NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ceritinib for previously treated anaplastic-lymphoma-kinase-positive non-small-cell lung cancer [ID729]

This premeeting briefing presents:

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

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

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Evidence of the efficacy of ceritinib comes from 2 studies without a control group. There is no direct evidence comparing ceritinib with the relevant comparator of best supportive care (BSC). The company states that there is a survival benefit of about 10 months for ceritinib compared with BSC, based on a naive indirect comparison with a retrospective analysis of 37 patients.
    - The comparison differed (and did not control for) any potential differences in the studies which might also be associated with time to progression, and/or mortality.

        - What are the risk factors for disease progression and survival in anaplastic-lymphoma-kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC)? Is ALK-positive itself a risk factor for disease progression and death?
    - The Shepherd et al. (2005) study (for progression-free survival [PFS]) had epidermal growth factor receptor (EGFR)-positive rather than ALK-positive patients.
    - Is this comparison robust?

- The company's estimate of survival time with BSC comes from a retrospective study (Ou et al. [2014]) in which treatment choice was determined by clinical judgement, not a study protocol.
    - Are the survival times in Ou et al. (2014) likely to be representative of patients in the NHS?
    - The treatment choice was determined by the clinician, what further bias could this add? Was this representative of BSC in English clinical practice?

- The European Medicines Agency noted that in the clinical studies, almost all patients (99.8%) experienced an adverse event, of which 73% were grade 3-4, and over half of the adverse events were suspected to be drug-related. Dose reductions were performed for 57.8% of the patients.
    - Is ceritinib tolerated by patients?
    - How would adverse events be managed in clinical practice?

- Ceritinib is licensed for treating ALK-positive advanced NSCLC previously treated with crizotinib. Crizotinib is licensed for previously treated ALK-positive NSCLC; it is not recommended by NICE but is currently funded via the Cancer Drugs Fund. There were approximately 110 notifications for crizotinib over the last year, accordingly, only a small number of patients would be eligible for ceritinib.

Cost effectiveness

- In the company's model, the curves for overall survival and progression-free survival used data from 4 studies (ASCEND 1 and 2 for ceritinib; Ou et al. [2014] and Shepherd et al. [2005] for BSC). The comparison between treatments was not randomised and there was no adjustment for differences in population between studies. Are the modelled estimates of overall survival and progression-free survival likely to be robust?
- For extrapolating overall survival data for BSC, the company used a Weibull curve. The ERG commented that the best-fitting log-normal curve should be used instead. Which approach is the most appropriate?
- In the base case the company assumed that treatment with ceritinib would be continued until disease progression, but the ERG's scenario analyses assumed it was continued after progression for an average of 1.6 months (based on the ASCEND-2 study). Which scenario is the most appropriate?
- In the base case the company applied dose reductions for ceritinib and assumed that, on average, patients took [redacted] of the licensed dose of ceritinib. Would this be realised in practice? Is it appropriate to apply a dose reduction?
- The company's model assumed that the benefits of ceritinib persisted beyond the duration of the study and the end of treatment. Is this a reasonable assumption?
- The progression free health state in the company's model used a utility value of [redacted] for ceritinib and [redacted] for BSC. The ERG stated that the difference between these values was not justified in the submission. Instead the ERG used [redacted] for both arms. Which approach is the most appropriate?
- Does ceritinib meet the end-of-life criteria?

Table 1 Base case results from the company and the ERG

Scenario	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£)
Company's base case					
BSC	7203	0.25			
Ceritinib	59,155	1.08	51,952	0.83	62,456
ERG base case - using log-normal curve to extrapolate OS with BSC, instead of Weibull curve; - assuming that patients continue ceritinib treatment after disease progression for a median of 1.6 months; - including all grade 3 and 4 adverse events observed in the ASCEND studies for ceritinib; - include costs of 2 blood tests and 2 outpatient visits for managing lab abnormalities for ceritinib; - using the same utility values for both ceritinib and BSC for the progression-free health state and adjust the utility value for the BSC arm to reflect the lower rate of adverse events with BSC					
BSC	7339	0.27			
Ceritinib	70,620	1.06	63,281	0.80	79,528
Abbreviations: Incr. – incremental; BSC – best supportive care; QALY – quality-adjusted life years; ICER - incremental cost-effectiveness ratio Source: table 7 and table 8					

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ceritinib within its marketing authorisation for previously treated anaplastic- lymphoma-kinase-positive non-small-cell lung cancer.

Table 2 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with ALK-positive advanced non-small-cell lung cancer previously treated with crizotinib.		None	None
Int.	Ceritinib		None	None
Com.	Best supportive care		BSC means that	None

		patients receive no active treatment but receive passive therapy aimed at symptom management and palliative care.	
Out.	The outcome measures to be considered: overall survival progression-free survival overall response rate adverse effects of treatment health-related quality of life	None	None
ALK: anaplastic lymphoma kinase positive; BSC: best supportive care; ERG: Evidence Review Group.			

2 The technology and the treatment pathway

2.1 Ceritinib (Zykadia, Novartis) has a marketing authorisation in the UK for the treatment of adult patients with anaplastic-lymphoma-kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib. Ceritinib is an ALK tyrosine kinase inhibitor, which aims to reduce cell proliferation and tumour development. The summary of product characteristics states that clinicians should assess patients' ALK status before starting ceritinib. However, the company advised that the marketing authorisation states ceritinib can only be used after crizotinib, which is also an ALK inhibitor. ALK testing would therefore be done before starting treatment with crizotinib. The summary of product characteristics states that patients require monitoring for liver dysfunction, hyperglycaemia and pulmonary symptoms during treatment with ceritinib.

2.2 For untreated advanced NSCLC, current treatment options include:

- Chemotherapy with docetaxel, gemcitabine, paclitaxel or vinorelbine plus a platinum-based drug (carboplatin or cisplatin; NICE clinical guideline 121).

- Pemetrexed in combination with cisplatin, for cancer with adenocarcinoma or large-cell carcinoma histology (NICE technology appraisal guidance 181).

For previously treated advanced NSCLC, treatment options include:

- Nintedanib in combination with docetaxel, for cancer with adenocarcinoma histology (NICE technology appraisal guidance 347).
- Docetaxel monotherapy should be considered if second-line treatment is appropriate (NICE clinical guideline 121).

There are 2 types of targeted treatments for NSCLC; those for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations, and those for ALK-positive NSCLC. The EGFR-TK targeted treatments are not relevant for the ALK-positive population. There is one ALK-positive targeted treatment, crizotinib, which has a marketing authorisation for previously treated ALK-positive advanced NSCLC. NICE technology appraisal guidance 296 did not recommend crizotinib for this indication, but it is available via the Cancer Drugs Fund. The company submission stated that NHS patients whose disease progressed after crizotinib would have best supportive care (BSC).

2.3 Approximately 5% of people with advanced or metastatic NSCLC have ALK-positive NSCLC. The marketing authorisation states that ceritinib is only licensed for those previously treated with crizotinib. The company estimated that this would equate to 66 patients per year in England and Wales; the ERG agreed with this estimate.

Table 3 Technology

	Ceritinib
Marketing authorisation	Indicated for the treatment of adult patients with anaplastic-lymphoma-kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib.
Administration method	Oral

Cost information	NHS list price: £4923.45 for a 30-day supply.* Dosing: 750 mg once daily (5 x 150 mg capsules). The summary of product characteristics states that treatment should continue as long as clinical benefit is observed. The company stated that treatment duration was expected to be the same as progression-free survival (PFS). The median PFS across ASCEND-2 and ASCEND-1 was [redacted], which the company estimated would cost [redacted] per patient.
See summary of product characteristics for details on adverse reactions and contraindications. *stated in company submission	

3 Comments from consultees

Submissions were received from the Roy Castle Lung Cancer Foundation and the National Lung Cancer Forum for Nurses. There was a joint submission from the National Cancer Research Institute, Royal College of Physicians, Royal College of Radiologists Association of Cancer Physicians and British Thoracic Oncology Group. A patient expert (nominated by Independent Cancer Patients Voice) submitted a statement.

3.1 Consultees emphasised that currently there are no targeted treatments funded by the NHS for ALK-positive NSCLC after an ALK inhibitor fails. Crizotinib was the first licensed ALK inhibitor and was not recommended by NICE (TA296). Currently after failure of crizotinib, crizotinib treatment could continue or platinum-doublet chemotherapy could be used.

3.2 The professional groups noted that the ALK-positive patient population is younger than the overall NSCLC population, and has a greater proportion of non-smokers. The professional groups explained that this predicts better results with treatment than the overall NSCLC population, including in overall survival gain.

3.3 The Roy Castle Lung Cancer Foundation explained that ALK-positive advanced NSCLC is incurable. Therefore, treatment aims to improve quality of life and extend life. Treatment outcomes remain poor, therefore the availability of a new drug is important. It emphasised that people with

NSCLC often experience multiple and distressing symptoms, such as breathlessness; and therapies with anti-tumour activity provide better symptom relief. Given the poor prognosis for these patients the potential of improving quality of life is a considerable benefit of ceritinib.

3.4 The patient expert stated that ceritinib improves patients' quality of life, gives patients the opportunity to live a more normal life, and gives them hope for the future. The patient expert noted that many patients with ALK-positive advanced NSCLC have brain metastases and that these can be controlled with ceritinib, which positively affects quality of life.

3.5 Consultees emphasised that treatment with ceritinib tolerable in the clinical studies and has a better adverse-event profile than other treatments. However, a professional group highlighted that the adverse events identified in the clinical studies should be communicated to clinicians, because pneumonitis is likely to occur more often and may be misdiagnosed in clinical practice. Ceritinib is administered orally, therefore it is easy to use.

3.6 Professional groups explained that implementing this new technology would involve diagnostic testing for the ALK mutation, which is not current clinical practice. The testing would need to be done in specialist clinics, therefore ceritinib would only be used in specialist clinics.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company presented efficacy data from 2 single-arm studies identified through a systematic review:

- **ASCEND-1 (n=304)**: multicentre, open-label, dose escalation and expansion study (Shaw et al. 2014).
- **ASCEND-2 (n=140)**: multicentre, open-label study with 750 mg ceritinib once daily.

ASCEND-1

4.2 The ASCEND-1 study recruited people with anaplastic-lymphoma-kinase (ALK)-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC) with progressed disease and prior chemotherapy who may or may not have had crizotinib. The trial was single armed; all patients received the drug, and there was no control group. The dose-escalation phase of ASCEND-1 determined the optimal dose (the licensed dose of 750 mg), which was then used in the expansion phase of the study (n=255). The company's analysis only included the subgroup of people in the expansion phase who had previously been treated with crizotinib (n=163). The inclusion criteria for these 163 patients were:

- Adults with ALK-positive locally advanced or metastatic NSCLC that had progressed despite standard therapy
- Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less
- Life expectancy of at least 12 weeks
- Prior treatment with crizotinib.

The mean age of the 163 patients was 51.5 (standard deviation 11.6) years and [redacted] were from the UK. Treatment with ceritinib was continued until unacceptable toxicity, disease progression, or until patients and clinicians decided to stop. Patients remained in the study until death unless they withdrew their consent or were lost to follow-up.

4.3 In the expansion phase the 2 primary outcomes were overall response rate (ORR) and duration of response, assessed by the investigator. The secondary outcomes were duration of response and ORR assessed by a Blinded Independent Review Committee (BIRC), overall intracranial response rate, overall survival (OS), progression-free survival (PFS) and safety.

ASCEND-2

4.4 ASCEND-2 was also a single arm study in which all patients received the drug, and no control group existed. The ASCEND-2 inclusion criteria were:

- Adults with ALK-positive stage IIIB or IV NSCLC
- World Health Organization (WHO) performance status of 0 to 2
- Life expectancy of at least 12 weeks
- Previously treated with chemotherapy
- Progressed disease despite therapy with crizotinib.

The study included people with asymptomatic or controlled central nervous system metastases. The mean age of patients was 51.2 (SD: 11.62) and [redacted] patients were from the UK.

4.5 The primary outcome was ORR measured by the investigator. Secondary outcomes included duration of response, overall intracranial response rate, ORR (assessed by a BIRC), PFS, OS and safety.

ERG comments

4.6 The ERG advised that ASCEND-1 and 2 were of reasonable quality, but it identified some limitations:

- Neither study included a control group
- BIRC assessment was not provided for all outcomes
- The prior treatment in the studies might differ (not be generalisable) to established NHS practice
- The results are from interim analyses and not the final analysis.

4.7 The ERG noted that the ASCEND studies included small numbers of UK patients and advised that the results may not be generalisable to the NHS. On average, the study participants were younger than the people eligible for ceritinib in England, most of whom would be older than 60 years. The ethnic mix of the patients in the study was different from the population of England. The average time from initial diagnosis to starting ceritinib in the ASCEND studies ([redacted] months and [redacted] months for

ASCEND 1 and 2 respectively) is likely to be substantially longer than in clinical practice in the NHS.

4.8 The percentage of patients who had received at least 3 treatment regimens before entering the study was 56.5% and 56.3% in ASCEND-1 and 2 respectively. In its response to clarification questions from the ERG, the company provided further information about which treatment regimens patients had used before entry in the trials. However, the ERG advised that it was unclear which order these regimens had been given in.

Clinical trial results

4.9 The results of the ASCEND trials are in table 4. The results of the pooled analysis, using individual patient data from the BIRC assessments in ASCEND 1 and 2, showed that the median PFS was [redacted] and the median OS was [redacted].

Table 4 Clinical study results

	ASCEND-1 Investigator Assessment (n=163)	ASCEND-1 BIRC Assessment (n=163)	ASCEND-2 Investigator Assessment (n=140)	ASCEND-2 BIRC Assessment (n=140)	Pooled ASCEND-1 and ASCEND-2 BIRC assessment
ORR – n (%) [95% CI]	92 (56.4) [48.5, 64.2]	75 (46.0) [38.2, 54.0]	54 (38.6) [30.5, 47.2]	50 (35.7) [27.8, 44.2]	NR
DOR[1] – Median (Min-Max), months	8.25 [6.80, 9.69]	8.77 [5.98, 13.11]	9.7 [7.1, 11.1]	9.7 [5.6, 12.9]	NR
PFS – Median [95% CI], months	6.93 [5.55, 8.67]	6.97 [5.65, 8.67]	5.7 [5.4, 7.6]	7.2 [5.4, 9.0]	[redacted]
OS – Median [95% CI], months	16.72 [14.78, NE]	NR	14.9 [13.5, NE]	NR	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence interval; ORR, Overall response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NR, not reported; NE, not estimable

Source: table 19 of company submission.

4.10 Health related quality of life (HRQoL) was not measured in ASCEND-1. In ASCEND-2 it was measured using the European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30). The EORTC - QLQ-C30 includes 5 functional scales (physical, role, emotional, cognitive and social), 3 symptom scales (fatigue, nausea & vomiting and pain) and a global health status/quality of life scale. In total 125 patients completed the EORTC, of whom 69 (55.2%) showed improved global health status and 26 (20.8%) showed poorer global health status. The company submission did not provide the actual scores for none of the different scales, nor did it state the time point at which the summary of results was calculated.

ERG comments

4.11 For ASCEND-1, the company's analysis of adverse events used data from the analysis in August 2013 but for all other outcomes it used updated data from April 2014. For ASCEND-2, the company's analysis of HRQoL used data from the analysis in February 2014 but for all other outcomes it used updated data from August 2014. The ERG noted that it was unclear whether the different data cuts were defined at the start of the study.

4.12 The ORR was defined as the percentage of patients with complete response or partial response using the Response Evaluation Criteria in Solid Tumors (RECIST). ASCEND -1 and ASCEND-2 used different versions of the RECIST criteria, and the ERG advised that this might have affected the results. In its clarification response, the company acknowledged that the different RECIST criteria could explain the difference in ORR between the 2 studies. Nonetheless, the company stated that patients in both studies derived similar benefit from ceritinib, as shown by the similar disease control rate, duration of response and PFS.

4.13 The ERG conducted further analysis of patients with brain metastases in ASCEND-2 (n=100; 72%). The results suggested that the disease of patients with brain metastases responds to treatment with ceritinib on a similar scale as the disease of patients without brain metastases. Moreover even active brain metastases may respond to ceritinib treatment (see section 4.5.2 of ERG report).

Naive indirect comparison

4.14 The ASCEND studies did not include a control group, so the company could not compare ceritinib with best supportive care (BSC) directly. To determine whether ceritinib made patients live longer than best supportive care, the company compared the ASCEND studies to Ou et al. (2014). To determine whether ceritinib delayed disease progression, the company compared the ASCEND studies to Shepherd et al. (2005). The company conducted a literature search to identify relevant clinical evidence for

patients who have BSC. It then conducted a naive indirect comparison of ceritinib with BSC (meaning not adjusted for differences in patient or study characteristics). Ou et al. (2014) was a retrospective analysis of people with advanced ALK-positive NSCLC that had progressed after crizotinib treatment and who had participated in 2 clinical trials of 2nd line crizotinib (PROFILE 1001 and PROFILE 1005). Ou et al. (2014) analysed data from 3 groups:

- BSC only (that is, no active treatment) (n=37)
- systemic chemotherapy (n=37)
- crizotinib (n=120)

The results from the crizotinib group are not relevant to the appraisal. Across the BSC and systemic chemotherapy groups, 65% of patients had an ECOG performance status of 1 at baseline and 80% had had 2 or more prior therapies. The company advised that the only outcome measure that could be included in the indirect comparison was median OS.

4.15 The company concluded that there were no major differences between Ou et al. (2014) and the ASCEND studies in terms of patient characteristics (that is, sex, age, smoking history and prior lines of therapy), although the company noted that patients in Ou et al. (2014) had a slightly higher ECOG status at baseline. The results of the naive indirect comparison are shown in table 5. By comparing the ASCEND studies with the pooled results for the BSC and chemotherapy groups in Ou et al. (2014), the company advised that the median overall survival gain for ceritinib compared with BSC was approximately 10 months (see section 4.13.4 of the submission).

Table 5: Results of the naive indirect comparison

	Ceritinib (Pooled results of ASCEND 1 and 2, BIRC assessment) n= 303	**BSC Ou et al. (2014) n=37**	**Systemic chemotherapy Ou et al. (2014) n=37**	**Pooled results for BSC and Systemic chemotherapy Ou et al. (2014) n=74**
OS – Median [95% CI], months	[redacted]	2.2 [1.1–3.8]	5.4 [3.8, 12.3]	3.9 [2.7–5.1]
Abbreviations: BSC, best supportive care; CI, confidence interval; NE, not estimable; OS, overall survival. Source: table 31 of the company submission.				

ERG comments

4.16 The ERG noted that Ou et al. (2014) was at risk of bias due to its retrospective design. Moreover, only a small number of patients were relevant to this appraisal (n=37) and limited information was provided about what was considered to be BSC or systemic chemotherapy. The ERG also advised that the naive indirect comparison was at risk of bias because Ou et al. reported limited information about potentially confounding variables.

4.17 The ERG noted that there were differences between the ASCEND and PROFILE studies in inclusion and exclusion criteria, specifically: prior treatment(s), ECOG performance status and the inclusion of people with symptomatic brain metastases. The ERG's clinical adviser stated that the PROFILE studies excluded patients with symptomatic brain metastases, whereas the ASCEND studies included these patients if they were stable.

4.18 The ERG noted that the company's submission presented baseline patient characteristics for the combined BSC and chemotherapy subgroups in Ou et al. (2014). Consequently, the characteristics of the BSC group (which in the ERG's opinion is the relevant subgroup for the appraisal) are unknown. The ERG noted there were differences in ECOG performance status and prior treatments between the ASCEND patients

and those in the combined BSC and chemotherapy subgroups in Ou et al. (2014), but the differences were not statistically significant (see section 4.3 of the ERG report).

Adverse effects of treatment

4.19 The company presented data on adverse events in the ASCEND studies (see sections 4.14.1 and 4.14.2 of the submission). In both studies, most people experienced drug-related adverse events ([redacted] in ASCEND-1 and [redacted] in ASCEND-2). In ASCEND-1 [redacted] experienced grade 3 or 4 adverse events, of which [redacted] were drug related. In ASCEND-2 [redacted] experienced grade 3 or 4 adverse events, of which [redacted] were suspected to be drug related. The most common grade 3 or 4 adverse events were aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increase, gamma-glutamyltransferase (GGT) increase, diarrhoea, nausea, fatigue, dyspnoea and vomiting. The percentage of patients who stopped taking ceritinib due to adverse events in ASCEND-1 and ASCEND-2 was [redacted] and 7.9%, respectively.

ERG comments

4.20 The ERG noted that a high proportion of patients experienced drug-related adverse events and approximately 54% of patients required a dose adjustment due to an adverse reaction. The median time to first dose reduction was approximately 7 weeks. The ERG referred to the Food and Drug Administration's review of ceritinib, which stated a concern about the '*appropriateness of the dose used in the major efficacy trial, which is poorly tolerated and may be higher than required to achieve the observed anti-tumor effect*'. Besides this, the European Medicines Agency noted in its assessment report that in the clinical studies, almost all patients (99.8%) experienced an adverse event, of which 73% were grade 3-4, and over half of the adverse events were suspected to be drug-related. Dose reductions were performed for 57.8% of the patients.

4.21 The ERG requested pooled data on adverse events for all patients who received 750 mg of ceritinib. In its response to clarification, the company provided data from 525 ALK-positive patients, 10 of whom had malignancies other than NSCLC. These patients were enrolled in 4 open-label single-arm studies including ASCEND 1 and 2. The median duration of ceritinib treatment was 33 weeks. Adverse events with an incidence of at least 10% were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, constipation, rash, increased blood creatinine, oesophageal disorder and anaemia.

5 Cost-effectiveness evidence

Model structure

5.1 The company's Markov model compared the cost effectiveness of ceritinib with best supportive care (BSC) for people with advanced anaplastic-lymphoma-kinase (ALK) positive non-small-cell lung cancer (NSCLC) that had been previously treated with crizotinib. The model contained 3 mutually exclusive health states:

- Progression free
- Progressed disease
- Death

The time horizon was 10 years and cycle length was 1 month. A half-cycle correction was applied. The evaluation took an NHS and Personal Social Services perspective. Discount rates for both costs and benefits were 3.5%.

5.2 For ceritinib, the company took data from the Blinded Independent Review Committee (BIRC) assessment of progression free survival (PFS) and overall survival (OS) from the pooled results of the ASCEND-1 and 2 studies. For ASCEND-1 it used data from the relevant patient population (that is, people who received prior crizotinib treatment and who received 750 mg of ceritinib). To extrapolate beyond the study period, the company

fitted several parametric models to the data and selected the best-fitting curve on the basis of visual inspection, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), internal validity and external validity. The company chose a Weibull curve for OS and a log-logistic curve for PFS.

5.3 For best supportive care (BSC), the company took OS data from Ou et al. Data on PFS were not reported by Ou et al., so the company used PFS data from the placebo group (n=243) in Shepherd et al. (2005) – a randomised double-blind placebo-controlled trial of erlotinib in patients with Epidermal Growth Factor Receptor (EGFR) positive advanced NSCLC, which is a different genetic mutation to ALK-positive mutation. For ceritinib, for BSC the company chose a Weibull curve for OS and a log-logistic curve for PFS.

5.4 The company used an 'area under the curve partitioned survival analysis' technique, where the number of patients in each health state was based on the survival curves described in sections 5.2 and 5.3. Patients entered the model in the progression free-health state and received ceritinib or BSC until progression, when they moved to the progressed-disease health state. Patients could move to the death state from either the progression-free or progressed-disease health state.

ERG comments

5.5 The ERG noted that results from the ASCEND studies, Ou et al. (2014) and Shepherd et al. (2005) were not adjusted for differences in baseline patient characteristics. Therefore, the model results rely on the assumption that the study populations were the same. The ERG advised that in Ou et al. (2014) the choice of treatment was based on clinical advice rather than a study protocol, so the patients in the BSC group may have had more severe disease than those in the active treatment groups. Accordingly, the ERG advised that the BSC arm of the model may be informed by data from patients who were more ill than those in the

ASCEND studies, potentially underestimating survival with BSC. The ERG also noted that there might be differences between the modelled population and NHS patients. The ERG also noted that the Shepherd et al. (2005) study, which the company used to model PFS with BSC, recruited patients with the EGFR mutation, whereas the ASCEND and Ou et al. studies recruited patients with the ALK-positive mutation. The ERG's clinical advisor confirmed that due to the lack of data using data from this population was relevant. However the ERG noted that this introduced a number of further uncertainties to the model (see section 5.2.6.3 of the ERG report).

5.6 The ERG commented that it was appropriate to use the Weibull curve for extrapolating OS with ceritinib. However, for BSC the ERG noted that Weibull was the worst-fitting curve and a log-normal curve should have been used instead (this was done in the ERG's scenario analysis). The ERG advised that the company's choice of a log-logistic curve for PFS for both ceritinib and BSC was appropriate.

5.7 The ERG noted that, by using parametric survival curves for modelling transitions between health states, the company had assumed that the benefits of treatment with ceritinib persist beyond the study period and after stopping treatment. The ERG conducted sensitivity analyses to test the impact of this assumption on the results.

Model details

5.8 For ceritinib, the company included the cost of grade 3 and 4 drug-related adverse events that had occurred in at least 5% of patients in the pooled analysis of ASCEND 1 and 2. The included events were:

- diarrhoea,
- abnormal liver function tests (increased alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase)
- nausea.

The one-off cost associated with adverse events was £71.11 (value taken from model; not stated in submission). A utility decrement for adverse events was not applied in the base case. In a scenario analysis, the company applied utility decrements for adverse events based on Nafees et al. (2008). The company assumed there were no adverse events with BSC (see section 5.4.5 of the submission).

5.9 The company estimated utility values by mapping EORTC QLQ-C30 data from ASCEND-2 to the EQ-5D (see section 5.4.5 of the submission). The mapping used an UK-specific algorithm developed in multiple myeloma (Proskorovsky et al. 2014). The company submission stated that, for the progression-free health state, it used a utility value of [redacted] for both ceritinib and BSC based on patients with stable disease in ASCEND-2. The ERG advised that, for the progression-free health state, the utility values in the company's model did not match the description in its submission (see section 5.14).

5.10 For the progressed disease health state, the company stated it was not appropriate to use the ASCEND-2 utility values, so it used published EQ-5D data from patients with advanced NSCLC instead (Chouaid et al. 2013). The justification for not used ASCEND-2 was that in ASCEND-2 quality-of-life data collection stopped after disease progression. The ASCEND-2 data therefore represented people whose disease had progressed recently and their quality of life was likely to be higher than those at later stage of progression. The published data from Chouaid et al. (2013) reported utility values by line of treatment and the company used the mean utility value for people with progressed disease while on third- or fourth-line treatment. The utility value in the model for the progressed-disease health state was 0.460 for both ceritinib and BSC. The company's scenario analyses used alternative utility values (see section 5.8.3 of the submission). The analyses using utility values from Chouaid et al., but adjusted for overall response rate (0.620, 0.639 and

0.460 for progression-free disease, treatment response and progressed disease health states respectively) had the biggest impact on the ICERs.

5.11 The model included the costs of ceritinib, BSC and post-progression treatments.

- The acquisition cost of ceritinib in the base-case model was £4076.62 per month. This included a dose intensity of [redacted] (meaning that, on average, patients took [redacted] of the licensed dose of ceritinib), to account for people who did not take the full course of the treatment due to interruption, adverse events, or non-compliance. This assumption was based on the pooled ASCEND data. The company assumed there were no administration costs for ceritinib. In the base case, treatment was continued until disease progression. In sensitivity analyses the company used 100% dose intensity for ceritinib (£4995.25 per month) and, separately, assumed that ceritinib was continued after progression based on the ASCEND studies.
- BSC was associated with no treatment costs in the base case. One of the company's scenario analyses included 2.8 months of docetaxel treatment in the BSC arm of the model, at a monthly acquisition cost of £68.07 (see section 5.5.2 of submission).
- The treatments in the progressed disease health state included steroids, nonsteroidal anti-inflammatory drugs, morphine and bisphosphonate at a total acquisition cost of £93.92 per month.

5.12 The resource use included in the model included clinic appointments, scans and laboratory tests. The model did not include the cost of diagnostic testing for the ALK mutation; the company assumed that this testing would already have been done because the modelled population had previously had crizotinib. Resource use assumptions were based on TA162 (Erlotinib for the treatment of non-small-cell lung cancer) and TA258 (Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer). The

total cost per month for the progression-free health state was £180.88 (excluding medication costs), for progressed disease £313.70 (including medication costs) and for death £6079.40 (including palliative care only) (see section 5.5.3 of the submission).

Table 6 Parameter inputs used in the model

	Ceritinib arm	BSC arm
Utilities		
Progression-free health state	[redacted]	[redacted]
Progressed disease health state	0.460	0.460
Utility decrements applied for AEs	0.0	0.0
Costs		
Drug acquisition costs (per cycle, including [redacted] dose intensity)	£4,076.62	NA
Progression-free health state	£180.88	£180.88
Progressed disease health state	£313.70	£313.70
Death	£6,079.40	£6,079.40
Cost of AEs (one off cost)	£71.11	NA
BSC, best supportive care; AE, adverse events; NA, not applicable Source: Company submission		

ERG comments

5.13 The ERG noted that the company included only those adverse events that occurred in more than 5% of people, and it advised that serious but rare adverse events may have been excluded. The ERG's exploratory analyses included all grade 3 and 4 events from the ASCEND studies.

5.14 The ERG noted an inconsistency between the model and the company submission in the utility values. The company submission stated a utility value of [redacted] was used for both ceritinib and BSC. The ERG advised that in the model the utility values for stable disease and responding disease were taken from ASCEND-2. A weighted average was calculated separately for ceritinib and BSC based on the proportion of patients who responded to treatment in ASCEND-2 and Shepherd et al. (2005)

respectively. The ERG advised that the progression-free health state used a utility value of [redacted] for ceritinib and [redacted] for BSC. The ERG commented that the company's method was not justified in its submission. The ERG's exploratory analyses used a utility value of [redacted] for both treatments for the progression-free health state (see section 5.2.7 of the ERG report).

5.15 The ERG agreed with the company's decision not to apply a utility decrement for adverse events with ceritinib, because disutilities would be captured in the utility values from ASCEND-2. However, the same utility values were used for ceritinib and BSC, which the ERG considered inappropriate because disutilities for adverse events were also included in the BSC arm. Therefore, the ERG's exploratory analyses increased the utility value for the progression-free health state for BSC with the disutility values from Nafees et al. (2008).

5.16 The ERG noted that in ASCEND-2 patients continued ceritinib treatment after disease progression for a median of 1.6 months. However, the company's base case assumed that ceritinib treatment would only be continued until disease progression. The ERG's clinical expert advised that, in clinical practice, it is likely that patients would continue treatment after progression. Therefore, the ERG's exploratory analyses included these extra treatment costs for ceritinib.

5.17 The company conducted a literature search to identify data on resource use, but the ERG noted that the search terms were limited to the UK so relevant articles may have been missed (such as those for a specific region or hospital). Because the company's search did not find relevant studies, the company estimated resource use using previous technology appraisals of second-line treatments for NSCLC. The ERG noted that these appraisals were not specific to ALK-positive advanced NSCLC (see section 5.2.8 of ERG report).

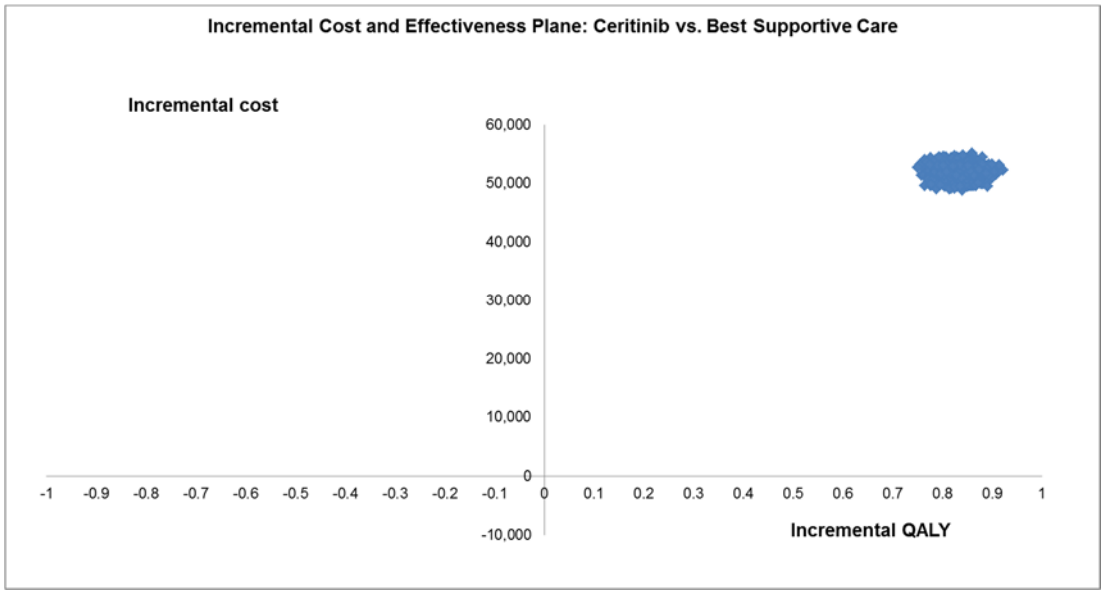
5.18 In the company's base-case analysis the cost of adverse events was included as a one-off cost in the first month of treatment. The ERG noted

that, if adverse events are expected to occur beyond the study duration, then the cost of these later adverse events would not be included in the model. The company assumed that lab abnormalities would incur no costs and would be managed by dose reductions. The ERG did not think this was plausible, so its exploratory analyses included the cost of 2 additional blood tests and 2 additional outpatient visits.

Company's base-case results and sensitivity analysis

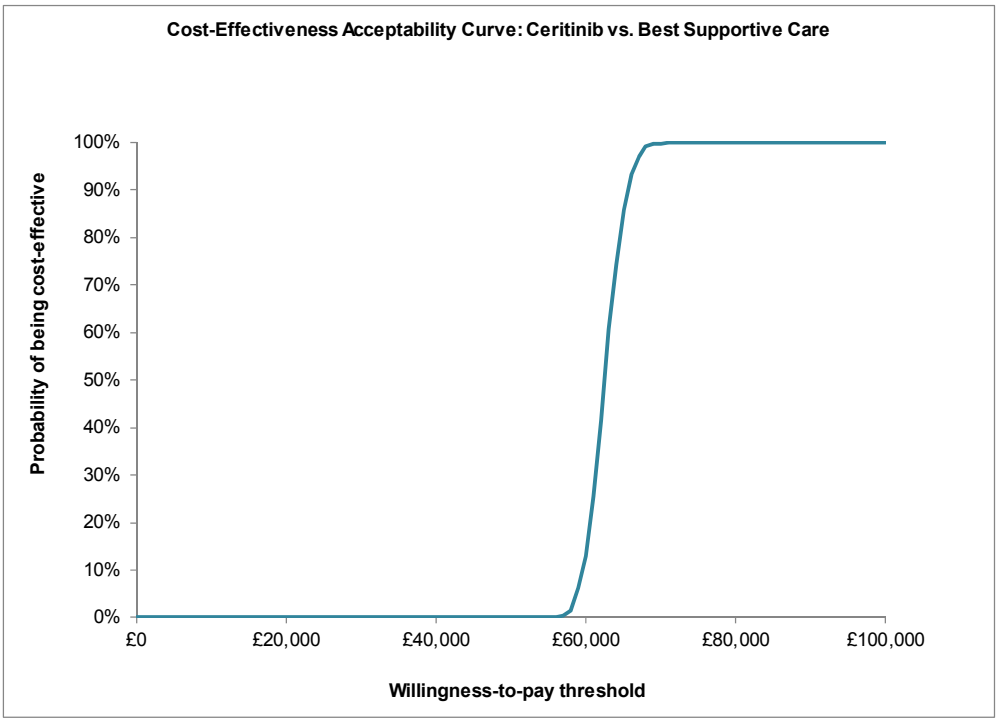
5.19 The company's deterministic base case resulted in an incremental cost-effectiveness ratio (ICER) of £62,456 per QALY gained for ceritinib compared with BSC (table 7). Deterministic sensitivity analyses showed that the key drivers of cost effectiveness were the cost of ceritinib, the discount rate and the utility values for the progressed-disease and progression-free health states.

Figure 1 The ICER plane of the company base case analysis



Source: company submission figure 25, page 124

Figure 2 The Cost-effectiveness Acceptability Curve for the company base case analysis



Source: company submission figure 25, page 124.

ERG comments

5.20 The ERG advised that the main drivers of the model were the cost of ceritinib and the way OS was modelled.

5.21 The ERG noted that the model seemed to underestimate OS with BSC. The average OS was 5.57 months (median 2.2 months) in the Ou et al. study but only 4.77 months (median 3 months) in the BSC arm of the model; The ERG advised that this was because the model used a Weibull curve, instead of the best fitting log-normal curve.

5.22 The ERG noted that the company conducted a number of sensitivity analyses, where they increased or decreased the model parameters by a fixed percentage. For parameters where upper and lower confidence intervals were available, the ERG though that using those would have been a better approach.

Company scenario analyses

5.23 The company presented a range of deterministic scenario analyses. table 7 summarises the scenarios which had the largest impact on the ICER (see section 5.8.3 of the submission).

Table 7 Company's base case results and scenario analyses

Scenario	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£)
Base case					
BSC	7203	0.25	-	-	-
Ceritinib	59,155	1.08	51,952	0.83	62,456
Treatment with ceritinib for a median of 1.6 months after disease progression	Not reported				£76,039
Health state utility values from Chouaid et al. (2012)	Not reported				£69,896
100% dose intensity for ceritinib	Not reported				£74,519

Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio

Source: table 72 of the company's submission.

ERG exploratory analyses

5.24 The ERG made the following changes to the company's model (see section 5.3 of ERG report):

- Use a log-normal curve to extrapolate OS with BSC.
- Assume that patients continue ceritinib treatment after disease progression for a median of 1.6 months.
- For ceritinib, include all grade 3 and 4 adverse events observed in the ASCEND studies.
- For ceritinib, include costs of 2 blood tests and 2 outpatient visits for managing lab abnormalities.
- For the progression-free health state, use the same utility values for both ceritinib and BSC. The utility value for the BSC arm was then adjusted to reflect the lower rate of adverse events with BSC.

Combining all of these parameters, the ERG's deterministic analysis resulted in an ICER of £79,528 per QALY gained for ceritinib compared with BSC (table 8). The ERG advised that the increase in the ICER was mostly due to using a log-normal curve to model OS with BSC and including the costs of ceritinib treatment after disease progression.

5.25 In further exploratory analyses, the ERG reduced the duration of treatment benefit with ceritinib from 10 years (as assumed in the company's base case) to between 2 and 9 years. Beyond the selected time point, the probabilities of future transitions (progression and death) were set to be the same as for BSC. All the scenarios increased the ICER, but assuming 2 years duration of treatment benefit had the biggest impact on the ICER and increased it to £99,703 per QALY gained (see table 8)

Table 8 ERG exploratory analyses

Scenario	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£)
Company's base case					
BSC	7203	0.25			
Ceritinib	59,155	1.08	51,952	0.83	62,456
ERG base case					
BSC	7339	0.27			
Ceritinib	70,620	1.06	63,281	0.80	79,528
Reduce duration of treatment benefit with ceritinib to 2 years	Not reported				99,703
Reduce duration of treatment benefit with ceritinib to 5 years	Not reported				80,312

Abbreviations: BSC, best supportive care; Inc., incremental; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
Source: ERG report, table 42, page 96.

Innovation

5.26 Reasons for considering ceritinib to be innovative:

- The patient expert and company considered ceritinib to be an innovative treatment because currently there is no targeted treatment available for patients who relapse after crizotinib. The available options are best supportive care (BSC) or standard chemotherapy. The company noted the high level of unmet need of this patient population due to limited treatment options and short life expectancy.
- Ceritinib received 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-positive advanced NSCLC.
- The company noted that ceritinib is associated with substantial progression-free survival, following progression after crizotinib.

6 End-of-life considerations

Table 9 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Ou et al. (2014) found that patients with ALK-positive NSCLC that has progressed after crizotinib treatment have a median survival of 2.2 months when treated with BSC.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The pooled results of ASCEND 1 and 2 show median survival of [redacted] months for patients treated with ceritinib. Ou et al. showed median survival of 2.2 months with BSC. The company advised that this shows a survival gain of 10 months, based on a naive indirect comparison.
The treatment is licensed or otherwise indicated for small patient populations	The company estimated that approximately 120 patients would be eligible for ceritinib treatment each year in England and Wales.

7 Equality issues

7.1 No equality issues were raised.

8 Authors

Boglarka Mikudina

Technical Lead

Dr Rosie Lovett

Technical Adviser

with input from the Lead Team (Chris O'Regan, Dr Sanjay Kinra and Matt Campbell Hill).

Appendix A: Clinical efficacy section of the draft European public assessment report

European Medicines Agency. Zykadia. Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003819/WC500187506.pdf

2.6.1. Discussion on clinical safety

In the pooled dataset, almost all patients (99.8%) experienced an adverse events, 73% being grade 3-4, and over half of the adverse events were suspected to be drug-related. The majority of patients (78%) experienced >10 adverse events, with a median of 17 adverse events (ranging from 1 to 171). Almost half of the adverse events (4483/11157) required additional therapy. Dose reductions were performed at least once in more than half of the patients (57.8%) treated with ceritinib however treatment discontinuations due to adverse events were not frequent (8.8%).

2.6.2. Conclusions on the clinical safety

The most frequent adverse drug reactions are gastrointestinal disorders and increased liver enzymes. The most serious adverse drug reactions are hepatotoxicity, ILD/pneumonitis, QT prolongation and bradycardia. Although ceritinib is not a well-tolerated treatment, the safety profile appears to be clinically manageable.