated

There are no key differences in baseline characteristics between trials. In the Ou *et al*. analysis, a greater proportion of patients have a slightly higher ECOG rating. In terms of prior therapy, patients enrolled in ASCEND-2 all had at least 2 prior lines of therapy whereas 20% of patients assessed by Ou *et al.* had only received 1 prior therapy in the advanced/ metastatic disease phase. However, as described previously in Section 4.10, Ou *et al.* represents the only available, relevant evidence source in the population of under consideration and these differences in baseline characteristics are not considered to render a naïve indirect comparison inappropriate.

4.13.4 Clinical effectiveness

The median OS post-crizotinib for patients who received BSC (n=37) was 2.2 months (95% CI: 1.1, 3.8).

For patients who received systemic therapy (n=37), the median OS was 5.4 months (95% CI: 3.8, 12.3), resulting in a pooled estimate across all patients who did not continue crizotinib (BSC and systemic therapy) of 3.9 months (95% CI: 2.7, 5.1) (Table 31).

Table 31: Overall survival in post-crizotinib population

	Ou *et al*. 2014 OS from the time of PD
BSC (n=37, months) [95% CI]	2.2 [1.1–3.8]
Systemic therapy (n=37, months) [95% CI]	5.4 [3.8, 12.3]
Did not continue CBPD (n=74)	
Median (months) [95% CI]	3.9 [2.7–5.1]
6-month OS probability (%) [95% CI]	31.2 [20.0, 43.0]
12-month OS probability (%) [95% CI]	23.9 [13.3, 36.1]

Abbreviations: BSC, best supportive care; CBPD, crizotinib beyond progressive disease; OS, overall survival; PD, progressive disease
Source: Ou *et al.* (2014)(1)

As a naïve indirect comparison, median OS on ceritinib based on the ASCEND-2 and ASCEND-1 trials is considerably longer than median OS with BSC (no active treatment) as determined by the Ou *et al.* publication. Median OS was 14.9 months (95% CI: 13.5, NE) and 16.7 months (95% CI: 14.8, NE) in the ASCEND-2 and ASCEND-1 trials, respectively, and the pooled estimate across these two trials was [redacted].(9, 14) In comparison, the estimate in patients who received BSC (no active treatment) in the Ou *et al.* publication of 2.2 months (95% CI: 1.1, 3.8).

4.14 *Adverse reactions*

4.14.1 ASCEND-2

Data on the safety profile of ceritinib in ASCEND-2 is available up to a period of 48 weeks. The safety profile of ceritinib over this time period was seen to be consistent with that observed across the clinical trial programme to date for ceritinib at the 750 mg dose and the rate of AEs leading to discontinuation was relatively low (7.9%) (Table 32).(9) A total of [redacted] died during the study period with [redacted] deaths observed on-treatment (up to 30 days after the last dose of ceritinib) (Table 32).(11)

Table 32: Overall Summary of Adverse Events (Safety Set). Data cut-off 13th August 2014.

Category	ASCEND-2 Ceritinib 750 mg (n=140) All Grades n (%)	ASCEND-2 Ceritinib 750 mg (n=140) Grade 3/4 n (%)
All Deaths[a]	[redacted]	[redacted]
On-treatment Deaths[b]	[redacted]	[redacted]
Adverse Events	140 (100.0)	[redacted]
Suspected to be Drug Related	[redacted]	[redacted]
Serious Adverse Events	57 (40.7)	[redacted]
Suspected to be Drug Related	24 (17.1)	[redacted]
AEs Leading to Discontinuation	11 (7.9)	[redacted]
AEs Requiring Dose Adjustment or Interruption	[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.
AEs are graded according to the CTCAE V4.03; MedDRA version 17.0 is used.
Abbreviations: AE, adverse event
Source: Felipe *et al.(10)* ASCEND-2 updated results (cut-off August 2014)(11)

The most common AEs were gastrointestinal (diarrhoea, nausea, vomiting, constipation), increases in transaminases and fatigue. A summary of all (≥25%) and Grade 3/4 (≥5%) adverse events regardless of study drug relationship can be seen in Table 33.

Table 33: Summary of Safety Data from ASCEND-2. Data cut-off 13th August 2014.

	AEs (≥25% all grades)	Gr 3/4 AEs (≥ 5%)
ASCEND-2	• Diarrhoea • Nausea • Vomiting • AST/ALT increase • Decreased appetite • Fatigue • Weight decreased • Abdominal pain • Constipation	• AST/ALT increase • GGT increase • Diarrhoea • Nausea • Fatigue • Dyspnea

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, Gamma-glutamyl transpeptidase; GI, gastrointestinal; NSCLC, non-small cell lung cancer

Source: Felipe *et al.(10)* ASCEND-2 updated results (cut-off August 2014)(11)

A summary of all adverse events (greater than 10%) and Grade 3/4 adverse events (greater than 2%) regardless of study drug relationship can be seen in Table 34.

Table 34: All and Grade 3/4 Adverse Events, Regardless of Study Drug Relationship, by Preferred Term (Greater than 10% for All Grades or Greater than 2% for Grades 3/4) for ASCEND-2 (Safety Set). Data cut-off 13th August 2014.

	ASCEND-2 Ceritinib 750 mg (n=140) All Grades n (%)	ASCEND-2 Ceritinib 750 mg (n=140) Grades 3/4 n (%)
Total	140 (100.0)	[redacted]
Nausea	114 (81.4)	9 (6.4)
Diarrhoea	112 (80.0)	9 (6.4)
Vomiting	88 (62.9)	6 (4.3)
Alanine Aminotransferase Increased	61 (43.6)	24 (17.1)
Decreased Appetite	57 (40.7)	5 (3.6)
Fatigue	51 (36.4)	9 (6.4)
Weight Decreased	48 (34.3)	6 (4.3)
Aspartate aminotransferase Increased	45 (32.1)	7 (5.0)
Abdominal Pain	44 (31.4)	2 (1.4)
Constipation	40 (28.6)	3 (2.1)
Cough	30 (21.4)	0
Dyspnoea	29 (20.7)	8 (5.7)
Pyrexia	29 (20.7)	4 (2.9)
Asthenia	[redacted]	[redacted]
Gamma-glutamyl transferase Increased	[redacted]	[redacted]
Blood Creatinine Increased	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Non-cardiac Chest Pain	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Back Pain	[redacted]	[redacted]
Blood Alkaline Phosphatase Increased	[redacted]	[redacted]
Oedema Peripheral	[redacted]	[redacted]
Abdominal Pain Upper	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Upper Respiratory tract Infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Pericardial Effusion	[redacted]	[redacted]
General Physical Health Deterioration	[redacted]	[redacted]
Hepatic Function Abnormal	[redacted]	[redacted]

Source: Felipe *et al.(10)* ASCEND-2 updated results (cut-off August 2014)(11)

A summary of Grade 3/4 adverse events (greater than or equal to 1%) suspected to be related to the study drug in the ASCEND-2 clinical trial is provided in Table 35 below.

Table 35: Grade 3/4 Adverse Events Suspected to be Study Drug Related, by Preferred Term for ASCEND-2 (Safety Set). Data cut-off 13th August 2014

	ASCEND-2 Ceritinib 750 mg (n=140) Grades 3/4 n (%)
Total	[redacted]
Nausea	[redacted]
Diarrhoea	[redacted]

Vomiting	[redacted]
Alanine aminotransferase increased	[redacted]
Decreased appetite	[redacted]
Aspartate aminotransferase increased	[redacted]
Fatigue	[redacted]
Gamma-glutamyltransferase increased	[redacted]
Blood alkaline phosphatase increased	[redacted]
Asthenia	[redacted]
Neutropenia	[redacted]
Pneumonia	[redacted]
Hepatic function abnormal	[redacted]
Hypophosphataemia	[redacted]

Source: ASCEND-2 updated results (cut-off August 2014)(11)

4.14.2 ASCEND-1

In ASCEND-1, ceritinib demonstrated a low rate of AEs leading to discontinuation ([redacted]). A total of 63 patients (38.7%) died during the study period, with [redacted] deaths observed on-treatment (up to 28 days after the last dose of ceritinib) (Table 36).

Table 36: Overall Summary of Adverse Events (Safety Set). Data cut-off April 14th 2014.

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

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 > 28 days after the last dose of study drug.
[b] Deaths occurring more than 28 days after the last dose of study drug are not included.
AEs occurring more than 28 days after the last dose of study drug are not summarised.
Missing grades are included under 'All grades' column.
AEs are graded according to the CTCAE V4.03; MedDRA version 17.0 is used.
Abbreviations: AE, adverse event
Source: Felipe *et al.(10)* ASCEND-2 updated results (cut-off August 2014)(11)

The most common AEs were diarrhoea, nausea, vomiting, alanine aminotransferase increase and fatigue.(10) A summary of all (≥25%) and Grade 3/4 (≥5%) adverse events regardless of study drug relationship in the relevant subgroup of ASCEND-1 can be seen in Table 37.

Table 37: Summary of Safety Data from ASCEND-1. Data cut-off 14th April 2014.

	AEs (≥25% all grades)	Gr 3/4 AEs (≥ 5%)
ASCEND-1	• [redacted]	• [redacted]

	• [redacted]	

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase
Source: ASCEND-1 updated results (cut-off August 2014)(14)

A summary of all adverse events (greater than 10%) and Grade 3/4 adverse events (greater than 2%) regardless of study drug relationship can be seen in Table 38.

Table 38: All and Grade 3/4 Adverse Events, Regardless of Study Drug Relationship, by Preferred Term (Greater than 10% for All Grades or Greater than 2% for Grades 3/4) for ASCEND-1 (Safety Set). Data cut-off 14th April 2014.

	ASCEND-1 Ceritinib 750 mg (n=163) All Grades n (%)	ASCEND-1 Ceritinib 750 mg (n=163) Grade 3/4 n (%)
Total	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Alanine Aminotransferase Increased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Abdominal Pain	[redacted]	[redacted]
Decreased Appetite	[redacted]	[redacted]
Aspartate Aminotransferase Increased	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Abdominal Pain Upper	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Back Pain	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Weight Decreased	[redacted]	[redacted]
Blood Alkaline Phosphatase Increased	[redacted]	[redacted]
Blood Creatinine Increased	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]

Source: ASCEND-1 updated results (cut-off August 2014)(14)

A summary of Grade 3/4 adverse events (greater than or equal to 1%) suspected to be related to the study drug in the subgroup of patients enrolled in ASCEND-1 previously treated with an ALK+ inhibitor is provided in Table 39 below.

Table 39: Grade 3/4 Adverse Events Suspected to be Study Drug Related, by Preferred Term for ASCEND-1 (Safety Set). Data cut-off 14th April 2014

	ASCEND-1 Ceritinib 750 mg (n=163) Grade 3/4 n (%)
Total	[redacted]
Diarrhoea	[redacted]
Nausea	[redacted]
Vomiting	[redacted]
Alanine Aminotransferase Increased	[redacted]
Fatigue	[redacted]
Aspartate Aminotransferase Increased	[redacted]
Decreased Appetite	[redacted]
Blood Alkaline Phosphatase Increased	[redacted]
Lipase Increased	[redacted]
Amylase Increased	[redacted]
Hypophosphataemia	[redacted]
Gamma-Glutamyltransferase Increased	[redacted]
Transaminases Increased	[redacted]
Pneumonitis	[redacted]
Hypokalaemia	[redacted]
Neutropenia	[redacted]
Hyponatraemia	[redacted]

Source: ASCEND-1 updated results (cut-off August 2014)(14)

4.14.3 Pooled adverse events

Grade 3/4 AE results suspected to be study drug related were pooled from ASCEND-2 and ASCEND-1 to inform the economic evaluation. Included AEs in this analysis were based on AEs occurring in ≥ 5% of patients in either trial. The results of the pooled analysis are presented in Table 40 below.

Table 40: Pooled analysis of grade 3/4 adverse events suspected to be study drug related from ASCEND-2 and ASCEND-1 (greater than or equal to 5%)

	ASCEND-2 Ceritinib 750 mg (n=140) Grades 3/4 n (%)	ASCEND-1 Ceritinib 750 mg (n=163) Grade 3/4 n (%)	Pooled Analysis Ceritinib 750 mg (n=303) Grade 3/4 n (%)
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]

Source: Mok *et al.* (9), ASCEND-2 updated results (cut-off August 2014)(11); Source: ASCEND-1 updated results (cut-off August 2014)(14)

AEs from the pooled analysis that occurred in ≥5% of patients were included in the economic evaluation. Please see Section 5.4.4 for further details.

4.15 *Interpretation of clinical effectiveness and safety evidence*

Clinical effectiveness

Evidence for the clinical effectiveness of ceritinib is provided by two single-arm studies (ASCEND-2; ASCEND-1) that considered patient populations in line with the licensed indication of ceritinib and the scope of this submission; that is patients with advanced ALK+ NSCLC previously treated with crizotinib. A total of 140 patients from ASCEND-2 (entire study population) and 163 patients from ASCEND-1 (subgroup of total trial population) were treated with ceritinib at the licensed 750 mg dose and evaluated for clinically meaningful endpoints related to rate of response, duration of response and survival estimates in terms of both PFS and OS.

In this patient population for whom all other therapies have been unsuccessful in preventing disease progression, ceritinib demonstrated meaningful rates of overall response (complete response and partial response) and disease control across both trials (ORR [BIRC assessment] of 35.7% and 46.0% in ASCEND-2 and ASCEND-1, respectively; DCR [BIRC] of 62.9% in ASCEND-2).(9, 14) These responses were achieved relatively quickly (median TTR [BIRC] of [redacted] in ASCEND-2) and were seen to be durable (median duration of response [BIRC] of 9.7 months in ASCEND-2 and 8.8 months in ASCEND-1).(7, 9, 11)

These clinical trials also demonstrated meaningful survival outcomes in patients treated with ceritinib with estimates of median OS of 14.9 months (95% CI: 13.5, NE) in ASCEND-2 and 16.7 months (95% CI: 14.8, NE) in ASCEND-1.(9, 14) Ceritinib also provided patients with months of life without progression, with median PFS estimates ranging from 5.7 months (95% CI: 5.4 – 7.6) to 7.2 months (95% CI: 5.4, 9.0) across ASCEND-2 and ASCEND-1 depending on the assessment methodology used.(9, 10, 14)

The clinical effectiveness of ceritinib on overall survival must be considered in the context of the lack of treatment options available for this third-line population of patients who have progressed on crizotinib, and the resultant poor survival outcomes under current treatment strategies of BSC (no active treatment). The clinical systematic literature review presented in Section 4.1 identified only a single study providing estimates of the effectiveness of this comparator in the specific patient population of ALK+ NSCLC patients who have progressed on crizotinib that are under consideration in this submission. In this study, median OS post-crizotinib for patients who received BSC (no active treatment) was 2.2 months (95% CI: 1.1, 3.8). When patients treated with systemic therapy were also considered, the combined estimate of median OS post-crizotinib was 3.9 months (95% CI: 2.7, 5.1).

Although only a naïve indirect comparison associated with limitations as a result of the available data (discussed below), these results suggest that ceritinib offers an extension to life of approximately 10 months over currently available treatments for this patient population in considerable need of active therapies to treat their disease.

Clinical safety

It is important to consider the clinical benefits provided by ceritinib in the context of the safety profile of this therapy. A high proportion of patients experienced drug-related adverse events in the phase I ASCEND-1 trial ([redacted]) and the phase II ASCEND-2 trial ([redacted]).(11, 14) The most common adverse events (those occurring in more than 25% of patients) in these two trials were diarrhoea, nausea, vomiting, AST/ALT increase, decreased appetite, fatigue, weight decrease, abdominal pain and constipation, cough and dyspnea.(9, 10) This adverse event profile is consistent with early safety results with ceritinib.(74)

Grade 3/4 serious adverse events suspected to be study drug related occurred in [redacted] and [redacted] of patients in ASCEND-2 and ASCEND-1 (previously treated with crizotinib subgroup), respectively and the most common grade 3/4 adverse events generally across these patients were AST/ALT increase, blood alkaline phosphatase (ALP) increase, diarrhoea, nausea, fatigue, dyspnea and GGT increase.(9-11, 14)

Although these adverse events should be considered when evaluating the risk-benefit profile of ceritinib, it should be noted that adverse events led to study drug discontinuation in a relatively small proportion of patients in the ASCEND-2 trial (7.9%) and ASCEND-1 trial subgroup ([redacted]).(9, 14)

Limitations of the evidence

Ceritinib received a marketing authorisation from the European Medicines Agency (EMA) based on single-arm Phase I and II data. This accelerated approval inevitably leads to a limitation of the evidence in a health technology assessment setting, as only uncontrolled trials are available. Despite the uncontrolled nature of the trials, the regulatory approval demonstrates that in this case of extremely high unmet need, the efficacy and safety evidence provided by these two trials was sufficient for the EMA to conclude that ceritinib provides clinical benefit to patients at an acceptable risk/safety profile.

The systematic literature review did identify one study that reports outcomes for BSC (no active treatment) in the appropriate patient population. The Ou *et al.* study considered treatment of a total of 37 patients with BSC (no active treatment), and a further 37 patients treated with systemic chemotherapy, in the appropriate patient population. Given the uncontrolled nature of all the evidence due to the accelerated approval from the EMA, evaluation of comparative effectiveness has to be restricted to a naïve indirect comparison of absolute estimates of overall survival in the ASCEND-2 and ASCEND-1 trials compared to the relevant arms of the Ou *et al.* study. As far as possible given the evidence available, the patient populations of the ceritinib trials and the Ou *et al.* study have been assessed for comparability in order to evaluate the validity of any comparison based on outcomes from these studies. This comparison finds the trial

populations to be broadly similar, though the limited available information is acknowledged. The uncertainty in the results of the comparison resulting from the small patient numbers in the Ou *et al.* study is also acknowledged.

Whilst there are limitations to the interpretation of the clinical effectiveness of ceritinib relative to the relevant comparator presented in this submission, this comparison is considered to be the most appropriate comparison possible given the available evidence base, as it is the only comparison that can compare outcomes in the relevant patient population of advanced ALK+ NSCLC patients who have progressed on crizotinib.

Relevance of evidence based to the decision problem

- A key strength of the available evidence is that the population of the ASCEND-2 trial (n=140) and the subgroup of the ASCEND-1 trial (n=163) exactly match the licensed indication and the population stated in the decision problem of this submission. Therefore, the clinical effects observed in these trials can be considered directly relevant to expected effects in UK clinical practice.

- The dose of ceritinib considered in these two trials (750 mg) represents the licensed dose of ceritinib.

- Although the patient populations in these trials were not particularly large, given the small number of ALK+ NSCLC patients in the UK who will reach the third-line of treatment at which ceritinib is being considered, the total of 303 patients across which evidence is provided should be considered a meaningful sample size.

- The outcomes considered in the ASCEND-2 and ASCEND-1 trials are relevant outcomes to clinical practice, are meaningful to patients and clinicians and are consistent with previous trials in this disease.

Table 41: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The Ou *et al.* study provides the best estimate of life expectancy in the population of advanced ALK+ NSCLC patients who have progressed on crizotinib under the current treatment strategy of BSC (no active treatment).(1) For patients receiving BSC (no active treatment) (n=37), this study estimates median OS of 2.2 months (95% CI: 1.1–3.8). For patients receiving systemic therapy (n=37), this study estimates median OS of 5.4 months (95% CI: 3.8–12.3). Taken together, the median OS across these patients (n=74) is estimated at 3.9 months (95% CI: 2.7–5.1).
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	In ASCEND-2, median overall survival OS amongst 140 patients treated with ceritinib was 14.9 months (95% CI: 13.5, NE) and median progression-free survival (PFS) was 5.7 months (95% CI: 5.4, 7.6).(9) Overall survival estimates were similar in a phase I trial of ceritinib (ASCEND-1) in which 163 patients treated with ceritinib experienced a median OS of 16.7 [14.8, NE] and median PFS of 6.93 months (95% CI: 5.55, 8.67).(7, 10) The pooled estimate of median OS across the ASCEND-2 and ASCEND-1 clinical trials was

	[redacted]; the pooled estimate of median PFS was [redacted]. Compared to the estimates of survival on current treatment of BSC (see above), this represents an extension to life of approximately 10 months. In the Gainor *et al.* study, a subgroup of patients (n=32) received crizotinib treatment in a second-line setting, therefore reflecting the patient population of the crizotinib PROFILE 1007 trial.(29) For these patients, median OS for sequential treatment with crizotinib and ceritinib from the time of crizotinib initiation was 30.3 months. Compared to an estimated median overall survival in the crizotinib PROFILE 1007 study of 20.2 months, this suggests a 10 month extension to life through the use of ceritinb in the post-crizotinib setting.(30)
The treatment is licensed or otherwise indicated for small patient populations	There are expected to be approximately 120 patients eligible for ceritinib treatment each year in England and Wales (see Table 5), which represents a very small patient population.

Abbreviations: ALK, anaplastic lymphoma kinase; BSC, best supportive care; CI, confidence interval; NSCLC, non-small cell lung cancer; OS, overall survival; NE, non-estimable
Source: as indicated

4.16 *Ongoing studies*

The ASCEND-2 and ASCEND-1 studies presented in this submission are still ongoing. The data presented in this submission represents the results at the most recent data cut-off for each of these studies.

Importantly, there is one further currently ongoing trial in adult patients with advanced ALK+ NSCLC previously treated with chemotherapy and crizotinib ie. the population under consideration in this submission. The ASCEND-5 study (A2303; NCT01828112) is a phase III study comparing oral ceritinib 750 mg with an active chemotherapy comparator (pemetrexed or docetaxel) in this population. Results from this phase III trial are not currently available but are anticipated in the first half of 2016.

As discussed in Section 4.15, as a result of the accelerated approval process there are inevitable limitations to the evidence currently available for ceritinib in a health technology assessment setting. In the relatively near future, results from a phase III RCT of ceritinib against an active comparator and in the precise population defined in the scope of this appraisal will be available. This presents a strong case for a scheduled rapid review of this health technology once these results become available.

In addition, there are two further ongoing trials with results expected within 12 months:

- The ASCEND-3 study (NCT01685138) in crizotinib naïve patients is an actively ongoing study, for which only interim results are available. These interim results are presented in **Error! Reference source not found.**.

- The ASCEND-4 (A2301; NCT01828099) phase III study in adult patients with advanced ALK+ NSCLC who are previously untreated is also ongoing.

5. Cost effectiveness

- A de novo health economic model was developed using an "area under the curve" partitioned survival semi-Markov type analysis. This model was similar to previous examples in this indication.

- This model was used to perform a cost-effectiveness evaluation of ceritinib versus BSC (no active treatment) for the treatment of advanced ALK+ NSCLC previously treated with crizotinib.

- Three mutually exclusive health states (progression free; progressed disease and death) encompassed the 4 levels of response defined by RECIST criteria.

- The evaluation took an NHS/PSS perspective and evaluated costs and health outcomes (in terms of QALYs) over a time horizon of 10 years, both discounted at 3.5%.

- Median OS and median PFS data pooled across the ASCEND-1 and ASCEND-2 trials was used to inform survival estimates for the ceritinib arm. For the BSC (no active treatment) arm, OS was taken from the Ou *et al*. study in patients with ALK+ NSCLC who had progressed on crizotinib; due to lack of PFS data in this population, PFS estimates were taken from a study in the EGFR population (Shepherd et al.).

- Extrapolation of OS and PFS was based on parametric regression models. A variety of parametric curves were fitted to the OS data using exponential, Weibull, Gompertz, log-logistic, and log-normal functions and the best-fitting curves were selected based on multiple criteria.

- Adverse events selected for inclusion in the model were grade 3/4 AEs affecting >5% of patients for ceritinib (no adverse events were assumed for BSC). This is consistent with common practice for oncology cost-effectiveness models.

- Utility values were incorporated for individual health states with disutilities associated with adverse events applied in scenario analyses. Following a systematic literature review for utilities, a combination of trial-derived and literature-derived utilities was used. Costs relevant to the NHS and personal social services were considered.

- In the base case analsyis Ceritinib was found to be more costly (£59,155 vs. £7,203) but also more effective (1.08 QALY vs. 0.25 QALY) compared to BSC resulting in an incremental cost per QALY of £62,456

- Uncertainty in model assumptions and inputs was explored through sensitivity analysis:
    - The results of the PSA estimated an incremental cost per QALY based on 2,000 iterations of the model of £62,460
    - The results of the DSA showed little variations in the incremental cost per QALY. The model was most sensitive to assumptions around the cost of ceritinib per month, treatment discontinuation with ceritinib post-progression, choice of parametric model for ceritinib and the use of alternative published utility values.

5.1 *Published cost-effectiveness studies*

A systematic literature review was conducted to identify and review relevant sources of information relating to economic models of advanced or metastatic NSCLC. The review included studies of the economic models of NSCLC in patients with advanced or metastatic NSCLC from 2004 onwards.

The following databases were searched from the 1st January 2004 to 16th March 2015:

- Medline and Medlin In-Process (Ovid)
- EMBASE (Ovid)
- The Cochrane Library (incorporating the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database)

Relevant conference articles were searched from 2012 onwards. Please see **Error! Reference source not found.** for full details of the search strategy used.

The inclusion and exclusion criteria used to identify potentially relevant articles in the review are summarised in Table 42.

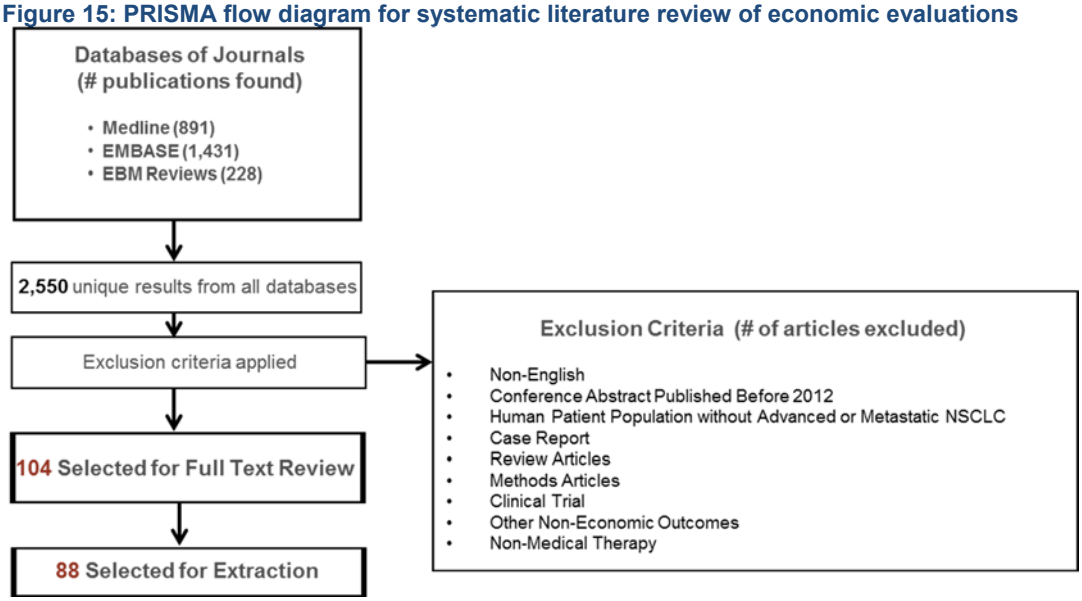
Table 42: Inclusion and exclusion criteria for the economic evaluation reviews

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

The electronic database search identified 3,148 potentially relevant articles (Medline: 891; EMBASE: 1,431; The Cochrane Library: 228). Following deduplication and application of the inclusion and exclusion criteria, 104 studies were selected for full text review of which 88 were selected for extraction. A PRISMA flow diagram is presented for the systematic literature review in Figure 15.

Figure 15: PRISMA flow diagram for systematic literature review of economic evaluations



Of the 88 economic studies that were identified in the systematic review, 10 studies evaluated the ALK+ NSCLC population, and of these, 6 were cost-effectiveness analyses. A summary of the identified studies is provided in Table 43 below.

Table 43: Summary of cost-effectiveness studies in ALK+ NSCLC

Author, Year	Title	Country or Region (perspective)	Region	Treatment
Atherly, 2012(80)	The cost-effectiveness of screening lung cancer patients for targeted drug sensitivity markers.	US	North America	Multiple therapies (ALK and crizotinib in initial model)
Djalalov S, 2013(81)	Cost-effectiveness of EML4-ALK fusion testing in combination with crizotinib treatment for patients with advanced non-small cell lung cancer living in Ontario.	Canada	North America	EML4-ALK genetic testing with crizotinib
Gay-Molina, 2012	Economic analysis of the use of crizotinib, a tyrosine kinase ALK inhibitor, in the treatment of ALK positive non-small cell lung cancer in the Mexican setting.	Mexico	North America	Crizotinib; gemcitabine + cisplatin; pemetrexed + cisplatin; docetaxel cisplatin
Djalalov S, 2014(82)	The cost-effectiveness of second-line crizotinib in EML4-ALK rearranged advanced non-small cell lung cancer.	Canada	North America	EML4-ALK genetic testing crizotinib treatment
Djalalov S, 2014(83)	The cost-effectiveness of 2nd line crizotinib in EML4-ALK rearranged advanced NSCLC in Ontario.	Canada	North America	EML4-ALK genetic testing with crizotinib treatment
Montero A.J., 2013(84)	Cost-effectiveness analysis of crizotinib in metastatic ALK+ non-small cell lung cancer (NSCLC).	US	North America	Crizotinib; pemetrexed; docetaxel

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

As can be seen from Table 43, no cost-effectiveness studies were identified that evaluated ceritinib in the relevant patient population for this submission; that is the treatment of patients with advanced ALK+ NSCLC previously treated with crizotinib in England and Wales.

5.2 *De novo analysis*

As the systematic literature review identified no cost-effectiveness studies relevant to the decision problem of this submission, a *de novo* health economic model was developed, details of which are provided below.

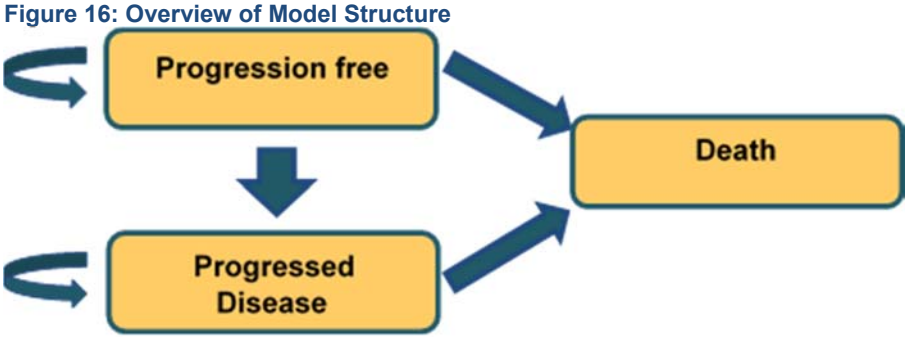
5.2.1 Patient population

The patient population consists of patients with ALK+ advanced NSCLC previously treated with crizotinib, in line with the population defined in the NICE scope and the decision problem presented in this submission, as well as the marketing authorisation for ceritinib. This modelled patient population is consistent with the patient population included in the ASCEND-2 trial, and a subgroup (n=163) of the patient population of the ASCEND-1 trial (see Section 4.11). Evidence for the clinical efficacy and safety of ceritinib in this patient population is reported in Section 4.11.10 and Section 4.14, respectively.

5.2.2 Model structure

To investigate the cost-effectiveness of ceritinib versus the relevant comparator, a *de novo* model was developed using an "area under the curve" partitioned survival semi-Markov type analysis. This model was developed in Microsoft Excel®. Partitioned survival analysis is a typical approach in modelling metastatic cancers, and has been used in many previous NICE submissions (eg, manufacturer's submission for crizotinib, TA296).(78) In this type of model, the number of patients in each health state at any time is determined directly from the underlying survival curves. An overview of the structure of the model is presented in Figure 16 below.

Figure 16: Overview of Model Structure



The model aims to capture the progressive nature of ALK+ NSCLC disease for the relevant patient population, and is aligned with the main aim of all treatment interventions for patients with ALK+ NSCLC; that is, to achieve and maintain a state of "progression free" survival and to extend overall survival. The chosen structure of the model is in line with the clinical treatment paradigm as described in Section 3.1.1 – whereby patients receive therapy with the aim of maintaining stable disease before then stopping or switching treatment as appropriate in the case of disease progression.

Three mutually exclusive health states were defined in the model: (i) progression free; (ii) progressed disease; and (iii) death (Figure 16). Patients enter the model after failure of prior crizotinib therapy; although this means that they have progressed on crizotinib therapy, patients are considered to enter the model in a defined "progression free" state because they will not have met the criterion for further progression. In this "progression free" state, patients receive either ceritinib or the comparator treatment, which is administered until the patient's disease progresses. At this point they move into the progressed disease state. The intervention and comparator arms are discussed further in Section 5.2.3.

Death is the absorbing state in the model and patients can experience death in either the "progression free" or "progressed disease" state.

The health states used in the economic model are reflective of the possible level of response to treatment, as measured on the basis of the Response Criteria Evaluation of Target Lesions (RECIST). Table 44 below shows the link between treatment response experienced by patients and the corresponding health state. Use of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) to define progression free and progressed disease health states within the model is consistent with the measurement of these response outcomes in the clinical trials of ceritinib (see Section 4.11.5).

Table 44: Response Criteria Evaluation of Target Lesions

Response level	Definition of response	Health state
Complete response (CR)	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm 1	Progression free
Partial response (PR)	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.	Progression free
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions sufficient to qualify for PD.	Progression free
Progressive disease (PD)	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm^2.	Progressed disease

Response to treatment were assessed using the RECIST criteria (version 1.0 for ASCEND-1; version 1.1 for ASCEND-2)
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease
Source: RECIST guidelines version 1.0 and version 1.1 (39, 85)

The cycle length adopted in the model corresponds to one month, with a half-cycle correction applied at the beginning and end of the model cycles. A lifetime horizon of 10 years has been adopted, with both costs and health outcomes (QALYs) discounted at the annual rate of 3.5%. Please see Table 45 for further details. The economic model generates incremental life years (LYs) and QALYs gained for ceritinib versus the comparator technologies, and estimates incremental cost per LY and per QALY gained.

Table 45: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	10 years	A lifetime time horizon of 10 years has been chosen in line with the life expectancy of adult patients with ALK-positive NSCLC in third-line treatment.
Cycle length	One month	Based on clinical trial

		measurement points and pack size for ceritinib. Cost adjustment was made for chemotherapy cycle length of 21 days.
Half-cycle correction	Yes	The perspective follows the NICE reference case
Were health effects measured in QALYs; if not, what was used?	Yes	
Discount of 3.5% for utilities and costs	Yes	
Perspective (NHS/PSS)	NHS and PSS	

Abbreviations: ALK, anaplastic lymphoma kinase; NHS, National Health Service; NICE, the National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PSS, personal social services; QALYs, quality-adjusted life years

5.2.3 Intervention technology and comparators

Intervention

The intervention assessed in the cost-effectiveness model is ceritinib. Within the model, ceritinib is evaluated in line with its marketing authorisation for the treatment of adults with ALK-positive advanced NSCLC previously treated with crizotinib. This is reflected by the use of the ASCEND-2 trial and the subgroup of ALK+ patients previously treated with crizotinib from ASCEND-1 (n=163) to inform clinical input parameters within the model (see Section 5.3).

In the model, ceritinib is administered in the intervention arm and treatment is continued until disease progression. This continuation rule is consistent with the SPC for ceritinib, which notes that treatment with ceritinib should continue for as long as clinical benefit is observed.(7) Progression of disease is therefore implicitly considered to represent an end to observed clinical benefit on ceritinib. Termination of current treatment upon disease progression is consistent with current clinical practice, as discussed in further detail in Section 3.

In the ASCEND-2 trial of ceritinib, at the data cut-off of 13th August 2014, patients had been exposed to ceritinib for a median duration of 8.8 months (range: 0.1–19.4) while the median PFS was 7.2 months (95% CI: 5.4–9.0). Hence, a median duration of 1.6 months for treatment continuation after disease progression is explored as a scenario analysis in this evaluation.

Comparators

As discussed in Section 3.3, the comparator defined by the final NICE scope for this appraisal is BSC (no active treatment). This comparator aligns with the treatment pathway as described in Section 3.2 and the base case comparator for this submission is therefore BSC (no active treatment), consistent with the NICE scope.

As outlined in Section 3.2, some patients may be treated with systemic chemotherapy (docetaxel) following progression on crizotinib, prior to receipt of BSC (no active treatment). Therefore, a scenario analysis is conducted for this economic evaluation using a composite comparator in which 70% of patients are assumed to receive BSC (no active comparator) and 30% of patients are assumed to received docetaxel for four cycles followed by BSC (no active treatment). The choice of the 70%/30% distribution is an assumption, based on the fact that many patients will not be considered fit enough to receive systemic chemotherapy following progression on crizotinib and a number of patients will have already received docetaxel at an earlier line of therapy and are therefore unlikely to be treated with this therapy again. Modelling patients to receive four cycles of docetaxel therapy before they move on to BSC (no active treatment) is consistent with clinical expert opinion on the number of cycles that patients would receive.

5.3 *Clinical parameters and variables*

5.3.1 Clinical evidence for ceritinib

Clinical evidence for ceritinib was sourced from ASCEND-2 and ASCEND-1, the two relevant trials providing clinical evidence for ceritinib in the population relevant to this submission (see Section 4.11). The clinical outcomes that inform the economic model are PFS and OS, both of which are reported for these two trials. There was no requirement to link intermediate trial outcomes to final outcomes within the cost-effectiveness model.

The ASCEND-2 (NCT01685060) trial is an ongoing Phase II, multicentre, open-label study of ceritinib, administered orally in adult patients with advanced or metastatic ALK+ NSCLC who have received prior chemotherapy regimens and progressed on prior crizotinib treatment (Section 4.11). Eligible patients had to be 18 years or older, and with stage IIIB or IV ALK+ NSCLC. Patients with symptomatic central nervous system metastases were excluded. Efficacy endpoints included ORR as per RECIST 1.1, duration of response, disease control rate, time to response, PFS as per RECIST 1.1 and OS. A total of 140 patients in this study (the whole study population) match the description of the relevant modelled population provided in Section 5.2.1.

The ASCEND-1 (NCT01283516) trial is an ongoing Phase I, multicentre, open-label, dose-escalation study of ceritinib, administered orally in adult patients with NSCLC characterised by genetic abnormalities in ALK (Section 4.11). Eligible patients must be 18 years or older, with locally advanced or metastatic cancer harbouring genetic alterations in ALK, an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0, 1, or 2, and an adequate end-organ function. Patients with asymptomatic untreated or treated central nervous system metastases were eligible, as were patients who had received prior treatment with one or more ALK inhibitors. Efficacy endpoints included overall response rate (ORR), duration of response, and PFS as per RECIST 1.0 and OS. A total of 163 patients, representing a subgroup of the total trial population, match the description of the relevant modelled population provided in Section 5.2.1.

Across both trials, there are therefore a total of 303 patients meeting the population criteria of the decision problem. Pooling of data from ASCEND-2 and ASCEND-1 has the advantage of increasing patient numbers; a larger dataset provides additional statistical power for estimation of long-term survival trends, allowing for more accurate estimation of this outcome. Appropriateness of pooling data from these two trials was considered on the basis of comparability of baseline characteristics and on comparability of survival trends.

The key demographic characteristics of patients in the studies were similar between studies in terms of age, sex and race; there were slight differences in the severity of disease between the two studies and the prior treatments received. A summary of baseline characteristics across the two trials is provided previously in Section 4.11.8, Table 18. Ultimately, the baseline characteristics of the two patient groups were considered sufficiently similar to permit an appropriate pooling of data.

In addition, survival trends were seen to be comparable between ASCEND-2 and the relevant patient subgroup of ASCEND-1, with similar reported estimates for both median OS and PFS. Upon data pooling, the resultant pooled OS and PFS estimates are seen to be similar to those reported for the individual trials (Table 46).

Table 46: Median OS and PFS estimates for ASCEND-2, ASCEND-1 NSCLC with prior ALK inhibitor population cohort and pooling of ASCEND-1 and ASCEND-2

	ASCEND-2(9)	ASCEND-1(7)	Pooled ASCEND-1 and ASCEND-2
Estimated median OS [95% CI]	14.9 [13.5, NE]	16.7 [14.8, NE]	[redacted]
Estimated median PFS [95%	7.2 [5.4, 9.0]	7.0 [5.7, 8.6]	[redacted]

CI]			

Abbreviations: OS, overall survival; PFS, progression-free survival

BIRC-assessed response data were used in the economic analysis to try to remove or lessen potential bias associated with investigator assessments. Although there are no precise guidelines in this regard, this approach is in line with some recently published opinion regarding the importance of independent data monitoring and assessment.(86)

5.3.2 Clinical evidence for comparators

As stated in Section 5.2.3, the base case analysis compares ceritinib to BSC (no active treatment).

As both ASCEND-2 and ASCEND-1 are single-arm studies, a naïve indirect comparison is required to inform the cost-effectiveness analysis. The systematic literature review described in Section 4.1 provides the relevant sources of clinical evidence used for the economic model. Out of 126 RCT and of 147 non-RCT studies included in the review, it was found that only one study (a retrospective cohort study by *Ou et al.*) provides evidence on BSC (no active treatment) used post-disease progression on crizotinib in an ALK+ NSCLC population.(1) A study by Guerin *et al.* evaluating survival patterns among ALK+ NSCLC patients was identified by the search terms outlined in Section 4.1, although it was excluded during Level 1 as the treatments patients received were not specified and no outcomes of a specific treatment was reported in the abstract. Regardless, data from this study was not considered appropriate to inform the model as its 60% of the patient cohort had received treatment with crizotinib in the 1st line setting. Therefore the patient population in the Guerin study was not comparable to the post-crizotinib patient population from the ASCEND trials, where patients received crizotinib in the 2nd line setting.

The use of the Ou *et al.* paper to inform the economic model involves several limitations. First, the paper is a retrospective study, and the allocation of patients to the different treatment options upon disease progression on crizotinib was not random. Instead, whether patients received BSC (no active treatment), systemic chemotherapy or continued on crizotinib was likely determined based on prognostic factors. Second, the paper does not specify what chemotherapeutic agents were used in the systemic chemotherapy group. Finally, the Ou *et al.* study only reports only the OS outcome; no data on PFS is provided for patients who had progressed on crizotinib.

In order to address these limitations, an extensive validation process was undertaken with a clinical expert, who confirmed that, upon progression on crizotinib, if they do not receive any alternative active treatment, ALK+ NSCLC patients would experience a very rapid and deteriorating progression of their disease. As a consequence, the outcomes reported for the BSC (no active treatment) arm of the Ou *et al.* paper can be considered representative of the outcomes (in terms of OS) that patients would experience in absence of active treatment upon disease progression on crizotinib in clinical practice. Given the lack of other data in this patient group, the OS data from the Ou *et al.* publication represents the best available source for modelling clinical effectiveness in the BSC (no active treatment) arm of the health economic model.

Given the lack of any appropriate studies providing PFS data for the BSC (no active treatment) comparator in the patient population relevant to this submission – that is patients with advanced ALK+ NSCLC previously treated with crizotinib – PFS for patients receiving BSC (no active treatment) in the model was estimated using the Kaplan-Meier curve from the placebo arm in a phase III, randomised, double-blinded, placebo-controlled trial of erlotinib in NSCLC patients positive for the EGFR mutation.(12) This study was identified in the systematic literature review of clinical evidence (see Section 4.1) and is summarised in **Error! Reference source not found.**. The Shepherd *et al.* trial was large, being conducted in 731 patients (243 in the placebo arm), and, with the exception of the molecular subtype of NSCLC and the lack of prior treatment with crizotinib, aligns well with the patient population in the Ou *et al.* study, the ASCEND-2 study, and the relevant patient subgroup of the ASCEND-1 study: patients in the Shepherd *et al.* study

had stage IIIB or IV NSCLC, ECOG score of 0 to 3, and had received one or two prior chemotherapy regimens.

However, as noted in Section 3.1.2, the population of patients with EGFR+ NSCLC is a genetically distinct population from those with ALK+ NSCLC. The specific licensing of therapies such as erlotinib, crizotinib and ceritinib to a specific molecular subtype of NSCLC (either ALK+ or EGFR+, but not both) highlights the distinct nature of these two populations where clinical benefits provided by a targeted therapy in one molecular subtype are not considered to provide evidence of clinical efficacy in the other molecular subtype. However, given the lack of any PFS data in ALK+ NSCLC, and given that BSC (no active treatment) does not represent a therapy that acts on a specific molecular target (eg. ALK, EGFR), but rather represents a broad-based approach to symptom management and palliative care, estimates of PFS on BSC from the EGFR+ population are considered the most appropriate source of PFS data for patients receiving BSC (no active treatment) in the economic model. It should be noted that modelling PFS for patients receiving BSC (no active treatment) from the Shepherd *et al.* study implicity assumes, in line with the results of the Shepherd *et al.* study, that patients receiving no active therapy can still experience a period of benefit in terms of PFS. The clinical basis for patients who receive no active treatment experiencing a period of PFS is not well established; therefore a scenario analysis therefore explores the case where patients who receive the comparator treatment of BSC (no active treatment) do not experience any treatment benefit and effectively present with actively progressing disease (see Section 5.8).

For the scenario analysis in which the composite comparator is considered, PFS for patients receiving systemic chemotherapy (docetaxel) is also modelled from the same Shepherd *et al.* source described above. This assumption was made as a result of the lack of identified data for PFS outcomes for patients treated with systemic chemotherapy followed by BSC (no active treatment) in an appropriate population of ALK+ or EGFR+ patients specifically.

5.3.3 Extrapolation beyond trial follow-up period

Overall survival
For the ceritinib arm of the model, OS was extrapolated directly from the ASCEND-2 and ASCEND-1 studies with data cut-points of 13 August 2014 and 14 April 2014, respectively. Data from the ASCEND-1 and -2 studies were pooled without adjustment (i.e., duration from randomization to death or censoring were pooled directly. The median durations of follow-up were 11.3 months (range 0.1–18.9) for ASCEND-2 and [redacted] for ASCEND-1.(9, 14) The previously treated population from ASCEND-1 (n=163) was chosen, as it matches with the indication of ceritinib under review.

For the base case comparator of BSC (no active treatment), overall survival was extrapolated from Kaplan-Meier curves of the BSC (n=37) arm in the Ou *et al.* study. For the scenario analysis exploring the composite comparator (where the comparator consists of docetaxel followed by BSC for 30% of patients and by BSC only for the remaining 70%), OS for the patients receiving systemic chemotherapy followed by BSC (no active treatment) was extrapolated from the systemic therapy (n=37) arm of the Ou *et al.* study. In particular, OS was estimated by using a weighted average of two extrapolated OS curves (one for systemic chemotheray followed by BSC and the other by BSC alone, based on the Ou *et al*. study) to produce the mixed OS data. See Section 4.13.1 for a summary of study arms for the Ou *et al.* study.

Full methodology of the survival analysis is provided in Section 5.3.4.

Progression free survival
To incorporate ceritinib clinical data into the economic model, PFS was extrapolated directly from the ASCEND-2 and ASCEND-1 studies with data cut-points of 13 August 2014 and 14 April 2014, respectively. Data from the ASCEND-1 and -2 studies were pooled without adjustment (i.e., duration from randomization to progression, death, and/or censoring were pooled directly). The median durations of follow-up were 11.3 months (range 0.1–18.9) for ASCEND-2 and [redacted] for ASCEND-1.(9, 14) The subgroup population of ceritinib 750 mg/day that was previously treated with ALK inhibitor therapy (n = 163) from ASCEND-1 was chosen when pooling with ASCEND-2, as it matches with the indication of ceritinib.For the comparator of BSC (no active treatment), the PFS estimate was extrapolated indirectly from the Kaplan-Meier curve of PFS from the placebo arm of Shepherd *et al.*(87).

For the scenario analysis (where the comparator consists of docetaxel followed by BSC for 30% of patients and by BSC only for the remaining 70%), PFS was estimated by using a weighted average of two extrapolated PFS curves (one for docetaxel followed by BSC and the other by BSC alone, based on the Ou *et al.* study) to produce the mixed PFS data.

Full methodology of the survival analysis is provided in Section 5.3.4.

5.3.4 Survival analysis methodology

As PFS and OS data were incomplete (i.e., non-zero, meaning subjects were under observation in the trials without disease progression or death) in the pooled data, available survival data needed extrapolating in order to estimate PFS and OS benefits beyond observation. Extrapolation was based on parametric regression models in accordance with established criteria for extrapolating survival data.(88-90)

Relative efficacy is commonly used to establish differences between treatments when proportional hazards are applicable. In this approach, a hazard ratio (HR) is applied to a baseline model that represents the natural history of disease. This approach should only be used only when the proportional hazards assumptions can be supported; that is, when the relative treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape.(88-90)

Log-cumulative hazard plots can be used to determine whether the proportional hazards assumptions can be supported. The log-cumulative hazard OS plot constructed for ceritinib and BSC is shown in Figure 17; the log-cumulative hazard PFS plot is shown in Figure 18.

Figure 17: Log cumulative hazards plot for overall survival

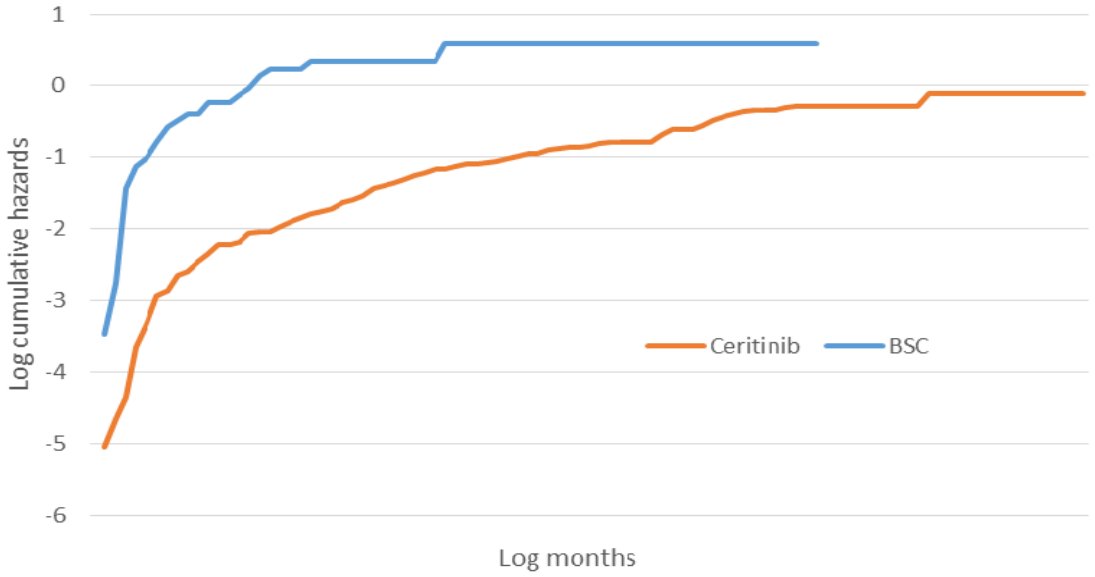
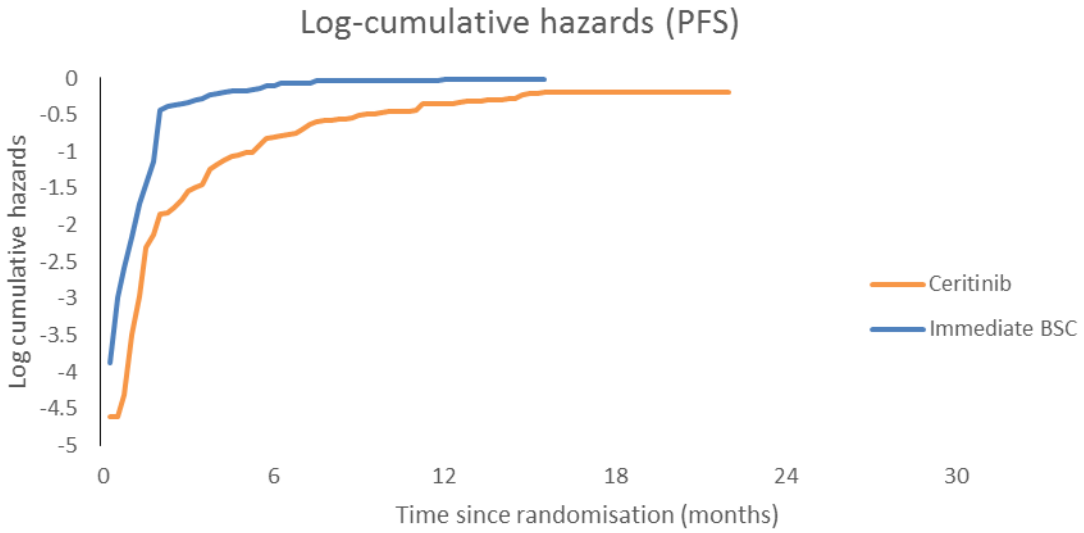


Figure 18: Log cumulative hazards plot for progression-free survival



The log-cumulative hazard curves were not straight, showing that the hazards between ceritinib and BSC were not constant with respect to time, or parallel, showing that the hazards were not proportional over time. Therefore, the proportional hazards assumption could not be supported, and hazard ratios were not used in the model base case to estimate the treatment effect of ceritinib relative to BSC (no active treatment).(91) Moreover, randomisation between treatment arms was already lost with the use of single-arm clinical trials and other independent sources of data (Section 5.3.1), and so fitting of separate and independent parametric models was appropriate.

For each treatment arm, the use of a single regression curve was explored by fitting a variety of parametric curves to the OS data using exponential, Weibull, Gompertz, log-logistic, and log-normal functions. Model selection was as follows: first, the steps described above established

benefits to fitting individual models with some potential preference to accelerated failure time models (log-logistic and log-normal) but not necessarily a clear indication of preference. In addition, since the data are incomplete in terms of PFS and OS events, statistical goodness of fit alone is not a sufficient criterion for model selection.

Although a point can be seen in the PFS log-cumulative hazards curve in Figure 18, the balance of the weight of the data is such that the OS data, and the ceritinib data, were thought to be more meaningful bases for the model selection than the PFS data for BSC, which is from another source, and so single-regression models still are preferred overall.

Statistical goodness-of-fit criteria are shown in Table 47.

Table 47: AIC and BIC criteria for parametric survival models

Parametric model	PFS for ceritinib		OS for ceritinib		PFS for BSC		OS for BSC	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	757.66	761.38	635.05	638.80	605.60	609.08	109.88	111.35
Weibull	751.57	759.02	634.24	641.74	585.21	592.17	110.12	113.05
Gompertz	758.46	765.91	634.38	641.87	607.35	614.31	104.26	107.19
Log-logistic	743.96	751.42	636.41	643.91	530.50	537.46	103.60	106.53
Log-normal	749.78	757.23	644.23	651.73	551.92	558.88	103.19	106.12
AIC, Akaike information criterion; BIC, Bayesian information criterion								

Therefore, the best-fitting curves were selected based on multiple criteria, including visual inspection, AIC/BIC, and internal validity (goodness of fit to the observed trial data) and external validity (plausibility of extrapolated portions validated with expert's opinion feedback).

In the case of BSC, the log-logistic and log-normal models did appear better fits according to statistical goodness-of-fit criteria (Table 48). However, their long-term extrapolated data were not considered as reliable, albeit very few patients receiving BSC are still alive after long-term extrapolation (using the log-logistic and log-normal models).

Table 48: 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]

The following best-fitting curves were used as the base case survival models for the model:

- Ceritinib and BSC OS: Weibull
- Ceritinib and BSC PFS: log-logistic

The best-fitting PFS curves and OS curves, as selected using the steps above, are shown in Figure 19 and Figure 20 respectively. Curves based on other models are presented in **Error! Reference source not found.**.

Figure 19: Kaplan-Meier curves and fitted parametric functions for progression-free survival, base case

[redacted]

Figure 20: Kaplan-Meier curves and fitted parametric functions for overall survival, base case

[redacted]

Finally, the survival functions were implemented in the Excel-based model through direct parametrisation of survival equations as functions of time. Second-order uncertainty surrounding parameter estimates for survival regression models was included in probabilistic sensitivity analysis by the use of Cholesky decomposition of the variance-covariance matrices from each regression model. This means that, during probabilistic sensitivity analysis, the survival function parameters are drawn randomly from their sampling distribution each time.(92)

Transition probabilities

The semi-Markov structure of the model does not use transition probabilities. The survival functions described above are used in the model to provide estimates, cycle-by-cycle, for (i) patients moving from progression-free disease to progressive disease, and (ii) progression-free or progressive disease to death. Using parametric survival functions fitted independently to ceritinib and BSC allows the risks of progression and death to change over time during the time horizon of the model.

5.3.5 Adverse events

Adverse events selected for inclusion in the model were grade 3/4 AEs affecting ≥5% of patients for any of the interventions in the base case of the model (ie. ceritinib, BSC or systemic chemotherapy). This is consistent with common practice for oncology cost-effectiveness models and with the approach taken in the previous submission of crizotinib in ALK+ NSCLC.(78)

For ceritinib, grade 3/4 adverse events suspected to be study-drug related that were observed in ≥ 5% of patients in either the ASCEND-2 (August 2014 cut-point) or ASCEND-1 (April 2014 cut-point) trial were considered for inclusion in the model. Rates of grade 3/4 adverse events suspected to be study-drug related are presented for ASCEND-2 and for ASCEND-1 in Section 4.14.1 and Section 4.14.2, respectively.

The decision on ultimate inclusion in the model was based on whether the pooled rate of a grade 3/4 adverse event across both the ASCEND-2 and ASCEND-1 trials was ≥5%. Data from a total of 303 patients (140 ASCEND-2 and 163 ASCEND-1) therefore contributed to the decision of inclusion of relevant adverse events. Rates of grade 3/4 adverse events suspected to be study-drug related in the pooled analysis are described in Section 4.14.3. Table 49 provides a summary of adverse events ultimately included in the analysis as a result of applying these criteria, and the rates applied in the respective treatment arm. AE rates for BSC were assumed to be zero.

Table 49: Pooled analysis of grade 3/4 adverse events from ASCEND-2 and ASCEND-1 (greater than or equal to 5%)

	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]

Source: ASCEND-2 updated results (cut-off August 2014)(11); Source: ASCEND-1 updated results (cut-off August 2014)(14)

BSC with the addition of active treatment (docetaxel) was explored in a scenario analysis on the composite comparator. AE rates for docetaxel were obtained from Hanna *et al*. (Table 50).(93)

Table 50: AEs rates applied in the sensitivity analysis incorporating active treatment (docetaxel)

	Ceritinib (rates pooled across ASCEND-2 and ASCEND-1)	Docetaxel (systemic chemotherapy) Rates based on Hanna *et al.(93)*
Neutropenia	[redacted]	111 (40.2)
Febrile neutropenia	[redacted]	35 (12.7)
Fatigue	[redacted]	15 (5.4)
Alanine transaminase elevation	[redacted]	0
Aspartate aminotransferase elevation	[redacted]	0
Diarrhoea	[redacted]	7 (2.5%)
Gamma-glutamyltransferase	[redacted]	0
Nausea	[redacted]	5 (1.8%)

5.3.6 Use of clinical experts

Previous NICE appraisals as well as published literature were considered in order to inform on the applicability of specific values and estimates of variables underpinning the cost-effectiveness analysis. In addition, a clinical expert [redacted] experienced in the treatment of ALK+

NSCLC patients in the NHS in England was also involved to discuss modelling assumptions and findings. In particular, the following issues were discussed: generalizability of findings from Ou *et al*. (2014) study; pooling of ASCEND-1 and ASCEND-2 data; use of docetaxel for some patients progressing on crizotinib; utility values for main health states (progression-free and post-progression) as well as for AEs (both for base case scenario and for alternative scenarios); health states associated costs; outcomes predicted by the model (PFS and OS) compared to outcomes observed in clinical practice. Communications took place through a teleconference, followed-up with email correspondence when necessary.

5.4 *Measurement and valuation of health effects*

5.4.1 Health-related quality-of-life data from clinical trials

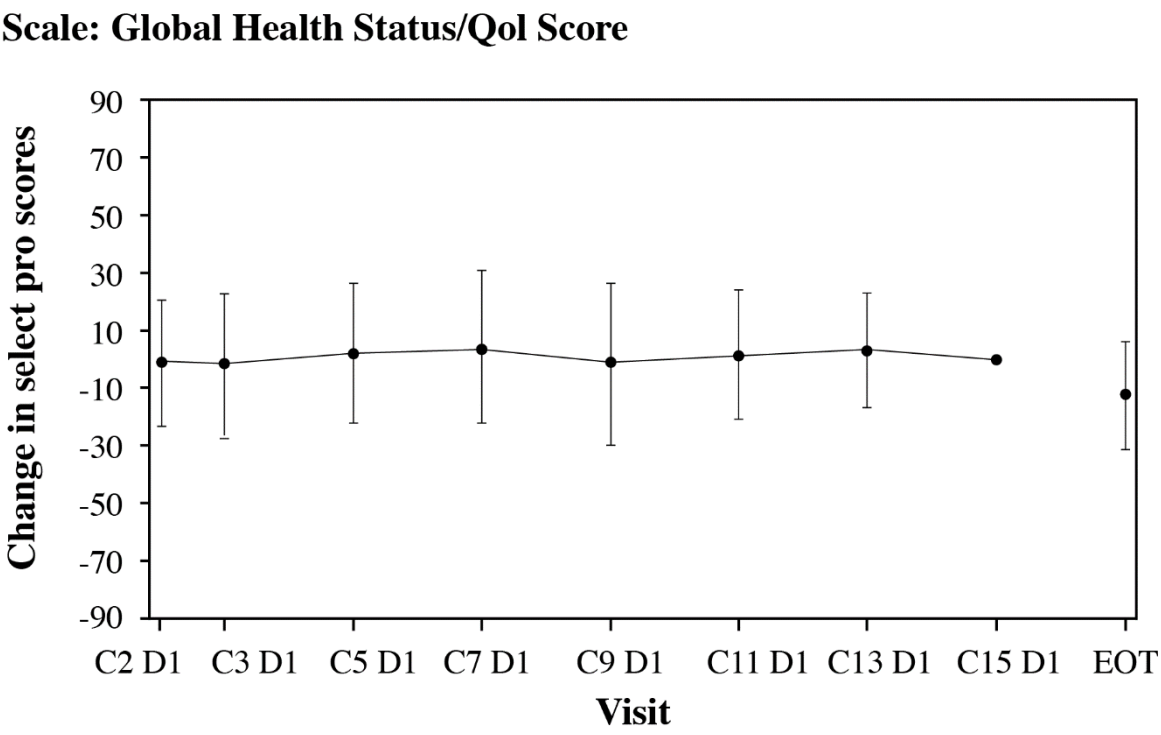
The European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) and lung cancer specific questionnaire (QLQLC13, version 1.0) were used to explore patient reported outcome (PRO) measures of health-related QoL, functioning, disease symptoms and treatment-related side effects in ASCEND-2. The EORTC QLQ-C30/LC13 are considered reliable and valid measures that are frequently used in clinical studies of patients with lung cancer.

Utilities for the cost-effectiveness evaluation were calculated by the use of mapping from the EORTC QLQ-C30 questionnaire to the EuroQoL EQ-5D (Section 5.4.2).

The Patient reported outcomes (PROs) including EORTC QLQ-C30/LC13 were summarised based on the full analysis set of patients in ASCEND-2 and descriptive statistics were used to summarise the individual items and scored sub-scale scores at each scheduled assessment time point. Change from baseline in the domain scores at the time of each assessment was summarised and patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period were included in the change from baseline analyses. The compliance of patients completing the EORTC QLQ-C30/LC13 was high; ≥ 90% of the patients completed the questionnaires at most of the time points during the course of the study (data cut-off 26 February 2014).

Of the 125 patients who completed the QLQ-C30 questionnaire, 69 patients (55.2%) showed an improvement in Global Health/QoL (best percentage change from baseline > 0), while for 26 patients (20.8%) Global Health/QoL deteriorated (best percentage change from baseline < 0). For 30 patients (24%), there was no change in Global Health/QoL. A similar trend was observed with the physical functioning and social functioning scales. The change from baseline in global health status was found to be close to zero throughout the treatment period, implying that the patient's QoL was maintained over the treatment period without worsening (Figure 21).

Figure 21: Mean change from baseline in EORTC QLQ-30 Global Health Status (26th February 2014)



5.4.2 Mapping

Utility mapping from the EORTC QLQ-C30 to the EQ-5D for the model was based on patient-level data from the ASCEND-2 trial. Utility measure described in a study by Proskorovsky *et al.* was used for the analysis.(94) The Proskorovsky algorithm was selected considering disease severity, variability outcomes, and country value sets: the QoL of patients in its estimation samples is most similar to ASCEND-2 and it was a UK-specific algorithm. The Proskorovsky algorithm ("Trimmed model") was derived from responses to the QLQ-C30 questionnaire that was administered to the trial participants.

The Proskorovsky mapping algorithm, using scores from the relevant EORTC QLQ-C30 questionnaire is:

- = 0.23004 + 0.00191*Global health state + 0.00478*Physical functioning + 0.00136*Emotional functioning - 0.00249*Pain
- Set to missing if any QLQ-C30 score used in the mapping algorithm is missing

To avoid that utilities fall outside the theoretically possible range (i.e., from 0 to 1, inclusive), utilities derived from the mapping algorithm were bound at 1.

For each assessment of HRQL, tumour response status was determined as the result from the response evaluation that was closest to the HRQL assessment, regardless of what the tumour response evaluation took place before or after the HRQL assessment. [redacted] Response status at baseline was assumed to be "stable disease". HRQL measurements with unknown response status were excluded from analyses. Response status was classified using Response Evaluation Criteria in Solid Tumours (RECIST) criteria as shown in Table 51.

Linear mixed models were fitted to the utility data as these models take into account that patients have repeated measurements over time.

Table 51: Definition of response status

RECIST response criteria	Response status
Complete response	Responding disease
Partial response	Responding disease
Stable disease	Stable disease
Progressive disease	Progressive disease

Mapped utility values by response state from ASCEND-2 by using the Proskorovsky algorithm are summarised in Table 52.(94) These utility values for stable disease and responding disease were used as base case for the economic model, while the utility value for progressive disease was from (Section 5.4.3) as the value for progressive disease from a published study was more clinically plausible in advanced ALK+ NSCLC (see Section 5.4.5 for further details).(13) The disutilities of AEs are therefore not included in the base case as trial-based utility values are used and any disutility would have already been captured through the elicitation of utilities from the trial. However, when different sources for utility values are used (for example, from published studies) in scenario analyses, then disutilies from AEs are applied in the model and are also informed on utility values from published studies.

Table 52: Mapped utility values by response state from ASCEND-2

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

5.4.3 Health-related quality-of-life studies

A systematic literature review was conducted to identify literature that reported health utility values for patients with advanced or metastatic NSCLC. All searches were conducted on the 10th March 2015, and the following databases were interrogated:

- MEDLINE (OvidSP)
- MEDLINE In-Process (OvidSP)
- EMBASE (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (OvidSP)
- Health Technology Assessment Database (HTA) (OvidSP)
- Health Economic Evaluations Database (HEED) (Wiley Interscience)
- CEA Registry (https://research.tufts-nemc.org/cear/default.aspx)
- PROQOLID (http:///www.proqolid.org/)
- National Institute for Health and Clinical Excellence (NICE) (http://www.nice.org.uk/)

The search strategy consisted of two parts. The first part captured the concept of metastatic or advanced NSCLC combined with the concept of utilities or quality of life or names of HRQoL instruments. The second part searched for specific records with NSCLC terms and utility terms in the title to find studies where utilities were being addressed without reference to the cancer stage. Please see **Error! Reference source not found.** or full details of the search strategy.

Titles and abstracts were screened in accordance with pre-defined eligibility criteria, outlined in Table 53 below.

Table 53: Inclusion and exclusion criteria of the systematic search

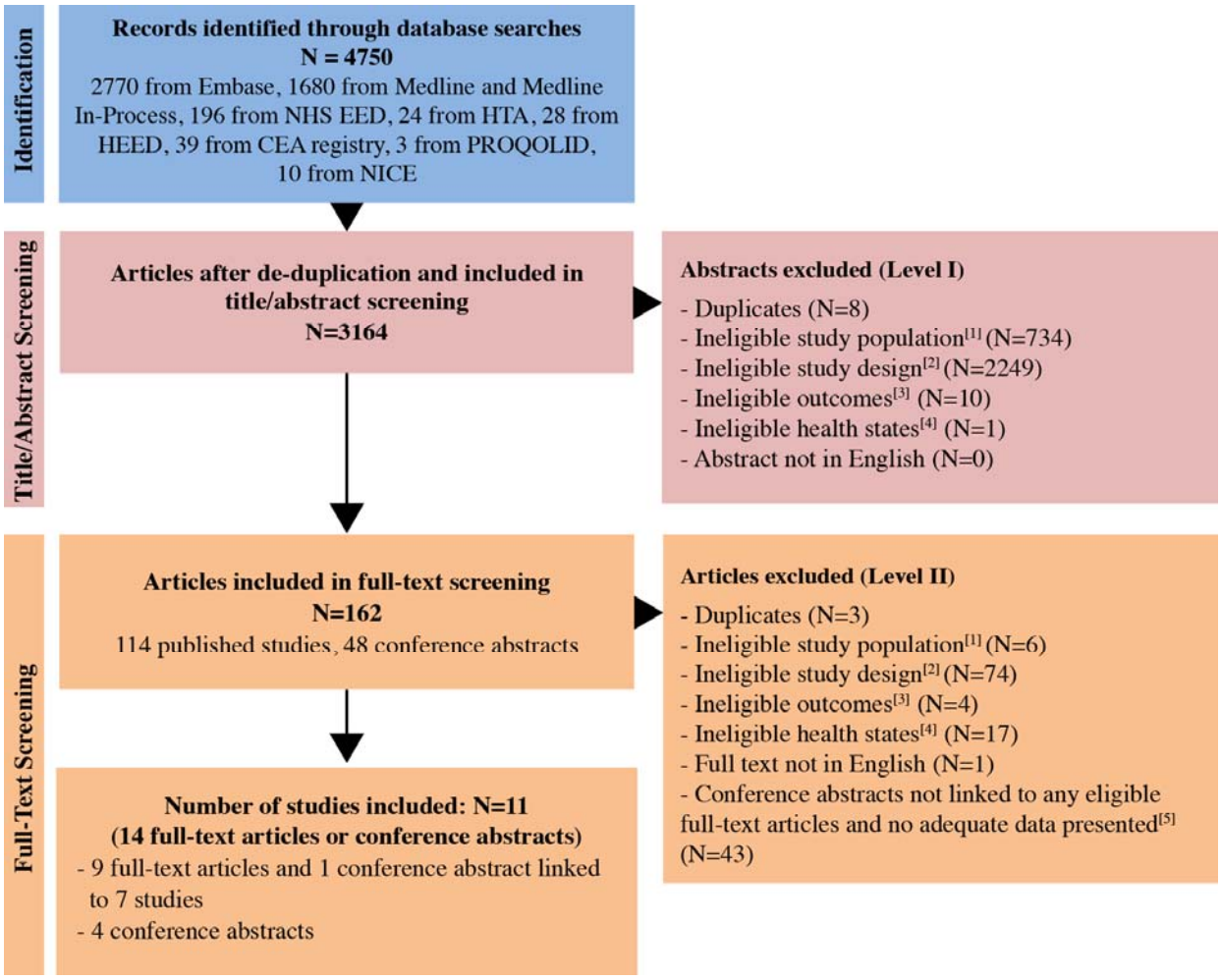
Inclusion criteria	**Population:** Eligible participants were patients with advanced or metastatic (stage IIIB or IV) NSCLC.

	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

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NSCLC, non-small cell lung cancer

Reapplication of the eligibility criteria was applied to the full text of publications deemed potentially relevant after the level 1 screening to determine the final included studies. A PRISMA flow diagram of included and excluded studies is presented in Figure 22.

Figure 22: PRISMA diagram for systematic literature review of health utility in advanced or metastatic NSCLC (search cut-off 10th March 2015)



The electronic database search identified 4,750 potentially relevant articles. Following de-duplication and application of the inclusion and exclusion criteria during level 1 screening, 162 studies were selected for full text review. A total of 11 unique studies met the met the eligibility criteria and were included in the review for extraction.

Full details of the included studies are presented in **Error! Reference source not found.**.

Of these included studies, there were two studies identified as providing utility values that were most appropriate for select inputs within the model. These included utility decrements associated with specific adverse events in a given health state and a utility estimate for the progressive disease health state. These literature-derived utility values are summarised in Table 54.

Table 54: Utility inputs from published literature used in the economic evaluation

Source	Utility

Chouaid (2013)(13)	**Third/fourth-line progressive disease** Mean: 0.46 Standard deviation: 0.38
Nafees (2008)(38)	**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

Comparison of literature-derived and trial-derived utilities

Health state utilities were available from both the ASCEND-2 study (see Section 5.4.2) and the identified literature (see Table 54).

5.4.4 Adverse reactions

Adverse events were incorporated into the health economic model as described in Section 5.3.5.

The systematic literature review for HRQL data captured three studies which have looked at the impact of adverse reactions for patients with advanced or metastatic NSCLC. These studies are summarised in Table 55 below.

Table 55: Identified studies providing HRQL data on adverse reactions

Study	Doyle	Lewis	Nafees(38)
Country	**United Kingdom**	**United Kingdom**	**United Kingdom**
Year of Publication	2008	2010	2008
Form of Publication	Full Text	Full Text	Full Text
Population Sampled	General public (n=101)	General public (n=154)	General public (n=100)
Measurement Instrument	Standard gamble	EQ-VAS	Standard gamble

Utility	Utility scores adjusted for average population age, gender, and EQ-5D VAS score Disease state (symptoms): Utility value Treatment response (no additional symptoms): 0.712 Stable disease (no additional symptoms): 0.626 Stable disease (cough): 0.580 Stable disease (dyspnoea): 0.576 Stable disease (pain): 0.557 Stable disease (cough, dyspnoea, and pain): 0.461	Health states Progression free (oral therapy): 0.451 Progression free (IV therapy): 0.426 Disease progression: 0.217 Adverse events Rash: 0.4 Diarrhoea: 0.32 Fatigue: 0.426 Anorexia: 0.426 Grade 4 neutropenia: 0.32 Febrile neutropenia: 0.19 Nausea: 0.32 Infection: 0.426 Stomatitis: 0.32 Neuropathy: 0.31	By Health states Responding: 0.673 Stable: 0.653 Progressive: 0.473 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

Doyle et al. was a UK standard gamble study capturing society utility scores for advanced NSCLC and specific adverse events. Health states were developed by adapting existing health states descriptions for metastatic lung cancer and were validated by five lung cancer clinicians through interviews. Using standard gamble method, the study gathered utility data from 101 members of the general public in U.K. for responding disease (i.e., disease that is responding to treatment and shows no additional symptoms) and stable disease, as well as cough, dyspnea, pain, or no additional severe symptoms on a VAS rating scale. EQ-5D and EQ-VAS scores were also collected from the general population.

Lewis et al. was a UK cost-effectiveness study comparing erlotinib with docetaxel as second-line treatment for advanced NSCLC. The utility data was collected from 154 members of the general population using EQ-VAS. Utility scores for progression-free were reported for oral therapy and intravenous therapy, respectively. Scores for progression health states and significant adverse events, including rash, diarrhea, fatigue, anorexia, grade 4 neutropenia, febrile neutropenia, nausea, infection, stomatitis, and neuropathy, were reported in general without differentiating route of administration.

Nafees et al. was a study eliciting UK societal based utility values for NSCLC patients receiving second line therapies and different grade 3/4 toxicities commonly associated with chemotherapy treatments.(38) Health states were generated by literature review and exploratory interviews with

oncology experts and were validated by oncology experts, psychometric experts. Utilities for responding disease with no toxicity, stable and PD states, and adverse event including neutropenia, febrile neutropenia, fatigue, nausea and vomiting, diarrhea, hair loss, and rash were obtained from 100 members of the general public in UK using the Standard Gamble (SG) method.

All the above studies clearly demonstrate the detrimental impact of adverse reactions on patients' overall HRQL.

The HRQL data collected in the ASCEND-1 and ASCEND-2 trials capture the adverse events of ceritinib. As for BSC, no disutilities associated with any adverse events are associated to it.

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

The model assigns the same utility level in the two health states irrespective of the treatment arm. As the ASCEND-trials are single-arm studies, for the PF health state, patients on BSC (no active treatment) are assumed to experience the same utility as patients on ceritinib. The utility values derived from the mapping exercise for the progression free health state were also applied for the BSC arm only of the model. This is likely to be a conservative assumption. It is important to note that the values derived from the mapped exercise of the patient-reported outcomes values from the ASCEND-2 study for the progression free health state are in line with the findings of Blackhall et al, that reports the baseline utility for patients on docetaxel is 0.67 at baseline and 0.66 overall. As a consequence, by using the utility from the ASCEND-2 trial also for patients on docetaxel in the scenario analysis on the composite comparator we are overestimating their HRQL in the progression free health state.

Trial-based utility values for the PD health state were not used in the model, as these values were considered to be too high, following discussion with a clinical expert. This is because in the ASCEND trials the patient-reported outcomes data were collected from patients at the time they had been just diagnosed as having progressed (on the basis of the RECIST criteria), and thus when the impact of the progressing disease on their HRQL had been minimal. There was no follow-up for these patients at the later stages of the disease progression. In order to adequately capture the impact of disease progression on patients' HRQL in the economic model, evidence from published literature was used, specifically the paper by Chouaid et al (2013) – see Section 5.4.3.(13) The study meets the NICE reference criteria in that it uses EQ-5Ds as instrument, with tariff from the UK general public. In addition, the study reports utility levels by line of treatment (up to 3rd line of treatment) for advanced NSCLC patients. In addition, the clinical stage at time of survey reported that 17.9% of patients were in stage IIIb and the remaining 82.1% in stage IV: this is in line with the findings of literature on ALK+ NSCLC, which states that the ALK-mutation is more commonly found in stages IIIb or IV of the disease (Gerber et al, 2010).

In a scenario analysis, utilities from Chouaid adjusted for response state are used for the progression free health state.(13)

Disutilities for adverse events are taken from Nafees et al. (2008).(38)

Utility values used in the cost-effectiveness analysis are summarized in Table 56.

Table 56: 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)(38)
Diarrhoea	-0.0468	0.01553		Nafees et al (2008)(38)
Neutropenia*	-0.08973	0.01543		Nafees et al (2008)(38)
Febrile neutropenia*	-0.09002	0.01633		Nafees et al (2008)(38)
Fatigue*	-0.07346	0.01849		Nafees et al (2008)(38)
HS, health state; AR, adverse reaction				

*Included in the scenario analysis involving the composite comparator only

5.5 *Cost and healthcare resource use identification, measurement and valuation*

5.5.1 Resource identification, measurement and valuation studies

An update of an existing systematic review for costs and resource use conducted for the crizotinib NICE submission in ALK+ NSCLC was carried out to identify potentially identify relevant studies reporting costs and resource use. This is because the resource use estimates are likely to be similar to those that would be required for ceritinib. Full details of the methodology used to update the existing systematic review and the articles identified in the previous review are presented in **Error! Reference source not found.**.

The existing crizotinib systematic review was conducted on 13th June 2012. The review update was conducted on the 13th May 2015.

The following databases were searched from 13th June 2012 to 13th May 2015:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations (Ovid)
- EMBASE (Ovid)
- EconLit (EBSCO)
- The NHS Economic Evaluation Database (NHS-EED)
- The Health Technology Assessment (HTA) Database

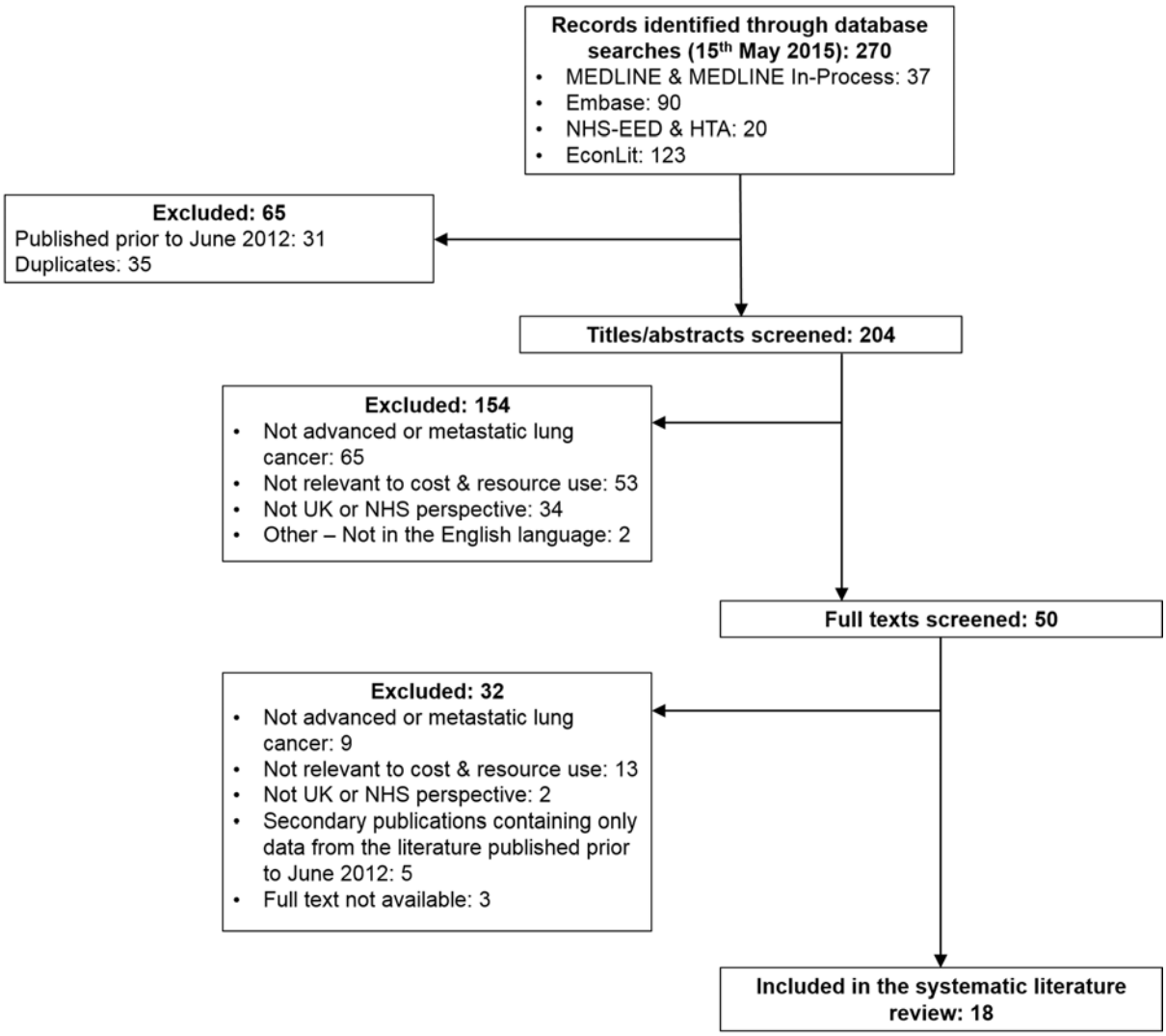
Inclusion and exclusion criteria used to identify potentially relevant articles in the review update are summarised in Table 57 below. These were in line with the eligibility criteria that were applied in the previous crizotinib systematic review.

Table 57: Inclusion and exclusion criteria used to identify potentially relevant articles

		Cost and Resource use associated with advanced or metastatic lung cancer
Inclusion criteria	Participants	• Adult patients with metastatic or advanced lung cancer
	Interventions	• Any
	Comparators	• Any
	Outcomes	• Costs and resource use from a UK NHS perspective
	Study design	• Any
Exclusion criteria		• Not in humans • Not English-language • Not in metastatic/advanced lung cancer • Not UK-specific • Not a public health care perspective • Publications/studies published prior to June 2012 • Non-primary publications/studies published since June 2012, but which present only costs and resource use data previously published prior to June 2012

The electronic database search identified 270, which following deduplication and date restriction (13th June 2012 to 13th May 2015), 204 were screened based on title ± abstract (Figure 23). On the reapplication of the inclusion criteria, 154 title ± abstracts were excluded and therefore 50 full text papers were further screened for inclusion, of which 32 were excluded. Therefore, 18 studies were included in the updated systematic review, although none were deemed relevant for this submission. The list of all included studies is presented in **Error! Reference source not found.**

Figure 23: PRISMA flow diagram of number of journal articles identified and included at each stage of the Cost and Resource Use Review Update



5.5.2 Intervention and comparators' costs and resource use

When estimating monthly drug costs, the following costs were considered: unit drug costs, dosing, proportion of planned dose consumed, and drug administration costs.

Ceritinib will be available as 3 packages of 50 capsules (each 150 mg). Unit drug costs (costs per package) for crizotinib were obtained from the British National Formulary (BNF), using the published price for 150 mg.(95) The dose schedule of ceritinib was in line with the SmPC.(7, 96)

The base case input accounted for patients who may not take the full course of doses due to dose interruption or reduction associated with AEs, or non-compliance. The dose intensity for ceritinib ([redacted]) was based on the weighted average of the mean relative dose intesitises from the ASCEND-1 and ASCEND-2 trials.(11, 14) Drug delivery costs were assumed to be zero for ceritinib as it is orally administered. The acquisition costs associated with treatment are presented in Table 58 (cost per month - dose intensity applied).

The dose intensity for the scenario analysis involving docetaxel was assumed to be 92.6%, based on the PROFILE 1007 trial which compared crizotinib with intravenous chemotherapy (docetaxel or pemetrexed).(15) The time-varying proportion of patients receiving treatment with docetaxel followed by BSC was estimated by a parametric projective survival model using exponential function. The parameter of the distribution (rate parameter, λ) was estimated based on a median treatment duration of 2.76 months (4 cycles, every 3-weeks) established from clinical expert opinion (see Section 5.3.6).

The unit cost of docetaxel was obtained from the Electronic Market Information Tool (eMIT) using code DHC029, which provides mean product prices for generic medicines drawn from information from around 95% of NHS Trusts (DH, 2011). The dose schedule for docetaxel was obtained from European Medicines Agency (EMA) drug label.[83] The cost of outpatient parenteral administration was included for docetaxel as a drug delivery cost for IV treatments. The unit costs of drug delivery for docetaxel were obtained from NHS reference costs 2013-2014.(18) According to the EMA labels, dexamethasone is also required for administering docetaxel; Piriton and paracetamol were included as per their inclusion in TA296 for crizotinib.(19) The dosing schedule of the pre-medications for docetaxel followed EMA labels and TA296. Please see Table 58 for a summary of the docetaxel unit costs.

Table 59 presents the inputs for docetaxel delivery costs and chemotherapy pre-medicine costs.

In a further scenario analysis, patients would receive ceritinib until discontinuation followed by BSC. The same time-varying proportion of such patients was estimated by using exponential function. Durations of treatments for these patients were estimated to be a median of 1.6 months based on ASCEND-2 (median duration of exposure minus median time to progression).(9)

Table 58: 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		

Table 59: Administration costs for docetaxel (for scenario analysis)

Resources	Frequency	Unit cost	Reference
Deliver simple Parenteral Chemotherapy at first attendance	One time for the first month	£225.26	National Schedule of Reference Costs Year: 2013-14, SB12Z (18)
Deliver subsequent elements of a chemotherapy cycle	1 per chemotherapy cycle (21 days)	£320.35	
Deliver exclusively oral chemotherapy	One per cycle	£156.68	
Dexamethasone	Dexamethasone 16 mg * 3 days per chemotherapy cycle (21 days)	£42.30 (2mg/5mL; 150 mL) £48.34 per month [((42.30/60)*16*3)/21*30]	Crizotinib submission, expert opinion (resource use), BNF (unit cost)
Piriton	4 mg per chemotherapy cycle (21 days)	£1.62 (28 tablets, 4 mg) £0.08 per month [(1.62/28)/21*30]	
Paracetamol	500 mg x2 per chemotherapy cycle (21 days)	£20.00 (500mg/5mL, 150 mL) £1.90 per month [(20/15)/21*30]	
Total cost per month, docetaxel administration			
First month			£733.23
Subsequent month			£507.97

Table 60 presents total drug acquisition and administration costs for each treatment. The drug and drug administration costs for the BSC (no active treatment) comparator were assumed to be zero as patients in this arm are not treated with active drug therapies.

Table 60: Total costs (£) associated with the technologies in the economic model

Items	Ceritinib	Docetaxel (scenario analysis)
Mean cost of technology treatment per month	4,076.62	68.07
Administration cost, per month (first month)	0 (oral route of administration)	733.23
Administration cost, per month (subsequent months)		507.97
Total (first month)	**4,076.62**	**801.31**
Total (subsequent month)		**576.05**

5.5.3 Health-state unit costs and resource use

Pre-progression costs

Costs associated with the pre-progression state included healthcare provider's visit costs (ie., cancer nurse visits, outpatient visits, general practitioner [GP] visits), and laboratory test and procedure costs (ie., complete blood count, computerized tomography [CT] scan, X-ray, and serum chemistry). Resource assumptions for routine medical management in the progression-free disease state were derived from TA162 and TA258.(16, 17) These estimates were considered to be the most appropriate estimates available in the literature, as they have been presented in previous NICE submissions and hence assessed by the NICE ERGs and appraisal committees. (16, 17) Although the estimates do not specifically focus on patients with an ALK mutation, they are applicable for patients with NSCLC receiving second-line treatment with an oral agent.

The unit cost for a GP visit was obtained from PSSRU 2013-2014 (per patient contact lasting 17.2 minutes, including direct care staff costs, without qualification costs).(97) The unit cost for palliative radiotherapy was based on the cost reported by and inflated to 2014 GBP.(97, 98) For other types of resource use, unit costs were obtained from NHS reference costs 2013-2014.(18) The monthly frequencies of resource use were based on expert panel opinion reported in TA296.(19) Total pre-progression costs per patient per month were estimated to be £180.88 (Table 61).

Post-progression costs

Costs associated with post-progression state included healthcare provider's visit costs (ie., cancer nurse visits, outpatient visits, and GP visits), medications (i.e., steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), morphine, bisphosphonate, and dietary supplements), and laboratory tests and procedure costs (i.e., complete blood count, serum chemistry, CT scan, home oxygen, and X-ray). Resource utilisation assumptions for routine medical management in the progressive disease state were derived from TA162 and TA258.(16, 17) The unit cost for palliative care physician and the unit cost for GP visits were obtained from PSSRU 2013-2014.(97) The unit cost for terminal care was based on the cost reported by Coyle *et al.*and inflated to 2014 GBP.(97, 98)

The unit costs (cost per package) for post-progression medications (as above) were obtained from BNF April 2015.(95) The monthly usage were based on expert panel opinion reported in TA162.(16) Total post-progression costs per patient per month were £313.70. (Table 61).

All post-progression costs were applied for the entire time patients were in PD state, regardless of the treatment they received before progression.

Table 61: 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 patients 1 per month	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)
	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, 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 (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**
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

5.5.4 Adverse reaction unit costs and resource use

Determination of adverse events for inclusion in the model is described in Section 5.3.5.

Clinical opinion was sought in order to ascertain the type of treatment that these AEs would require.

The AE costs for the lab abnormalities (ALT elevation, AST elevation, blood alkaline phosphatase increase) were assumed to be zero as they would be managed by dose reductions or interruptions as per SmPC of ceritinib. The cost of managaing fatigue was also assumed to be zero. The costs of managing nausea and diarrhoea were based on the the day case costs for PA28A (Feeding Difficulties and Vomiting, with CC Score 1 370 Oncology) and PA21A (Infectious or Non-Infectious Gastroenteritis, with CC Score 1+ 370 Oncology) from the NHS reference costs 2012/2013.(99) Adverse event costs were taken from the 2012/13 reference costs as these provided relevant HRG groups for adverse events included into the economic model.

For the scenario analysis including adverse events associated with docetaxel, the cost assigned to the medical management of neutropenia induced by chemotherapy was based on the calculations presented in TA296 (page 205) and summarised in the Table 62 below:(19)

Table 62: Resource use and unit costs associated with chemotherapy-induced neutropenia

Item	Resource use	Unit cost (£)	Cost (£)	Reference
Neutropenia (chemotherapy induced)	Net price for GcSF - 1-mL vial = £52.71. Treatment assumed to be delivered for 4 days (3 to 5 days) based on expert opinion	£210.84	18.1%*£210.84 = £38.16	BNF Neupogen® (Amgen) , Injection, filgrastim 30 millionunits (300 micrograms)/mL

The clinical expert consulted by the ERG for TA296 agreed that chemotherapy-induced neutropenia requires treatment consisting of granulocyte colony stimulating factor (GcSF) for approximately 3 to 5 days.(19) In the same appraisal, the clinical advisor to the ERG also reported that neutropenia induced by the use of ceritinib would not require treatment as it could be managed by dose reduction or by interruption of treatment. Therefore, the same assumption was considered appropriate for modelling Neutropenia AE in this submission.

The cost of febrile neutropenia was taken from NHS reference costs (PA45Z), which provides a cost of £5,993.03 for treatment of febrile neutropenia with malignancy. The model considered there to be no cost associated with a fatigue adverse event.

Within the model, patients incurred a one-time cost for the management of AEs. Table 63 below summarises the unit costs used in the model for each included AE.

Table 63: Costs associated with each AE (>5% of patients receiving any treatment)

Grade 3/4 adverse events (AEs)	AE cost (2014 GBP)	Notes
Neutropenia	£38.16	NICE TA296; Pfizer submission(19)
Febrile neutropenia	£5,993.03	PA45Z, febrile neutropenia with malignancy

5.5.5 Miscellaneous unit costs and resource use

No miscellaneous unit cost or resource were incorporated.

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 Summary of base-case de novo analysis inputs

Table 64 provides a summary of all the variables included in the de novo economic model.

Table 64: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI/SE (distribution)			Reference to section in submission
Patient characteristics					
Starting Age	52	Not varied in sensitivity analyses			Section 4.11.8
Ceritinib, OS					
Parameter	Value	SE	Covariance 1	Covariance 2	
Weibull constant	0.0266	0.2493	0.0621		Section 5.3
Weibull p	1.1474	0.0917	-0.0213	0.0084	
log logistic constant	0.0560	0.0976	0.0095		
log logistic gamma	0.7662	0.0602	0.0026	0.0036	
Gompertz constant	0.0312	0.1625	0.0264		
Gompertz gamma	0.0302	0.0182	-0.0025	0.0003	
log normal constant	2.9589	0.1182	0.0140		
log normal sigma	1.4708	0.1020	0.0066	0.0104	
exponential constant	0.0386	0.0905			
Ceritinib, PFS					
Parameter	Value	SE	Covariance 1	Covariance 2	
Weibull constant	0.0632	0.1723	0.0297		Section 5.3
Weibull p	1.1887	0.0695	-0.0109	0.0048	
log logistic constant	0.1447	0.0677	0.0046		
log logistic gamma	0.6336	0.0374	0.0003	0.0014	
Gompertz constant	0.0871	0.1159	0.0134		
Gompertz gamma	0.0182	0.0164	-0.0015	0.0003	
log normal constant	1.9263	0.0721	0.0052		
log normal sigma	1.1253	0.0591	0.0010	0.0035	
exponential constant	0.0961	0.0714			
BSC (no active comparator), OS					
Parameter	Value	SE	Covariance 1	Covariance 2	
Weibull constant	0.2852	0.2913	0.0849		Section 5.3

Weibull p	0.8246	0.1263	-0.0272	0.0160	
log logistic constant	0.4181	0.2341	0.0548		
log logistic gamma	0.7538	0.1223	0.0024	0.0150	
Gompertz constant	0.3628	0.2644	0.0699		
Gompertz gamma	-0.1690	0.0736	-0.0130	0.0054	
log normal constant	0.9337	0.2325	0.0541		
Log normal sigma	1.2798	0.1857	0.0049	0.0345	
exponential constant	0.2085	0.1961			
BSC (no active comparator), PFS					
Parameter	Value	SE	Covariance 1	Covariance 2	
Weibull constant	0.2393	0.1111	0.0124		Section 5.3
Weibull p	1.2814	0.0620	-0.0054	0.0038	
log logistic constant	0.4864	0.0475	0.0023		
log logistic gamma	0.4226	0.0249	0.0001	0.0006	
Gompertz constant	0.3366	0.0922	0.0085		
Gompertz gamma	0.0128	0.0253	-0.0016	0.0006	
log normal constant	0.7285	0.0538	0.0029		
Log normal sigma	0.8085	0.0395	0.0001	0.0016	
exponential constant	0.3470	0.0688			
Utility					
Variable	Value	SE (beta)			Reference to section in submission
Utility for progression-free disease	[redacted]	[redacted]			Section 5.4.5
Utility for response	[redacted]	[redacted]			
Utility for progressive disease	0.460	0.12			
Overall response rates					
Variable	Value	SE (beta)			Reference to section in submission
Ceritinib	[redacted]	0.1 * value			Section 4.11.10

			(ORR pooled across ASCEND-2 and ASCEND-1)
BSC (no active comparator)	0.9%	0.1 * value	This value represents the average of the response rates in the two relevant identified studies.(12, 100)
Safety			
Grade 3/4 adverse events (AEs) ≥ 5%	Value	SE (beta)	Reference to section in submission
ALT elevation	[redacted]	0.1 * value	Section 4.14.3
AST elevation	[redacted]	0.1 * value	
Diarrhoea	[redacted]	0.1 * value	
GGT elevation	[redacted]	0.1 * value	
Nausea	[redacted]	0.1 * value	
Costs			
Variable	Value	SE (gamma)	Reference to section in submission
Drug acquisition costs			
Ceritinib, cost per month (including dose intensity)	£4,076.62	n/a – assumed to be fixed	Section 5.5.2
Medical management costs			
Pre-progression medical cost	£180.88	0.1 * value	Section 5.5.3
Post-progression medical cost	£313.70	0.1 * value	
Terminal care costs (one-off)	£6,079.40	0.1 * value	
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferas; CT, computerised tomography; GP, general practitioner; NSAID, nonsteroidal anti-inflammatory drug; OS, overall survival; PFS, progression-free survival			

5.6.2 Assumptions

Table 65 provides a list of all assumptions used in the de novo economic model with a justification of each assumption.

Table 65: Lists of assumptions

Assumptions	Assumption description	Justification
Time horizon	10 years (lifetime)	A 10 year time horizon reflects the expected life expectancy of ALK-positive NSCLC patients after second-line treatment and enables the analysis to capture all relevant health

		consequences and costs.
Pooled data on PFS and OS from ASCEND-1 and -2	In the base case analysis the effectiveness of ceritinib (PFS and OS) is based on pooled data from the ASCEND-1 and -2 trials.	The use of pooled data from the ASCEND-1 and -2 trials provides a broader sample size which enables a more reliable assessment of the PFS and OS in this patient population. The patient populations in ASCEND-1 and -2 populations are sufficiently similar to be pooled (see Section 4.11.8).
OS data from Ou *et al.*are assumed to reflect OS trends in patients continuing treatment after disease progression.(1)	Data on overall survival and progression free survival for patients with advanced ALK-positive NSCLC receiving BSC beyond initial disease progression were estimated by applying parametric functions to survival data (K-M) from published clinical trials	Since there are no head to head studies comparing ceritinib with BSC in ALK-positive NSCLC patients it was necessary to use published sources to predict PFS and OS for BSC and systematic therapy ALK-positive NSCLC patients
PFS data from Shephard *et al*. are assumed to reflect PFS trends in patients continuing treatment after disease progression.(12)		
Adverse Events	All treatment-related adverse events of grade 3/4 with an incidence of equal to or greater than 5% were included in the base case.	As assumed in a previous NICE HTA (TA 296) in ALK-positive NSCLC patients.(19)
Scheduling and duration of AEs	AEs only occur in the first month of treatment and are assumed to last for 1 model cycle (one month).	AEs are applied as one-time events (as the severity of grade 3/4 AEs means they are likely to be dealt with immediately, with treatment being discontinued if not resolved)
Disutility due to AEs	Disutility due to adverse events are not included in the base case analysis	The base case analysis uses utility values mapped from the EORTC QLQ-C30 from the ASCEND-2 trial for the progression free which already account for the reduced quality of life due to AEs.
Assumptions relating to the scenario analysis exploring the composite comparator		
Systemic therapy	The economic analysis assumes	Based on the National Chemotherapy

in patients with advanced ALK-positive NSCLC	that all patient with advanced ALK-positive NSCLC receiving systemic therapy would be receiving docetaxel	Algorithm for NHS England for NSCLC docetaxel is the systemic therapy of choice in patients with advanced ALK-positive NSCLC.(66)
BSC plus systemic therapy PFS	PFS with BSC plus systemic therapy is assumed to be equal to PFS with BSC alone	Since there is no published evidence on the PFS of patients receiving BSC with systemic therapy, the base case analysis assumes similar efficacy (PFS) between BSC and BSC plus systemic therapy (although BSC plus systemic therapy has been shown to result in significantly higher 1-year survival rates compared with BSC only.(1)
Body surface area	The average body surface area was considered to be 1.79 m². This was used to calculate the monthly cost for intravenous docetaxel.	Obtained from a UK study reporting the average BSA in adult cancer patients in UK.(101)
Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine transaminase; AST, aspartate aminotransferase; BSA, body surface area; BSC, best supportive care; DSU, Decision Support Unit; NICE, The National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival		

5.7 *Base-case results*

Table 66 presents the base-case results for ceritinib vs. BSC (no active treatment). Ceritinib was found to be more costly (£59,155 vs. £7,203) but also more effective (1.08 QALY vs. 0.25 QALY) compared to BSC (no active treatment) resulting in an incremental cost-effectiveness ratio (ICER) per QALY of £62,456.

5.7.1 Base-case incremental cost effectiveness analysis result

Table 66: 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

5.7.2 Clinical outcomes from the model

The clinical outcomes from the model, as compared with the clinical trial results, are summarised in Table 67.

Table 67: Summary of modelled outcome estimates compared with clinical data, accumulation until last observation using the AUC method

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
Abbreviations: OS, overall survival; PFS, progression-free survival		

*Ceritinib last observation PFS (21.9 months), OS (24.1 months), +BSC last observation PFS (15.5 month), OS (17.75 months(11, 14))

5.7.3 Markov traces - survival

The Markov traces for health states are provided in **Error! Reference source not found.**.

5.7.4 Markov traces - QALYs

QALYs are accrued by applying QALY weights to health state (progression-free and post-progressive disease). The Markov traces for health states are provided in **Error! Reference source not found.**.

5.7.5 Disaggregated results of the base case incremental cost effectiveness analysis

Details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost are summarized in Table 68, Table 69 and Table 70, respectively.

Table 68: 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%
Total numbers may not sum due to rounding errors Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year					

Table 69: 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%
Total numbers may not sum due to rounding errors Abbreviations: BSC, best supportive care					

Table 70: 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%
Total numbers may not sum due to rounding errors Abbreviation: BSC, best supportive care					

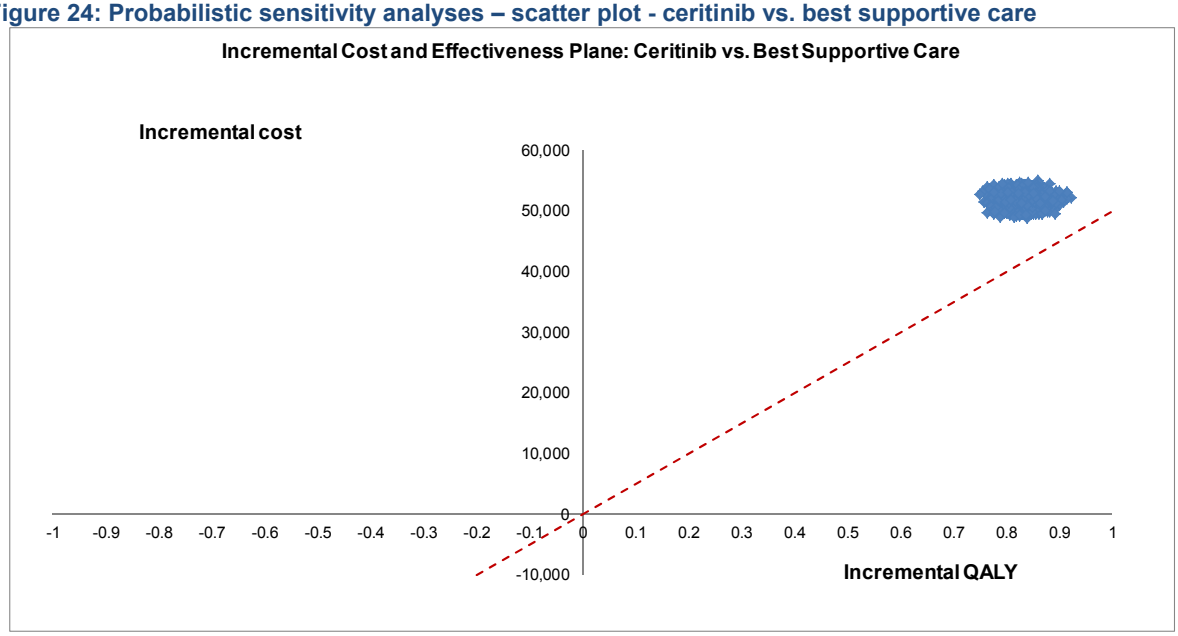
5.8 *Sensitivity analyses*

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to estimate the probability of ceritinib being cost-effective compared to BSC (no active treatment) at a willingness-to-pay threshold of £50,000 using a second-order Monte Carlo simulation. The uncertainty in the survival probabilities was captured through the joint variance-covariance matrix of parameter estimates. Beta distributions were assumed for utilities of health states. Overall response and adverse events rates were also varied using beta distributions. All costs (pre-progression, post-progression and terminal care) were assumed to follow gamma distributions. Drug costs of ceritinib and BSC (including dose intensity) were not varied in the PSA. A total of 2,000 iterations were performed with each selected variable drawn randomly and simultaneously adjusted to calculate an adjusted ICER value. All the pre-specified distributions are detailed in Table 64.

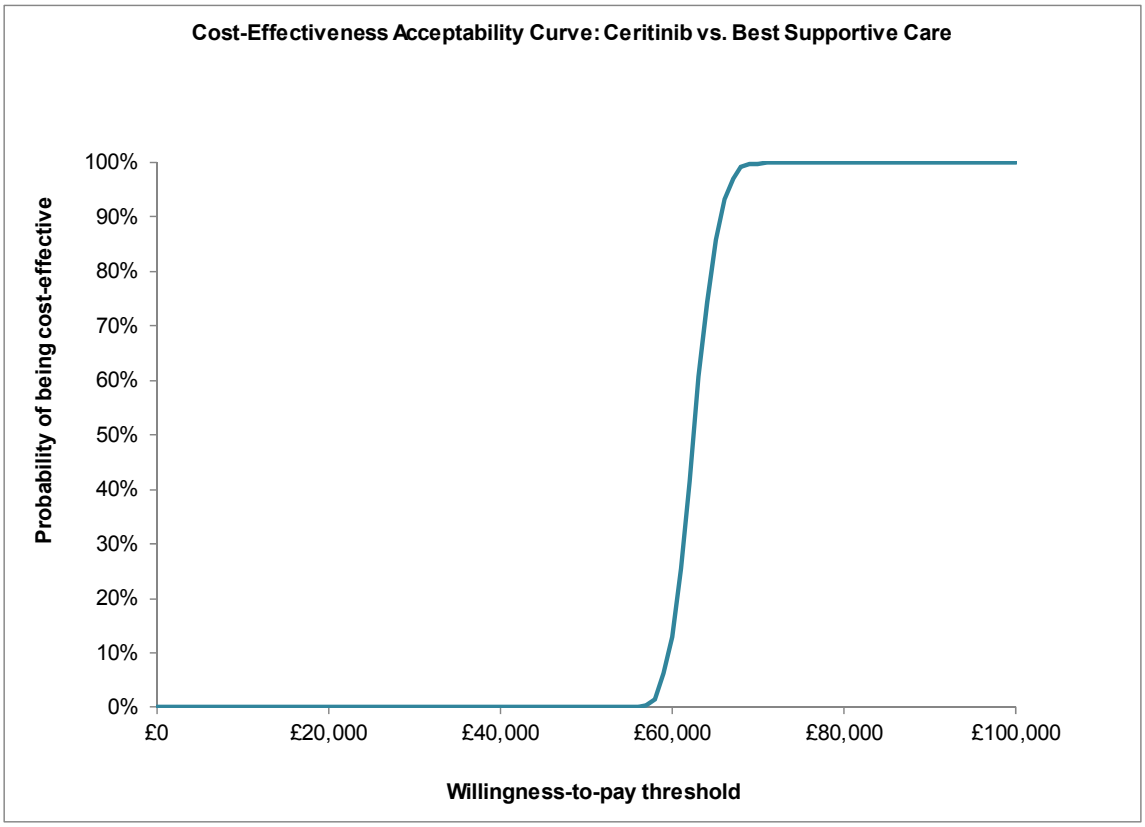
The results of the PSA are presented below using a scatter plot (Figure 24) and a cost effectiveness acceptability curve (CEAC) (Figure 25).

Figure 24: Probabilistic sensitivity analyses – scatter plot - ceritinib vs. best supportive care



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 25: Cost-effectiveness acceptability curve for ceritinib vs. best supportive care



5.8.2 Deterministic sensitivity analysis

In order to test the robustness of the model results, deterministic sensitivity analyses (DSA) were conducted by varying key variables on the model outcomes. All costs were varied in the range by ±25% from the base-case value. Utilities were varied by ±10% from the base-case value.

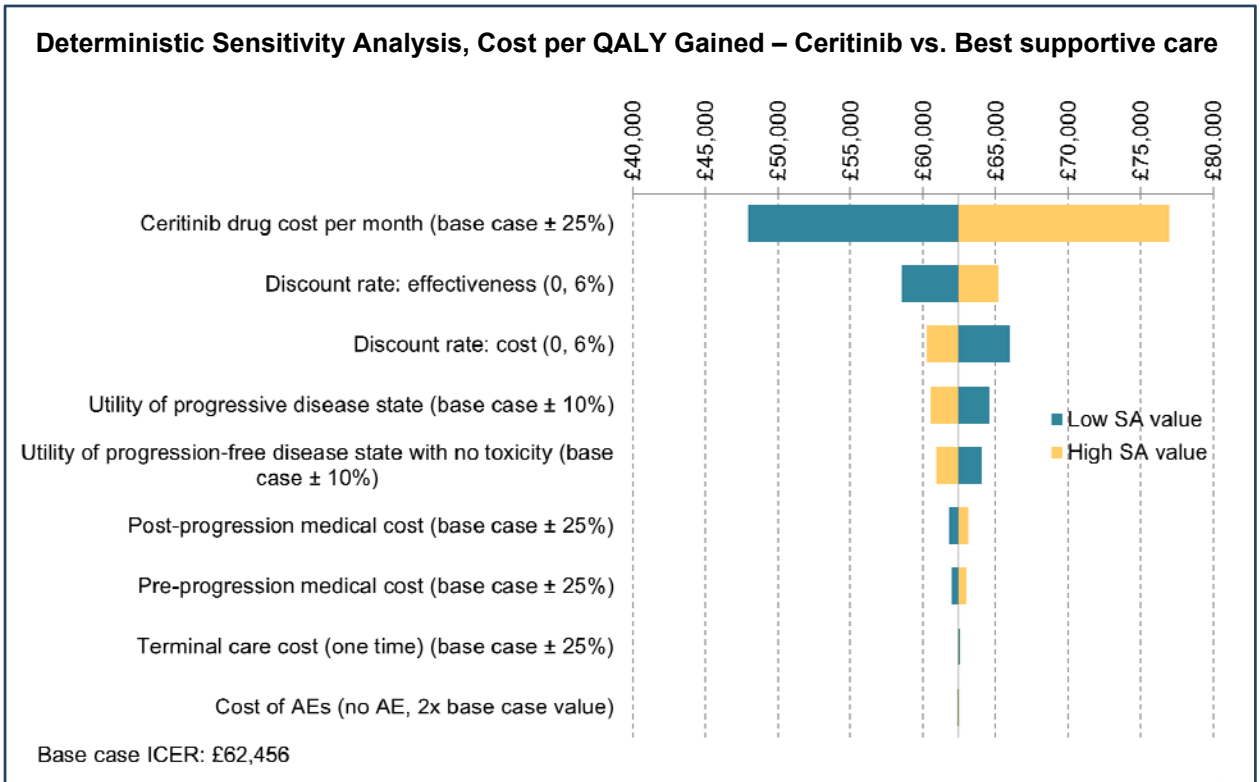
Alternative discount rates for cost and outcomes were also explored (0%, 6%). The following variables and lower/upper ranges were used in the deterministic sensitivity analyses (DSA).

Table 71: 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%

Results of the deterministic sensitivity analyses for ceritinib vs. BSC are presented using a tornado diagram below in Figure 26.

Figure 26: Deterministic sensitivity analyses for ceritinib vs. best supportive care



5.8.3 Scenario analyses

The structural assumptions of the model were tested in scenario analyses. The scenario analyses covered:

- Treatment continuation with active drug therapies after disease progression (BSC + systemic therapy)
- Treatment continuation with ceritinib post-progression
- Time horizons (5 and 20 years)
- Use of alternative survival distributions to model PFS and OS for ceritinib
- Use of different sources of HSUVs
- Assumption around PFS for patients on BSC
- Assumptions around ceritinib dose intensity, administration costs and systemic therapy acquisition cost

Table 72: Scenario Analyses – ceritinib vs. best supportive care

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)(9)	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%
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	Nafees *et al.*(38)	66,130	6%
		Chouaid *et al.*	69,896	12%

	for progression free from ASCEND-2 trial data adjusted by ORR	(13)		
		Chouaid *et* al.with ORR adjusted (13)	69,060	11%
PFS for patients on BSC	Asssume 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%

Abbreviations: BSC, best supportive care; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

5.8.4 Summary of sensitivity analyses results

The model was most sensitive to the assumption around treatment discontinuation with ceritinib post-progression, assuming no dose intensity for ceritinib and the use of alternative published utility values. However, overall the model results showed little variation when tested using different structural assumptions. This gives reassurance that the results that are generated by the model can be relied upon despite the efficacy data in the model coming from different sources.

5.9 *Subgroup analysis*

No subgroups were considered for this cost effectiveness analysis.

5.10 *Validation*

The model was subjected to pressure testing in order to identify potential errors. An Internal validation was undertaken by varying an extensive list of inputs and comparing the impact against expected results. In addition, a detailed testing of the model's formulas and functionality was undertaken.

5.11 *Interpretation and conclusions of economic evidence*

To date, no published data exist on the incremental cost effectiveness of ceritinib. Therefore, it is not possible to validate or compare these results with previous analyses. The modelled population from both ASCEND-1 and ASCEND-2 matches exactly the indication for which ceritinib will be available: the treatment of adults with advanced ALK+ NSCLC previously treated with crizotinib.

The main strengths of this evaluation are as follows:

- Data were derived for ceritinib from large clinical trials designed specifically for advanced ALK-positive NSCLC (Section 4.11).
- The utility data for the PF state was derived directly from the key ASCEND-2 trial using a mapping algorithm (Section 5.4.2). This dataset is important to the economic analysis as it the only QoL data collected in this setting for this group of patients. As highlighted in Section 5.4.1, the quality of life data showed that patient's QoL was clearly maintained without worsening over the treatment period with ceritinib.
- Parametric survival curves that were used to extrapolate efficacy data are selected on the basis of a comprehensive assessment of goodness of fit, internal and external validations (Section 5.3.4).
- The clinical results predicted by the model are comparable or conservative compared to those observed in the ASCEND clinical trials (Section 5.7.2). This gives reassurance that the predicted benefits of ceritinib are not overestimated.
- The scenario analyses conducted clearly show that there is great stability around the ICERs generated by the cost-effectiveness analyses, which gives confidence in determining the most-plausible ICER for decision-making purposes (Section 5.8.3).

The main weaknesses associated with the cost-effectiveness analyses are the lack of an active-comparator RCT or efficacy data on comparators from a head-to-head study with ceritinib. The study by Ou *et al.* (2014) used to inform the naïve comparison in the cost-effectiveness model has limitations linked to the retrospective nature of the analysis, and, more importantly, the circumstance that patients' response to BSC or to systemic chemotherapy after disease progression on crizotinib is due to a range of prognostic factors, rather than actual treatment effect.

Another weakness, in common with TA296 and the modelling of crizotinib, is a lack of certainty around treatment duration for therapies used after progression with crizotinib, in terms of both trial-based data and clinical practice.

Finally, the lack of trial-based utility values (for the PD health state) as well as time-varying utility values generally, constrains the analysis to assuming generalisability of published data to the clinical trial data used, and to the UK general patient population. However, this is not uncommon in NICE appraisals of treatments in oncology.

Key messages/conclusions

Ceritinib is the only licensed treatment option for patients who progress on crizotinib. There are no other effective treatments options for these patients and ceritinib fulfills a significant unmet need in this setting. Ceritinib would represent a step-change in the current management of ALK+ NSCLC patients previously treated with crizotinib. This patient group represents a population with considerable unmet need, for which limited treatment options are available.

Ceritinib is an innovative targeted therapy and has been shown to confer benefits in patients who have brain metastasis (the majority of patients will have brain metastases in this setting). The innovative nature of ceritinib has been recognised with the granting of a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA).(20)

Ceritinib has shown that it can also prolong survival without a detrimental impact on quality of life. The AEs associated with ceritinib are manageable and do not lead to a deterioration in QoL in

the majority of patients (see Section 4.14 and Section 5.4.1). Ceritinib also fulfills the end of life criteria (please refer to Section 5.5 for more details).

Given the relative development timelines, there is currently no data on the efficacy of ceritinib post 1st line crizotinib (i.e. when crizotinib is used upfront, without prior chemotherapy). However, data from the ASCEND clinical studies clearly demonstrate that the efficacy of ceritinib is better when used in patients who have fewer previous lines of therapy. It is, therefore, fair to assume, in the absence of data, that the efficacy of ceritinib post 1st line crizotinib would be at least equivalent to that seen when ceritinib is used after multiple lines of therapy.

A positive recommendation for ceritinib will provide patients and clinicians with a treatment option that is the only licensed targeted and effective therapy available in this setting.

6. Assessment of factors relevant to the NHS and other parties

6.1 *State how many people are eligible for treatment in England. Present results for the full marketing authorisation or CE marking and for any subgroups considered. Also present results for the subsequent 5 years.*

The total number of patients who would be eligible to receive treatment with ceritinib in any given year in England and Wales was estimated at 66 patients (see derivation of eligible patient numbers in Section 3.1.3). In order to estimate the projected number of patients eligible for treatment with ceritinib over the subsequent 5 years a projected annual increase in incidence of -0.72% is assumed which reflects the change in the annual incidence of lung cancer cases in the UK between 1985 and 2009 (based on the same approach as the one used in the crizotinib manufacturer's submission for TA 296).(19). Table 73 presents the ceritinib projected eligible patient population for years 1 to 5.

Table 73: Projected eligible patient population

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients eligible for 3rd line treatment	66	66	65	65	65

6.2 *Explain any assumptions that were made about current treatment options and uptake of technologies*

Currently there are no licensed treatment options available in England and Wales for ALK+ NSCLC patients who have progressed on crizotinib with best supportive care being the only alternative available. As such it is assumed that all patients (100%) would be receiving BSC in absence of ceritinib.

6.3 *When relevant, explain any assumptions that were made about market share in England*

It is anticipated that ceritinib will achieve a market share of 70% in the first year after introduction rising to 90% in year 5. The number of patients anticipated to receive ceritinib in each of the next 5 years is presented in Table 74.

Table 74: Number of patients receiving ceritinib and BSC based on anticipated market share

	Year 1	Year 2	Year 3	Year 4	Year 5
Ceritinib market share	70%	75%	80%	85%	90%
Patients receiving ceritinib	46	50	52	55	59
BSC	20	16	13	10	7

6.4 *In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, administration costs, monitoring costs and the costs of managing adverse reactions)*

The costs included in this analysis include all the direct costs to the NHS associated with the management of ALK+ NSCLC patients who have progressed on crizotinib. These include: drug costs, routine medical management costs and the cost of treating AEs

6.5 *State what unit costs were assumed and how they were calculated. If unit costs used in the health economic modelling were not based on national reference costs or payment-by-results tariff, explain how a cost for the activity was calculated.*

The costs estimated for the purpose of this section are based on the inputs (and outputs) of the cost-effectiveness analysis as described in Section 5.

6.6 *Were there any estimates of resource savings? If so, what were they?*

There are no estimates of resource savings associated with the introduction of ceritinib.

6.7 *State the estimated annual budget impact on the NHS in England*

In order to estimate the annual budget impact to the NHS with the introduction of ceritinib the annual cost per patient of each treatment option (ceritinib and BSC) in Year 1 is multiplied by the total number of patients eligible for each treatment option in each of the years considered in the analysis. The total budget impact for ceritinib is calculated as the difference between the total costs of treatment if ceritinib is adopted minus the total cost of treatment if patients continued to receive BSC (no active treatment).

Table 75 below reports the cost per patient per year for Ceritinib and BSC estimated from the cost effectiveness analysis for years 1 to 5.

Table 75: Cost per patient per year as estimated in the cost effectiveness analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Ceritinib cost per year, £	33,562	12,495	6,380	3,751	2,391
BSC cost per year, £	6,378	774	137	28	6

The total annual treatment costs with ceritinib introduction are presented in Table 76.

Table 76: Total annual treatment costs with ceritinib introduction

Eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patients population for 3rd line treatment	66	66	65	65	65
Ceritinib market share	70%	75%	80%	85%	90%
Patients receiving ceritinib					
Patients per year on ceritinib	46	50	52	55	59
Total cost of patients receiving ceritinib	£1,550,549	£1,678,084	£1,758,632	£1,854,283	£1,963,358
Patients not receiving ceritinib					
Patients per year on BSC	20	16	13	10	7
Total cost of patients receiving BSC	£126,277	£102,042	£83,547	£62,182	£41,455

The total annual treatment costs without ceritinib introduction are presented in Table 77.

Table 77: Total annual treatment costs without ceritinib introduction

Eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patients population for 3rd line treatment	66	66	65	65	65
Ceritinib market share	0%	0%	0%	0%	0%
Patients not receiving ceritinib					
Patients per year on BSC	66	66	65	65	65
Total cost of patients receiving BSC	£420,925	£420,925	£417,736	£414,547	£414,547

The incremental budget impact of ceritinib introduction is presented in Table 78

Table 78: Incremental budget impact of ceritinib introduction

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs with introduction of ceritinib	£1,676,827	£1,780,126	£1,842,179	£1,916,465	£2,004,813
Total costs without introduction of ceritinib	£420,925	£420,925	£417,736	£414,547	£414,547
Incremental overall budget impact	£1,255,902	£1,359,202	£1,424,443	£1,501,918	£1,590,266

7. References

1. Ou S-H, Jänne P, Bartlett C, Tang Y, Kim D-W, Otterson G, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. Annals of oncology. 2014;25(2):415-22.
2. NICE. Final Scope: Ceritinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer. Available at https://www.nice.org.uk/guidance/gid-tag478/documents/lung-cancer-nonsmallcell-anaplastic-lymphoma-kinase-positive-previously-treated-ceritinib-id729-final-scope2 (accessed 10.04.15).
3. Rothschild SI. Ceritinib—a second-generation ALK inhibitor overcoming resistance in ALK-rearranged non-small cell lung cancer. Translational Lung Cancer Research. 2014;3(6):379-81.
4. Friboulet L, Li N, Katayama R, Lee CC, Gainor JF, Crystal AS, et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov. 2014;4(6):662-73.
5. Novartis: ASCEND-1 Clinical Study Report CLDK378X2101 A phase I, multicenter, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK).
6. European Medicines Agency Assessment report: Zykadia, International non-proprietary name: CERITINIB. 26th February 2015 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003819/WC500187506.pdf (Accessed June 2015)
7. Ceritinib (Zykadia) Summary of Product Characteristics. European Medicines Agency. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003819/WC500187504.pdf (last accessed 04.06.15).
8. Novartis: ASCEND-2 Clinical Study Report CLDK378A2201. A phase II, multicenter, single-arm study of oral LDK378 in adult patients with ALK-activated non-small cell lung cancer previously treated with chemotherapy and crizotinib.
9. Tony Mok DS, Enriqueta Felip, Filippo De Marinis, Myungju Ahn, Harry J.M. Groen, Heather Wakelee, Toyoaki Hida, Lucio Crino, Makoto Nishio, Giorgio Scagliotti, Fabrice Branle, Chetachi Emeremni, Massimiliano Quadrigli, Jie Zhang, Alice Shaw. ASCEND-2: A Single-arm, Open-label, Multicenter Phase 2 Study of Ceritinib in Adult Patients (pts) With ALK-Rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC) Previously Treated With Chemotherapy and Crizotinib (CRZ). Poster 8059, presented at the American Society of Clinical Oncology, Chicage, 90052015 - 02062015.
10. Felip E KD-W, Mehra R et al. Efficacy and Safety of Ceritinib in Patients with Advanced Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC): An Update of ASCEND-1. Poster Presented at European Society of Medical Oncology (ESMO), Madrid, Spain 26 – 30 September 2014,. 2014.
11. Novartis: ASCEND-2 Updated Results CLDK378A2201. A phase II, multicenter, single-arm study of oral LDK378 in adult patients with ALK-activated non-small cell lung cancer previously treated with chemotherapy and crizotinib. 48-Week efficacy and safety results (13-Aug-2014 cut-off).
12. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353(2):123-32.
13. Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. J Thorac Oncol. 2013;8(8):997-1003.
14. Novartis: ASCEND-1 Clinical aspects appendix: Appendix 1, D120 response statistical outputs for Clinical Aspects CLDK378X2101 A phase I, multicenter, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK) (14-Apr-2014 cut-off).
15. Australian Therapeutic Goods Administration. Australian Public Assessment Report for Crizotinib. 2014; http://www.tga.gov.au/auspar/auspar-crizotinib [Accessed May 2015].
16. Roche. NICE STA: Tarceva® (erlotinib) for second-line treatment of NSCLC (TA162; manufacturer's submission). Available at: https://www.nice.org.uk/guidance/ta162/documents/manufacturer-submission3 (accessed 10.04.15).
17. NICE. Technology appraisal TA258: Lung cancer (non-small cell,EGFR-TK mutation positive) - erlotinib (1st line) 2012.
18. National schedule of NHS reference costs 2013-2014: the main schedule. https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 [Accessed May 2015].

19. NICE. Technology Appraisal 296: Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. Available at: https://www.nice.org.uk/guidance/ta296 (Accessed 10.04.15).
20. Medicines and Healthcare Products Regulatory Agency (MHRA) Promising Innovative Medicine (PIM) designation https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams (Accessed June 2015)
21. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561-6.
22. Grande E, Bolós M-V, Arriola E. Targeting oncogenic ALK: a promising strategy for cancer treatment. Molecular cancer therapeutics. 2011;10(4):569-79.
23. Camidge D, Bang Y, Kwak E, Shaw A, Iafrate A, Maki R, et al. Progression-free survival (PFS) from a phase I study of crizotinib (PF-02341066) in patients with ALK-positive non-small cell lung cancer (NSCLC). J Clin Oncol. 2011;29(Suppl 15):2501.
24. Zhang X, Zhang S, Yang X, Yang J, Zhou Q, Yin L, et al. Fusion of EML4 and ALK is associated with development of lung adenocarcinomas lacking EGFR and KRAS mutations and is correlated with ALK expression. Molecular cancer. 2010;9(1):188.
25. Martelli MP, Sozzi G, Hernandez L, Pettirossi V, Navarro A, Conte D, et al. EML4-ALK Rearrangement in Non-Small Cell Lung Cancer and Non-Tumor Lung Tissues. The American Journal of Pathology. 2009;174(2):661-70.
26. Shaw A, Solomon B. Anaplastic lymphoma kinase (ALK) fusion oncogene positive non-small cell lung cancer. Available at: http://www.uptodate.com/contents/anaplastic-lymphoma-kinase-alk-fusion-oncogene-positive-non-small-cell-lung-cancer?source=search_result&search=anaplastic+lymphoma+kinase+alk+fusion+oncogene+positive+non+small+cell+lung&selectedTitle=1~150 (accessed 10.04.15).
27. National Institute for Health and Care Excellence. Clinical Guideline 121 – Lung cancer: the diagnosis and treatment of lung cancer. Available at https://www.nice.org.uk/guidance/cg121 [last accessed 12/05/2015]. Due for review in June 2015.
28. Shaw AT, Kim D-W, Nakagawa K, Seto T, Crinó L, Ahn M-J, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. New England Journal of Medicine. 2013;368(25):2385-94.
29. Gainor JF, Tan DS, De Pas T, Solomon BJ, Ahmad A, Lazzari C, et al. Progression-Free and Overall Survival in ALK-Positive NSCLC Patients Treated with Sequential Crizotinib and Ceritinib. Clin Cancer Res. 2015.
30. Shaw A, Kim D-W, Nakagawa K, Seto T, Crino L, Ahn M-J, et al. Phase III study of crizotinib vs pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive NSCLC (PROFILE 1007). [Abstract LBA1 PR, presented at the 37th ESMO Congress, 2012].
31. Thomas RK. Overcoming drug resistance in ALK-rearranged lung cancer. N Engl J Med. 2014;370(13):1250-1.
32. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. The Lancet Oncology. 2013;14(12):1165-74.
33. Sasane, M., Zhang, J., Culver, K. W., Nitulescu, R. & Wu, E., Guerin, A. 2014. Economic Burden of Brain Metastases Among Lung Cancer Patients. AMCP's 2014 Nexus Meeting, October 7-10, 2014, Boston, MA.
34. Cancer Research UK. Lung cancer risks and causes. Available at: http://www.cancerresearchuk.org/about-cancer/type/lung-cancer/about/lung-cancer-risks-and-causes (accessed 10.04.15).
35. National Lung Cancer Audit Report 2014. Report for the audit period 2013. Available at http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2014-15/HSCICNLCA-2014finalinteractivereport.pdf (accessed 10.04.15).
36. Underwood JCE, (ed). General and Systematic Pathology, 4th edition. Churchill Livingstone p353. 2004:352-6.
37. Turner EJ, McClould P, Germanos P, Dehle F, Norris S, Tan J. Meta-analysis of progression-free survival as a predictor of overall survival in locally advanced or metastatic non-small cell lung cancer trials. J Clin Oncol. 2012;30(Suppl.) [Abstract 7604].
38. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84.
39. Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

40. NCBI. Gene: ALK anaplastic lymphoma receptor tyrosine kinase [Homo sapiens (human)]. Available at http://www.ncbi.nlm.nih.gov/gene/238 (accessed 10.04.15).
41. Gerber DE, Minna JD. ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. Cancer Cell. 2010;18(6):548-51.
42. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non–small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27(26):4247-53.
43. Sasaki T, Rodig SJ, Chirieac LR, Jänne PA. The biology and treatment of EML4-ALK non-small cell lung cancer. European Journal of Cancer. 2010;46(10):1773-80.
44. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, Barletta JA, et al. Unique Clinicopathologic Features Characterize ALK-Rearranged Lung Adenocarcinoma in the Western Population. Clin Cancer Res. 2009;15(16):5216-23.
45. Tembuyser L, Tack V, Zwaenepoel K, Pauwels P, Miller K, Bubendorf L, et al. The Relevance of External Quality Assessment for Molecular Testing for ALK Positive Non-Small Cell Lung Cancer: Results from Two Pilot Rounds Show Room for Optimization. PloS one. 2014;9(11):e112159.
46. Scagliotti G, Stahel RA, Rosell R, Thatcher N, Soria J-C. ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development. Eur J Cancer. 2012;48(7):961-73.
47. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. IASLC/ATS/ERS international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6(2):244-85.
48. The Royal College of Pathologists . Standards and datasets for reporting cancers. May 2014 Available at http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G048_LungDataset_May14.pdf (Accessed May 2015)
49. Sulu E, Tasolar O, Takir HB, Tuncer LY, Karakurt Z, Yilmaz A. Delays in the diagnosis and treatment of non-small-cell lung cancer. Tumori. 2011;97(6):693-7.
50. Cancer Research UK. Statistics and outlook for lung cancer. Available at: http://cancerhelp.cancerresearchuk.org/type/lung-cancer/treatment/statistics-and-outlook-for-lung-cancer (Accessed 10.04.15).
51. Yang P, Kulig K, Boland JM, Erickson-Johnson MR, Oliveira AM, Wampfler J, et al. Worse Disease-Free Survival in Never-Smokers with ALK+ Lung Adenocarcinoma. J Thorac Oncol. 2012;7(1):90-7.
52. Hopwood P, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. The Medical Research Council (MRC) Lung Cancer Working Party. Br J Cancer. 1995;71(3):633-6.
53. Hollen PJ, Gralla RJ, Kris MG, Eberly SW, Cox C. Normative data and trends in quality of life from the Lung Cancer Symptom Scale (LCSS). Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 1999;7(3):140-8.
54. Di Maio M, Gridelli C, Gallo C, Manzione L, Brancaccio L, Barbera S, et al. Prevalence and management of pain in Italian patients with advanced non-small-cell lung cancer. British Journal of Cancer. 2004;90(12):2288-96.
55. Arrieta O, Angulo LP, Nunez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martinez-Lopez D, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Annals of surgical oncology. 2013;20(6):1941-8.
56. American Association of Neurological Surgeons. Brain metastasis: Patient information. Available at http://www.aans.org/Patient%20Information/Conditions%20and%20Treatments/Brain%20Metastasis.aspx [Accessed 10/04/2015].
57. Costa DB, Shaw AT, Ou S-HI, Solomon BJ, Riely GJ, Ahn M-J, et al. Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non–Small-Cell Lung Cancer and Brain Metastases. Journal of Clinical Oncology. 2015:JCO. 2014.59. 0539.
58. Komatsu T, Kunieda E, Oizumi Y, Tamai Y, Akiba T. Clinical characteristics of brain metastases from lung cancer according to histological type: Pretreatment evaluation and survival following whole-brain radiotherapy. Mol Clin Oncol. 2013;1(4):692-8.
59. DVLA. DVLA's current medical guidelines for professionals. Available at: https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals-conditions-a-to-c (Accessed 10.04.15).

60. Cancer Research UK. Brain tumours and driving. Available at: http://www.cancerresearchuk.org/about-cancer/type/brain-tumour/living/brain-tumours-and-driving (Accessed 10.04.015).
61. Health Economics Research Centre. The economic burden of malignant neoplasms in the European Union. Available at: http://www.herc.ox.ac.uk/research/economicsofpopulationhealth/Malignant%20neoplasms (Accessed 10.04.15). 2011-2012.
62. National Cancer Research Institute. Lung cancer UK price tag eclipses the cost of any other cancer. Available at: http://conference.ncri.org.uk/archive/2012/press-releases/LUNG_CANCER_UK_PRICE_TAG_ECLIPSES_THE_COST_OF_ANY_OTHER_CANCER.pdf (Accessed 10.04.15).
63. Carrato A, Vergnenegre A, Thomas M, McBride K, Medina J, Cruciani G. Clinical management patterns and treatment outcomes in patients with non-small cell lung cancer (NSCLC) across Europe: EPICLIN-Lung study. Current medical research and opinion. 2014;30(3):447-61.
64. Yenikomshian M, Hackshaw M, Cai X, Trahey A, Arondekar B, Knoll S, et al. Health Care Resource Utilization And Cost Of Medicare Patients With Non-Small Cell Lung Cancer (Nsclc). Value in Health. 2013;16(3):A137.
65. NICE. Clinical Guideline 121: Lung Cancer. Available at: https://www.nice.org.uk/guidance/cg121 (Accessed 10.04.15). Due for review in June 2015.
66. NHS England. Proposed National Chemotherapy Algorithm (awaiting finalisation and publication).
67. NICE. NICE Pathway for lung cancer. Availalbe at: http://pathways.nice.org.uk/pathways/lung-cancer/treatment-for-non-small-cell-lung-cancer (Accessed 10.04.15).
68. NICE. Technology Appraisal 181: Pemetrexed for the first-line treatment of non-small-cell lung cancer. Available at: https://www.nice.org.uk/guidance/ta181 (Accessed 10.04.15).
69. NHS England. Cancer Drugs Fund Decision Summary January 2015: Crizotinib as 2nd line treatment for patients with anaplastic lymphoma kinase (ALK) positive lung cancer. Available at: http://www.england.nhs.uk/wp-content/uploads/2015/01/ncdf-summ-crizotnb-2nd-alk-nsclc.pdf (accessed 10.04.15).
70. Cancer Research UK. About chemotherapy for lung cancer. Available at http://www.cancerresearchuk.org/about-cancer/type/lung-cancer/treatment/chemotherapy/about-chemotherapy-for-lung-cancer [Last accessed 11/05/2015].
71. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012;13(10):1011-9.
72. Lee HY, Ahn HK, Jeong JY, Kwon MJ, Han JH, Sun JM, et al. Favorable clinical outcomes of pemetrexed treatment in anaplastic lymphoma kinase positive non-small-cell lung cancer. Lung Cancer. 2013;79(1):40-5.
73. Shaw AT, Engelman JA. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014;370(26):2537-9.
74. Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014;370(13):1189-97.
75. Novartis: ASCEND-1 Protocol CLDK378X2101 A phase I, multicenter, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK).
76. Centre for Reviews and Dissemination (CRD), University of York. Systematic reviews - CRD's guidance for undertaking reviews in health care 2008. Available from: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf [Last accessed 11/05/2015].
77. Novartis: ASCEND-1 Stastical Outputs (data cut-off April 2014) CLDK378X2101 A phase I, multicenter, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK).
78. Pfizer. NICE STA: Xalkori® (crizotinib) for the second line treatment of ALK positive non-small cell lung cancer (TA296; manufacturer's submission). Available at: https://www.nice.org.uk/guidance/ta296/documents/lung-cancer-nonsmallcell-anaplastic-lymphoma-kinase-fusion-gene-previously-treated-crizotinib-pfizer2 (accessed 10.04.15).
79. Ou S-H, Jänne P, Bartlett C, Tang Y, Kim D-W, Otterson G, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC: SupplementaryData. Annals of oncology. 2014;25(2):415-22.
80. Atherly AJ, Camidge DR. The cost-effectiveness of screening lung cancer patients for targeted drug sensitivity markers. Br J Cancer. 2012;106(6):1100-6.

81. Djalalov S, Hoch J, Beca J, Krahn M, Tsao M, Cutz J. ost-Effectiveness Of Eml4-Alk Fusion Testing In Combination With Crizotinib Treatment For Patients With Advanced Non-Small Cell Lung Cancer Living In Ontario. Value in Health. 2013;16(3):A142.
82. Djalalov S, Graham DM, Beca J, Hoch JS, Tsao MS, Leighl N. The Cost-Effectiveness of Second-Line Crizotinib in Eml4-Alk Rearranged Advanced Non-Small Cell Lung Cancer. Value in Health.17(7):A642.
83. Djalalov S, Graham DM, Beca J, Hoch JS, Tsao MS, Cutz JC, et al. The Cost-Effectiveness of 2nd Line Crizotinib in EML4-Alk Rearranged Advanced NSCLC in Ontario. Value in Health.17(3):A90.
84. Montero A, Lopes G. Cost-effectiveness analysis of crizotinib in metastatic ALK+ non-small cell lung cancer (NSCLC). Journal of Thoracic Oncology. Conference: 15th World Conference on Lung Cancer Sydney, NSW Australia. Conference Start: 20131027 Conference End: 20131030. Conference Publication: (var.pagings). 8 (pp S1211-S1212), 2013. Date of Publication: November 2013.
85. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205-16.
86. Wittes J, Schactman M. On independent data monitoring committees in oncology clinical trials. Chin Clin Oncol. 2014;3(3):40.
87. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non–small-cell lung cancer. New England Journal of Medicine. 2005;353(2):123-32.
88. Grieve R, Hawkins N, Pennington M. Extrapolation of survival data in cost-effectiveness analyses: improving the current state of play. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(6):740-2.
89. Latimer NR. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials- extrapolation with patient-level data. 2011.
90. Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(6):743-54.
91. Guyot P, Welton NJ, Ouwens MJ, Ades A. Survival time outcomes in randomized, controlled trials and meta-analyses: the parallel universes of efficacy and cost-effectiveness. Value In Health. 2011;14(5):640-6.
92. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. Value in Health. 2012;15(6):835-42.
93. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004;22(9):1589-97.
94. Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health Qual Life Outcomes. 2014;12:35.
95. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on May 2015].
96. European Medicines Agency http://www.ema.europa.eu/ema/ (accessed June 2015)
97. Unit Costs of Health and Social Care 2014. http://www.pssru.ac.uk/project-pages/unit-costs/2014/ [Accessed May 2015].
98. Coyle D, Small N, Ashworth A, Hennessy S, Jenkins-Clarke S, Mannion R, et al. Costs of palliative care in the community, in hospitals and in hospices in the UK. Critical reviews in oncology/hematology. 1999;32(2):71-85.
99. National schedule of NHS reference costs 2012-2013: the main schedule. https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013 [Accessed May 2015].
100. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000;18(10):2095-103.
101. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PloS one. 2010;5(1):e8933.