

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Ceritinib for previously treated anaplastic
lymphoma kinase positive non-small-cell
lung cancer**

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 Ceritinib is not recommended within its marketing authorisation, for treating advanced anaplastic lymphoma kinase positive non-small-cell lung cancer previously treated with crizotinib.
- 1.2 People whose treatment with ceritinib was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Ceritinib (Zykadia, Novartis) has a marketing authorisation in the UK for treating 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.

2.2 The summary of product characteristics lists the following grade 3 and 4 adverse reactions that occur in at least 5% of people having ceritinib: liver laboratory test abnormalities, fatigue, diarrhoea, nausea and hyperglycaemia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Ceritinib is taken orally, once daily. The recommended dose is 750 mg (5 × 150-mg capsules). The company submission stated that the NHS list price is £4923.45 for a 30-day supply. The summary of product characteristics states that treatment should be continued as long as clinical benefit is seen. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Novartis and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The company presented efficacy data from 2 single-arm studies identified by a systematic review: ASCEND-1 and ASCEND-2. These were multicentre, open-label studies of people with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small-cell lung cancer (NSCLC), whose disease had progressed after chemotherapy. All patients had ceritinib.

3.2 The phase I ASCEND-1 study (n=304) enrolled people with a range of treatment histories and explored several different doses of ceritinib. All patients had Eastern Cooperative Oncology Group

(ECOG) performance status of 2 or less and life expectancy of at least 12 weeks. The company's analysis included only the subgroup of 163 adults who had previously been treated with crizotinib and who had the licensed dose of ceritinib (750 mg). This subgroup had ALK-positive, locally advanced or metastatic NSCLC that had progressed despite standard therapy and a mean age of 51.5 years. People continued treatment with ceritinib until unacceptable toxicity or disease progression, or at the discretion of the investigator or by patient request.

- 3.3 The 2 primary outcomes were overall response rate (defined as complete or partial response using the Response Evaluation Criteria in Solid Tumours [RECIST]) and duration of response, both assessed by the investigator. The secondary outcomes included overall response rate assessed by a blinded independent review committee rather than by the investigator, overall survival, progression-free survival (defined as the time from starting treatment to the time of disease progression or death), and adverse events.
- 3.4 The phase II ASCEND-2 study enrolled 140 patients previously treated with crizotinib. The mean age of patients was 51.2 years. It included adults:
- with ALK-positive stage IIIB or IV NSCLC
 - with World Health Organization performance status of 0 to 2
 - with life expectancy of at least 12 weeks
 - who had previously had chemotherapy
 - whose disease had progressed after treatment with crizotinib.
- 3.5 The primary outcome was overall response rate measured by the investigator. Secondary outcomes included overall-response rate

assessed by a blinded independent review committee, progression-free survival, overall survival and safety.

3.6 The results of ASCEND-1 and ASCEND-2 are in table 1. The company also presented a pooled analysis using individual patient data assessed by the blinded independent review committee in ASCEND-1 and ASCEND-2. The pooled median progression-free survival was 7.0 months and the pooled median overall survival was 15.6 months.

Table 1 Clinical study results from ASCEND-1 and ASCEND-2

	ASCEND-1 investigator assessment (n=163)	ASCEND-1 BIRC assessment (n=163)	ASCEND-2 investigator assessment (n=140)	ASCEND-2 BIRC assessment (n=140)
ORR: n (%; 95% CI)	92 (56.4; 48.5 to 64.2)	75 (46.0; 38.2 to 54.0)	54 (38.6; 30.5 to 47.2)	50 (35.7; 27.8 to 44.2)
PFS: median (95% CI), months	6.9 (5.6 to 8.7)	7.0 (5.7 to 8.6)	5.7 (5.4 to 7.6)	7.2 (5.4 to 9.0)
OS: median (95% CI), months	16.7 (14.78, NE)	NR	14.9 (13.5, NE)	NR
Abbreviations: BIRC, blinded independent review committee; CI, confidence interval; NE, not estimable; NR, not reported; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.				

3.7 Health-related quality of life 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). In total, 125 patients completed the EORTC-QLQ-C30, of whom 69 (55.2%) showed improved global health status and 26 (20.8%) showed poorer global health status.

Naive indirect comparison

3.8 The ASCEND-1 and ASCEND-2 studies did not include control groups, so the company could not directly compare ceritinib with best supportive care (BSC). The company searched the literature to find evidence of outcomes for patients who had BSC. It then did a naive indirect comparison of ceritinib with BSC (meaning the comparison was not adjusted for differences in patient or study characteristics between the studies). To assess whether people lived longer with ceritinib than BSC, the company compared the ASCEND studies with Ou et al. (2014). The study by Ou et al. was a retrospective analysis of people with advanced ALK-positive NSCLC, whose disease had progressed after initial treatment and who had crizotinib as a second or subsequent treatment while in a clinical trial (PROFILE 1001 and PROFILE 1005). Ou et al. analysed data from 3 groups of patients whose disease had progressed after treatment with crizotinib:

- those who had BSC only (that is, no active treatment; n=37)
- those who had systemic chemotherapy (n=37)
- those who continued to have crizotinib (n=120).

The results from the crizotinib group were not relevant to the indirect comparison. The company deemed that BSC was an appropriate comparator. The company also compared ceritinib with chemotherapy in a scenario analysis. The company submission stated that the only outcome measure reported by Ou et al. was median overall survival.

Table 2 Results of the naive indirect comparison for overall survival

	Ceritinib ASCEND-1 (n=163)	Ceritinib ASCEND-2 (n=140)	BSC Ou et al. (2014) n=37	Pooled results for BSC and systemic chemotherapy Ou et al. (2014) n=74
OS: Median (95% CI), months	16.7 (14.8, NE)	14.9 (13.5, NE)	2.2 (1.1 to 3.8)	3.9 (2.7 to 5.1)
Abbreviations: BSC, best supportive care; CI, confidence interval; NE, not estimable; OS, overall survival.				

3.9 The company stated that there were no major differences in patient characteristics between Ou et al. (2014) and the ASCEND studies (that is, sex, age, smoking history and previous lines of therapy), although the company noted that patients in Ou et al. had a slightly higher (worse) ECOG status at baseline. By comparing the pooled results of the ASCEND studies (median overall survival 15.6 months) with the results for the BSC group in Ou et al. (median 2.2 months), the company advised that the median overall survival gain for ceritinib compared with BSC was approximately 10 months.

3.10 To assess whether ceritinib delays disease progression, the company compared the ASCEND-1 and ASCEND-2 studies with the control arm of Shepherd et al. (2005), which was a randomised double-blind placebo-controlled trial of erlotinib in patients with advanced NSCLC. It enrolled patients with all types of NSCLC, who had previously had 1 or 2 chemotherapy regimens. Half of the patients had adenocarcinoma and the proportion of patients with ALK-positive mutation is unknown. Shepherd et al. reported that median progression-free survival with BSC was 1.8 months and median overall survival was 4.7 months. For comparison, the pooled analysis of the ASCEND studies showed median progression-free survival with ceritinib of 7.0 months.

3.11 Everyone in ASCEND-1 and ASCEND-2 had adverse events. The percentage of people with grade 3 or 4 adverse events that were suspected to be drug-related was 44.2% in ASCEND-1 and 45.7% in ASCEND-2. The most common grade 3 or 4 adverse events were increases in aminotransferase activities (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]), increases in serum gamma-glutamyltransferase (GGT), diarrhoea, nausea, fatigue, dyspnoea, and vomiting. In both ASCEND-1 and ASCEND-2, 73.6% of patients had a dose reduction or an interruption to their treatment because of adverse events. In ASCEND-2, 7.9% of patients stopped taking ceritinib because of adverse events.

Cost effectiveness

3.12 The company's Markov model compared the cost effectiveness of ceritinib with BSC for people with advanced ALK-positive 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. The evaluation took an NHS and personal social services perspective. Discount rates for both costs and benefits were 3.5%.

3.13 For ceritinib, the company took data from the blinded independent review committee's assessment of progression-free survival and overall survival from the pooled results of the ASCEND-1 and ASCEND-2 studies. For ASCEND-1, it used data from the relevant patient population (that is, people who had previous crizotinib treatment and who had 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, statistical tests and external validity. The company chose a Weibull curve for overall survival and a log-logistic curve for progression-free survival.

- 3.14 To compare ceritinib with BSC, the company took overall-survival data from Ou et al. (2014) and progression-free survival data from Shepherd et al. (2005). For BSC, the company chose a Weibull curve for overall survival and a log-logistic curve for progression-free survival as it did for ceritinib.
- 3.15 The company used an 'area under the curve partitioned survival analysis' technique in which the number of patients in each health state was based on the survival curves described in sections 3.13 and 3.14. Patients entered the model in the progression-free health state and had 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.
- 3.16 For ceritinib, the company included the cost of grade 3 and 4 drug-related adverse events that had happened in at least 5% of patients in the pooled analysis of ASCEND-1 and ASCEND-2. The included events were:
- diarrhoea
 - abnormal liver function tests (increased ALT, AST and GGT)
 - nausea.
- 3.17 The one-off cost associated with adverse events was £71.11. In its base case, the company did not include a decrease in utility for patients who had adverse events. In a scenario analysis, the

company applied utility decrements for adverse events based on Nafees et al. (2008). The company assumed that patients having BSC did not experience adverse events.

3.18 The company estimated utility values by mapping EORTC QLQ-C30 data from ASCEND-2 to the EuroQol EQ-5D questionnaire. The mapping algorithm was developed in the UK for multiple myeloma (Proskorovsky et al. 2014). The company stated in its submission that, for the progression-free health state, it used the same utility value for both ceritinib and BSC based on patients with stable disease in ASCEND-2. The value is academic in confidence and cannot be reported here. The ERG advised that, for the progression-free health state, the utility values in the company's model did not match the description in the company's submission (see section 3.28).

3.19 For the progressed-disease health state, the company stated that it was not appropriate to use the data on quality of life from ASCEND-2, so instead it used published EQ-5D data from patients with advanced NSCLC (Chouaid et al. 2013). The company's rationale was that, in ASCEND-2, no data were collected on quality of life 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 for people at a later stage of progression. 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.

3.20 The model included the costs of treatment with ceritinib and BSC.

- The acquisition cost of ceritinib in the base-case model was about £4100 per month. This represented only 82.8% of the

licensed dose, to account for people who did not take the full course of the treatment because they interrupted their dose, had adverse events, or were non-compliant. This assumption was based on ASCEND-2 data. In a sensitivity analysis the company used full doses (100% dose intensity) for ceritinib.

- The company assumed that there are no administration costs for ceritinib.
- In the base case, patients continued treatment until their disease progressed. In a sensitivity analysis the company assumed that ceritinib was continued for a median of 1.6 months after disease progression, as had been seen in ASCEND-2.
- In the base case, the company assumed that BSC had no treatment costs.

3.21 The resource use 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 (for which ALK testing is needed). The company based its assumptions on resource use from NICE's technology appraisal guidance on [erlotinib for non-small-cell lung cancer](#) and for [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).

3.22 The company's deterministic base case resulted in an incremental cost-effectiveness ratio (ICER) of £62,456 per quality-adjusted life year (QALY) gained for ceritinib compared with BSC (table 3). The company stated in its submission that the key drivers of cost

effectiveness were the cost of ceritinib, the discount rate and the utility values.

Table 3 Company's results

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
Scenario analyses					
Treatment with ceritinib for 1.6 months after disease progression	Not reported				76,039
Utility values from Chouaid et al. (2013)	Not reported				69,896
100% dose intensity for ceritinib	Not reported				74,519
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life year.					

Evidence Review Group's critique

3.23 The ERG noted that only a small number of patients in Ou et al. (2014) were directly relevant to this appraisal (those who had only BSC after crizotinib, n=37), and there was limited information about what the authors considered to be BSC or systemic chemotherapy. The ERG also noted that the company's submission gave baseline patient characteristics only for the combined BSC and chemotherapy subgroups in Ou et al. (2014), so the characteristics of the BSC group (which in the ERG's opinion is the relevant subgroup for the appraisal) were not presented to the Committee.

3.24 The ERG noted that when indirectly comparing the ASCEND studies, Ou et al. (2014) and Shepherd et al. (2005), the company did not adjust for differences in baseline patient characteristics, so

the validity of the modelled results relied on assuming that the study populations were the same. However, the ERG noted that the ASCEND and Ou et al. studies differed in their inclusion and exclusion criteria, specifically previous treatment and ECOG performance status. Also, the ERG's clinical adviser stated that Ou et al. excluded patients with symptomatic brain metastases, whereas the ASCEND studies included these patients if their symptoms were stable. The ERG noted that Shepherd et al. recruited patients with all types of NSCLC, whereas the ASCEND and Ou et al. studies only recruited patients with the ALK-positive mutation.

- 3.25 Regarding the populations, the ERG noted that there were differences in ECOG performance status and previous treatments between the patients in ASCEND and those in the combined BSC and chemotherapy subgroups in Ou et al. (2014), but, based on small numbers, the differences were not statistically significant. The ERG advised that, because the choice of treatment for patients in Ou et al. was based on clinical advice rather than a study protocol, the patients in the BSC group may have had more severe disease than the patients in the active treatment groups. The ERG advised that the BSC arm of the model may be informed by data from patients who were more ill than the patients in the ASCEND studies, potentially underestimating survival with BSC.
- 3.26 Regarding extrapolating overall survival with BSC beyond that seen in Ou et al. (2014), the ERG noted that the company's choice of a Weibull curve was the worst-fitting curve (based on both Akaike and Bayesian information criterion), and it suggested that a log-normal curve should have been used instead (as the ERG did in its scenario analysis). 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.

- 3.27 The ERG noted that the company included only those adverse events that occurred in more than 5% of people, and it noted that the company may have excluded rare but serious adverse events. By contrast, the ERG's exploratory analyses included all grade 3 and 4 events from the ASCEND studies.
- 3.28 The ERG noted an inconsistency between the model and the company's submission in the utility values for the progression-free health state. The company's submission stated that the same utility value was used for both ceritinib and BSC. However, the ERG noted that, in the model, a weighted average utility value was calculated separately for ceritinib and BSC, based on the proportion of patients whose disease responded to treatment in ASCEND-2 and Shepherd et al. (2005) respectively. The ERG advised that the company's method was not justified in its submission and may not be appropriate. Accordingly, the ERG used the same utility value for both ceritinib and BSC, based on data from ASCEND-2. Because patients having BSC would not have the adverse reactions associated with ceritinib, the ERG increased the utility value for the progression-free health state for BSC using utility values from Nafees et al. (2008).
- 3.29 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 continue only until disease progression. The ERG's clinical expert advised that, in clinical practice, it is likely that patients would continue treatment beyond progression. Therefore,

the ERG's exploratory analyses included extra treatment costs for ceritinib.

3.30 The ERG changed the following in the company's model:

- Used a log-normal curve to extrapolate overall survival with BSC.
- Assumed that ceritinib treatment is continued after disease progression for a median of 1.6 months.
- For ceritinib, included all grade 3 and 4 adverse events seen in ASCEND-1 and ASCEND-2.
- For ceritinib, included costs of 2 blood tests and 2 outpatient visits for managing abnormal blood tests.
- For the progression-free health state, used the same utility values for both ceritinib and BSC. The ERG then increased the utility value for the BSC arm to reflect the lower rate of adverse events during treatment 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 4). The ERG advised that the increase in the ICER was mostly because it used a log-normal curve to model overall survival with BSC and because it included the costs of ceritinib treatment after disease progression.

3.31 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 any given time point reflecting the end of benefit, the ERG set the probabilities of progressing or dying on ceritinib to be the same as for BSC. Each scenario 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 4).

Table 4 ERG’s 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’s base case					
BSC	7339	0.27			
Ceritinib	70,620	1.06	63,281	0.80	79,528
ERG’s scenario analyses					
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; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life year.					

3.32 Full details of all the evidence are in the [Committee Papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ceritinib, having considered evidence on the nature of anaplastic lymphoma kinase (ALK) positive non-small-cell lung cancer (NSCLC) and the value placed on the benefits of ceritinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee heard from the clinical and patient experts about the impact of advanced or metastatic ALK-positive NSCLC on people with the condition. It noted that the most common effects of the disease are persistent cough, chest pain, breathlessness, chest

infections, fatigue and metastases to the brain and elsewhere. It also heard that currently there is no targeted treatment available for ALK-positive NSCLC when the disease progresses after treatment with crizotinib. The patient expert suggested that ceritinib provides hope because it has the potential to extend life and improve quality of life. The Committee concluded that additional treatment options would be of value to people with ALK-positive NSCLC.

- 4.2 The Committee discussed the treatment pathway for advanced or metastatic ALK-positive NSCLC and the relevant comparators for ceritinib. It heard from the clinical experts that most people with advanced or metastatic ALK-positive NSCLC would first have platinum-based chemotherapy. People whose disease progresses, and who have a confirmed ALK mutation, may have crizotinib which is available only via the Cancer Drugs Fund (NICE does not recommend crizotinib in its technology appraisal guidance on [crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene](#)). The Committee noted that the population relevant to this appraisal has ALK-positive NSCLC that has progressed after crizotinib. The Committee noted that both the company, and the clinical experts, advised that currently in the NHS there are no active treatments available, and that usually best supportive care (BSC) is offered. It heard from the clinical experts that a few people who are relatively fit are offered chemotherapy, but the clinical experts were not aware of evidence that chemotherapy at this stage of treatment improves outcomes. After consultation, the company suggested that systemic chemotherapy was a relevant comparator for ceritinib for fitter patients and for patients who have not yet had chemotherapy. The Committee noted that no additional evidence was presented to support chemotherapy as a comparator. The Committee was also aware of the comments from the clinical

experts about the lack of evidence for chemotherapy in this setting. The Committee concluded that the relevant comparator for ceritinib was BSC, which would not include any active chemotherapy.

- 4.3 The Committee discussed whether testing for the ALK mutation is established practice in the NHS. It heard from the clinical experts that currently there are differences across England. It understood that the summary of product characteristics for ceritinib states that, before starting treatment, clinicians should assess the person's ALK status. It noted that, according to the marketing authorisation, ceritinib can only be used after crizotinib, which is also an ALK inhibitor. The Committee was aware that ALK mutation testing would be done before starting crizotinib, so the relevant population for this appraisal would have been tested already. It concluded therefore that the costs and availability of ALK mutation testing was not a consideration for this appraisal.

Clinical effectiveness

- 4.4 The Committee discussed the clinical evidence presented by the company and its critique by the Evidence Review Group (ERG). It noted that the company presented efficacy data from the single-arm ASCEND-1 and ASCEND-2 studies. It noted that data on the efficacy of BSC came from 2 separate studies; to assess overall survival the company used Ou et al. (2014), and to assess progression-free survival the company used Shepherd et al. (2005). The company conducted a naive indirect comparison of the results from the ASCEND-1 and ASCEND-2 studies, Ou et al. and Shepherd et al.
- 4.5 The Committee discussed the differences in overall survival between ceritinib and BSC:

- The Committee was aware that median overall survival with ceritinib was 16.7 months in ASCEND-1 (data cut-off April 2014, duration of study 40 months) and 14.9 months in ASCEND-2 (data cut-off August 2014, duration of study 21 months) and that the pooled overall survival was 15.6 months. The Committee considered the number of patients on which these data were based and noted the company's submission stated that 59 people had died in ASCEND-2 (n=130). The Committee agreed that the data were immature.
- The Committee was aware that median overall survival with BSC was 2.2 months in Ou et al. (2014). The Committee noted that the BSC data were based on a small sample of patients, and so these results were uncertain.
- The Committee discussed the risk of confounding in the overall survival analysis by considering whether people in the ceritinib studies had a different underlying risk of dying than people in the Ou et al. (2014) study. The Committee was aware that the ASCEND studies only included people who had a life expectancy of at least 12 weeks, which was not true for the Ou et al. cohort. It was aware that in Ou et al., treatment was determined by clinician choice and people offered BSC may have been more unwell than those offered active treatment. The Committee understood from the ERG that the BSC group in Ou et al. may have been sicker than patients in the ASCEND studies, since these patients had higher ECOG values at disease progression than patients on the ASCEND trials. The Committee was aware that differences in baseline patient characteristics, such as age and ECOG status, were not statistically significant between the studies, but recognised the challenges of proving statistical significance with a small study population. The Committee acknowledged that if those on the

Ou et al. study were sicker than those on ASCEND, the overall survival benefit of ceritinib compared with BSC would be overestimated. The Committee heard from the company that because of limited data it could not compare the ASCEND and Ou et al. studies for other potential confounders, such as disease burden, which the clinical experts noted would reasonably be associated with mortality. So, the Committee considered that the results of the naive indirect comparison, and specifically the size of benefit, were uncertain because there was a high risk of bias from confounding.

The Committee concluded that ceritinib was likely to prolong life but the extent of treatment benefit was highly uncertain.

4.6 The Committee discussed the differences in progression-free survival between ceritinib and BSC:

- The Committee noted that median progression-free survival with ceritinib was 6.9 months in ASCEND-1 and 7.0 months in ASCEND-2 and that the pooled progression-free survival estimate was 7.0 months. For comparison, median progression-free survival with BSC was 1.8 months in Shepherd et al. (2005).
- The Committee discussed whether the difference in progression free survival could be attributed to differences between the studies rather than to the benefit of treatment with ceritinib itself. The Committee was aware that the company used the BSC arm from Shepherd et al. (2005), which although limited to NSCLC, was not limited to patients with ALK-positive tumours. The Committee was not presented with data on whether the disease in patients with ALK-positive NSCLC progresses faster or slower than in patients whose tumours are not ALK-positive, but heard from the clinical experts that ALK-positive NSCLC may have a natural history that differs from other types of NSCLC. The

Committee also heard that the Shepherd et al. trial was not limited to people receiving third-line treatment and that patients in Shepherd et al. had lower (that is, better) scores for ECOG performance status than patients in the ASCEND trials, so they might have been fitter and their disease less likely to progress.

The Committee concluded that ceritinib was likely to delay disease progression, but that the size of the difference in progression-free survival is highly uncertain.

4.7 The Committee considered whether the evidence for the clinical effectiveness of ceritinib could be generalised to people with advanced ALK-positive NSCLC in England. It noted that the company included only about 50% of the patients from ASCEND-1, but that the clinical experts felt that it represented the relevant population in England. The Committee was aware that the analysis included only about 20% of patients from Ou et al. (2014), making it difficult to determine whether they represented patients who might be offered BSC in England. The Committee also heard from the clinical experts that Shepherd et al. (2005) enrolled patients with all types of NSCLC, including different genetic mutations from the ALK-positive mutation. The proportion of patients with ALK-positive mutation in Shepherd et al. is unknown. The Committee concluded that the ASCEND studies were generalisable to people with ALK-positive tumours in England, but the Shepherd et al. study was not.

4.8 The Committee was aware that the marketing authorisation for ceritinib states that treatment should continue as long as clinical benefit is observed. It discussed whether, in clinical practice in England, people are likely to continue ceritinib after disease progression. It heard from the clinical experts that this was done for other targeted treatments for NSCLC (such as EGFR inhibitors)

and so it would be reasonable to expect ceritinib treatment to continue after progression. The Committee was aware from Ou et al. that crizotinib as second-line treatment is continued after disease progression. The Committee noted that in ASCEND-2, ceritinib was taken for a median of 1.6 months after disease progression. The Committee noted a comment received after consultation that in clinical practice, treatment after disease progression might be even longer but it was aware that no other real-world evidence is currently available. The Committee concluded that, in clinical practice, treatment with ceritinib could plausibly continue after disease progression and the best estimate of the duration of treatment came from ASCEND-2.

- 4.9 The Committee discussed the ongoing studies of ceritinib. It noted that the ASCEND-5 randomised controlled trial compares ceritinib with chemotherapy (pemetrexed or docetaxel) in people with ALK-positive NSCLC previously treated with crizotinib. The Committee heard from the company that the results of ASCEND-5 should be available in the second quarter of 2016. It concluded that the ASCEND-5 trial may give useful data about the clinical effectiveness of ceritinib compared with chemotherapy.
- 4.10 The Committee discussed the adverse events associated with ceritinib. It noted that in the ASCEND studies, all patients had adverse events and many had a dose reduction or interrupted treatment. It also considered the comments from the patient and clinical experts (both in their submissions and during the first meeting) that the adverse events associated with ceritinib are tolerable and manageable. The Committee concluded that, although many people had adverse events while taking ceritinib, these events were manageable.

Cost effectiveness

- 4.11 The Committee discussed the company's economic model, noting that it used clinical evidence from 4 different sources: ASCEND-1 and ASCEND-2, Ou et al. (2014) and Shepherd et al. (2005). The Committee was aware that the model used data from a naive indirect comparison and noted that this had weaknesses (see sections 4.5 and 4.6). However, it concluded that this was the best evidence available and the model was sufficient for current decision-making.
- 4.12 The Committee discussed the methods used by the company for modelling overall survival. It noted that the company used parametric curves to extrapolate overall survival over the 10-year time horizon of the model. For ceritinib, the company used pooled results from the ASCEND-1 and ASCEND-2 studies. For BSC, it used results from the BSC-only subgroup of patients from Ou et al. (2014). The Committee noted that the company chose the Weibull curve to extrapolate overall survival for both arms of the model whereas the ERG's exploratory analyses used a different curve for the BSC arm, the better-fitting log-normal curve. The Committee heard from the ERG that the log-normal curve predicts that an extremely small proportion of patients would be alive after 10 years, whereas the Weibull curve predicts that no patients would be alive after 10 years. The clinical experts advised that they would be surprised if people with ALK-positive NSCLC that had progressed after crizotinib were alive after 10 years. The Committee concluded that, for extrapolating overall survival with BSC, the log-normal curve was a better fit for the data whereas the Weibull curve gave results that better reflected clinical experience. So, the Committee considered both in its decision-making.

- 4.13 The Committee discussed the assumptions about how long patients take ceritinib. It noted that the company's base case assumed treatment until disease progression. The Committee recognised that the ERG presented analyses exploring the impact of treatment continuing after progression and assumed 1.6 months of treatment after progression based on the median seen in ASCEND-2. The Committee concluded that, in clinical practice, treatment could plausibly continue after progression, and the best estimate of the duration of treatment came from ASCEND-2 (see section 4.8), so it preferred the ERG's approach to modelling treatment duration.
- 4.14 The Committee discussed the assumptions about the duration of treatment benefit. It noted that the company's model assumed that the benefits of treatment with ceritinib persist beyond the study period and after stopping treatment. It also noted that the exploratory analysis by the ERG, which reduced the duration of treatment benefit with ceritinib to 2 years, substantially raised the incremental cost-effectiveness ratio (ICER). The Committee heard from the clinical experts at the meeting that it was unlikely that ceritinib would offer a benefit beyond the end of treatment, and if it did, it would not be as long as 2 years. The Committee was not given evidence that the treatment benefit from ceritinib would continue after the end of treatment, and concluded that it was not appropriate to model any benefit beyond stopping treatment with ceritinib.
- 4.15 The Committee considered the utility values in the company's model. It noted the inconsistency between the model and the company's submission and that the company used different utility values for ceritinib and BSC in the progression-free health state. It also noted the ERG's critique, that using the same utility value

would have been more appropriate and that the company did not justify its choice in its submission (section 3.28). The Committee concluded that the ERG's approach was more appropriate, and that the same utility values should be applied to both arms of the model; that is, the utility should depend on the health state rather than the treatment. The Committee then discussed whether the model should include utility decrements associated with adverse events. It considered the ERG's approach reasonable, that is, increasing the utility value for patients receiving BSC for the progression-free health state because patients having BSC would not experience adverse events associated with ceritinib.

- 4.16 The Committee discussed the cost of ceritinib treatment, noting that the company's model assumed that patients do not take all of the licensed dose of ceritinib and so the NHS would pay for only 82.8% of the licensed dose. It was aware that the dose intensity in the company's model was based on data from ASCEND-1 and ASCEND-2. It heard from the clinical experts that, for a short-term reduction in dose, people would continue to have a 30-day supply of their usual dose of ceritinib and unused tablets would be wasted. In contrast, for a long-term dose reduction, the lower dose would be prescribed and tablets were unlikely to be wasted. The Committee heard from the clinical experts that people who stop ceritinib because of adverse reactions cannot return unused tablets to the NHS. It also heard from the company that the recommended dose of ceritinib is 750 mg per day and would be given in 5 doses of 150 mg capsules. This allows people to easily reduce doses, which may mean less wastage. Based on this advice, the Committee concluded that on average in clinical practice the NHS would not pay for the full dose, but it was likely to pay for more than 82.8%, because of wastage. So, the Committee concluded that the dose

intensity in the model should be lower than 100% but higher than the estimate of 82.8% used by the company.

- 4.17 The Committee also discussed administration costs related to having ceritinib. It noted that the company assumed there were no administration costs for ceritinib because it is taken orally. However, the Committee noted a comment received during consultation that ceritinib would be available only through cancer centres, and so the company should have included pharmacy costs for a specialist cancer centre in the modelling. By contrast, BSC is currently shared between GPs and specialists. It heard from the ERG that compared with the high costs of ceritinib treatment, which is one of the key drivers of cost effectiveness, the impact of administration costs on the ICER is likely to be small. The Committee acknowledged this, but still concluded that administration costs for ceritinib should have been included in the modelling.
- 4.18 The Committee considered whether ceritinib was a cost-effective use of NHS resources compared with BSC for people with ALK-positive NSCLC. It noted that the company's base case resulted in an ICER of £62,500 per quality-adjusted life year (QALY) gained (incremental costs £51,952; incremental QALYs 0.83). It noted that the ERG's preferred parameters resulted in an ICER of £79,500 per QALY gained (incremental costs £63,281; incremental QALYs 0.80). However, the Committee was aware that both the company's and the ERG's base case included an indefinite treatment benefit from ceritinib after treatment with ceritinib had stopped, an assumption with which the Committee did not agree (see section 4.14). The Committee noted that accounting for this substantially increased the ICER, for example, when the duration of treatment benefit with ceritinib was decreased to 2 years, the ERG's ICER

increased to £99,700 per QALY gained. The Committee agreed that, of the ICERs presented, £99,700 per QALY gained was the most plausible, it recognised that:

- The Committee had not agreed with the ERG's extrapolation of overall survival with BSC (see section 3.30). The Committee agreed it was appropriate to take both the ERG's and company's approach for extrapolation into account, and it recognised this would decrease the ICER.
- The Committee recognised that modelling no benefit from treatment after stopping ceritinib (rather than 2 years of treatment benefit) would increase the ICER further.

The Committee concluded that, on balance, the most plausible ICER was likely to be greater than £99,700 per QALY gained.

4.19 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the lives of patients who have a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are

robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

- 4.20 The Committee discussed whether ceritinib for ALK-positive NSCLC met the first and third end-of-life criteria. It noted that the clinical evidence in the company's submission showed that the life expectancy for people with ALK-positive NSCLC is a median of 2.2 months with the currently available BSC. However, because there was significant uncertainty around this value, the Committee also considered the life expectancy for other types of NSCLC treated with BSC, noting that this was 4.7 months (Shepherd et al. 2005). It agreed that this life expectancy is significantly less than 24 months, and therefore it concluded that the life expectancy criterion was met. The Committee also discussed the size of the patient population eligible for ceritinib and noted that about 66 or 98 patients would be eligible for ceritinib treatment each year in England and Wales. It concluded that ceritinib is licensed for a small patient population and that the population-size criterion was met.
- 4.21 The Committee then discussed whether ceritinib is likely to offer an extension to life of an additional 3 months, compared with BSC. It was aware that the company's submission stated that ceritinib prolonged life by a median of 10 months compared with BSC, an approximation based on a naive indirect comparison using the results of ASCEND-1 and ASCEND-2 and Ou et al. (2014). The Committee noted the company's comment that this was the best available evidence and that trials could not directly compare ceritinib with BSC because of ethical considerations. The Committee recalled its conclusion that this naive indirect comparison was at high risk of bias because of confounding. It was also aware that the mean survival estimates for both ceritinib and

BSC were very uncertain because the ceritinib estimate came from interim analyses and the BSC estimate came from a very small number of patients. The Committee discussed all the estimates for overall survival without treatment with ceritinib, the risk factors for dying, the differences in these risk factors in the patients in the studies, and whether the degree of confounding, if accounted for, was likely to reduce the estimates to a mean difference in overall survival between ceritinib and BSC care of 3 months or less. The Committee concluded that controlling for confounding was unlikely to reduce the mean difference to less than 3 months. The Committee recognised the uncertainty, and called for future appraisals of ceritinib compared with BSC to objectively and robustly show a mean difference of greater than or equal to 3 months, but considered that it was reasonable to conclude that ceritinib offers an average extension to life of at least 3 months.

- 4.22 The Committee discussed whether ceritinib is an innovative treatment and whether it provides additional benefits to patients. The Committee was aware that the company and the patient expert considered ceritinib innovative. The Committee also acknowledged that ceritinib had a Promising Innovative Medicine designation from the Medicines and Healthcare products Regulatory Agency (MHRA). It also noted some further benefits of ceritinib: clinical experts advised that it may control brain metastases; and the patient expert advised that it allows people to continue to work and live a more normal life. However, the Committee noted that it had not been presented with evidence about the extent to which these benefits were realised in practice, compared with BSC. It also noted the comments from consultation that in the ASCEND-2 trial, patients having ceritinib had no deterioration in their symptoms or quality of life. The Committee concluded that ceritinib may be innovative, but it had not been presented with any additional

evidence of benefits that were not captured in the measurement of QALYs.

4.23 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising ceritinib. The Appraisal Committee noted NICE’s position statement about this, and accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The Committee heard nothing to suggest that there is any basis for taking a different view on the relevance of the PPRS to this appraisal of ceritinib. It therefore concluded that the PPRS payment mechanism was not applicable when considering the cost effectiveness of ceritinib.

4.24 The Committee noted that the company’s ICERs for ceritinib were above the range usually considered a cost-effective use of NHS resources and the ERG’s ICERs were even higher. Based on the available evidence, the Committee considered that although there was some uncertainty about whether ceritinib meets all 3 criteria for end-of-life consideration, it was satisfied that end-of-life criteria had been met. However, the Committee agreed that, even taking end-of-life criteria into account, the ICERs were above the range considered a cost-effective use of NHS resources. Therefore, the Committee could not recommend ceritinib for advanced ALK-positive NSCLC previously treated with crizotinib.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title: Ceritinib for previously treated anaplastic-lymphoma-kinase-	Section
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	positive non-small-cell lung cancer	
Key conclusion		
<p>Ceritinib is not recommended within its marketing authorisation, that is, for treating advanced anaplastic lymphoma kinase (ALK) positive non-small-cell lung cancer (NSCLC) previously treated with crizotinib.</p>	1.1	
<p>The clinical effectiveness data were based on single-arm phase I and II studies for ceritinib and on 2 observational studies for best supportive care. The Committee concluded that ceritinib was likely to prolong life and delay disease progression compared with best supportive care, but the extent of treatment benefit was highly uncertain because there was a high risk of bias from confounding.</p>	4.4 4.5 4.6	
<p>The key drivers of cost effectiveness were the survival functions used to extrapolate overall survival, assumptions about whether ceritinib treatment continues after disease progression and assumptions about the duration of treatment benefit. The company's base case ICER was £62,500 per QALY gained and this increased to £79,500 per QALY gained when the ERG incorporated its preferred estimates.</p>	3.30, 3.31 4.18	
<p>A key driver of the results is duration of treatment benefit: the company assumed that the benefits of treatment would continue indefinitely after treatment stopped. The ERG explored shorter periods of treatment benefit and found that decreasing the duration of treatment benefit with ceritinib to 2 years increased the ERG's ICER to £99,700 per QALY gained. The Committee was aware that that it had agreed that it is unlikely that ceritinib would give benefit beyond the end of treatment, and it noted that this would increase the ICER further.</p>	4.14	
<p>The Committee agreed that the most plausible ICER presented was</p>		

<p>£99,700 per QALY gained, and that even with the uncertainty about the extrapolation of overall survival with best supportive care, which may reduce the ICER, it was more likely that modelling no treatment benefit after ceritinib treatment had stopped would increase the ICER further. The Committee concluded that on balance, the ICER was likely to be greater than £99,700 per QALY gained.</p>		4.19
<p>Based on the available evidence, the Committee considered that although there was some uncertainty about whether ceritinib meets all 3 criteria for end-of-life consideration, it was satisfied that end-of-life criteria had been met. However, the Committee agreed that, even taking end-of-life criteria into account, the ICERs were above the range considered a cost-effective use of NHS resources. Therefore, the Committee could not recommend ceritinib for advanced ALK-positive NSCLC previously treated with crizotinib.</p>		4.24
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>Currently there is no targeted treatment available for ALK-positive NSCLC that has progressed after crizotinib; most patients have best supportive care.</p>	4.2
<p>The technology</p>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Ceritinib has the potential to extend life, improve quality of life and provide people with hope for the future.</p> <p>The Committee concluded that ceritinib may be innovative, but it had not been presented with evidence of benefits that were not captured in the measurement of quality-adjusted life years (QALYs).</p>	<p>4.1</p> <p>4.22</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>Most people with advanced or metastatic ALK-positive NSCLC first have platinum-based chemotherapy. People whose disease progresses, may have crizotinib which is only available through the Cancer Drugs Fund (NICE technology appraisal 296 does not recommend crizotinib). Ceritinib would be used after the disease progresses after treatment with crizotinib.</p>	<p>4.2</p>
<p>Adverse reactions</p>	<p>The Committee concluded that, although many people experienced adverse events while taking ceritinib, these events were manageable.</p>	<p>4.10</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The company presented efficacy data from the single-arm ASCEND-1 and ASCEND-2 studies of ceritinib. Evidence on the efficacy of best supportive care came from 2 separate studies; data on overall survival from Ou et al.</p>	<p>4.4</p>

	(2014) and data on progression-free survival from Shepherd et al. (2005). The company conducted a naive indirect comparison of the results from these studies.	
Relevance to general clinical practice in the NHS	The Committee concluded that the ASCEND studies were generalisable to people with ALK-positive tumours in England. The Shepherd et al. (2005) study was not generalisable because it included patients with all types of NSCLC, rather than ALK-positive NSCLC.	4.7

<p>Uncertainties generated by the evidence</p>	<p>The studies in the indirect comparison differed in eligibility criteria and patient characteristics. The Committee concluded that the results of the naive indirect comparison were uncertain because there was a high risk of bias due to confounding.</p>	<p>4.5 4.6</p>
	<p>Regarding progression free survival the data for best supportive care came from Shepherd et al. (2005), which included patients with all types of NSCLC. The Committee was not presented with data on whether the disease in patients with ALK positive NSCLC progresses faster or slower than in patients whose tumours are not ALK positive. It concluded that the size of the difference in progression-free survival is likely to be confounded.</p>	<p>4.6</p>
	<p>Regarding overall survival, the data for ceritinib were immature and the data for best supportive care came from only 20% of patients from Ou et al. (2014).</p>	<p>4.5</p>
	<p>The Committee concluded that ceritinib was likely to prolong life compared with best supportive care, but the extent of treatment benefit was highly uncertain.</p>	

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>No subgroups were considered.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The median overall survival with ceritinib was 16.7 months in ASCEND-1, 14.9 months in ASCEND-2 and the pooled result was 15.6 months. The median overall survival with best supportive care was 2.2 months in Ou et al. (2014).</p> <p>The median progression-free survival with ceritinib was 6.9 months in ASCEND-1, 7.0 months in ASCEND-2 and the pooled result was 7.0 months. The median progression-free survival with best supportive care was 1.8 months in Shepherd et al. (2005).</p>	<p>4.5</p> <p>4.6</p>
<p>Evidence for cost effectiveness</p>		

<p>Availability and nature of evidence</p>	<p>A Markov model was developed, which used data from ASCEND-1, ASCEND-2, Ou et al. (2014) and Shepherd et al. (2005). The Committee was aware that the model used data from a naive indirect comparison and noted that this had weaknesses. However, it concluded that this was the best evidence available and the model was sufficient for decision-making.</p>	<p>3.12, 4.11</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>For extrapolating overall survival with best supportive care, the Committee concluded that the log-normal curve (chosen by the ERG) was a better fit for the data whereas the Weibull curve (chosen by the company) gave results that better reflected clinical experience. It therefore considered both in its decision-making.</p> <p>The company's base case assumed treatment with ceritinib continued until disease progression, whereas the ERG assumed a median of 1.6 months of treatment after progression based on ASCEND-2. The Committee concluded that treatment could plausibly continue after progression.</p> <p>The company assumed that the benefits of ceritinib persist after stopping treatment, but the Committee heard from clinical experts that this was unlikely. It concluded that it was not appropriate to model any benefit beyond</p>	<p>4.12</p> <p>4.13</p> <p>4.14</p>

	<p>stopping treatment with ceritinib.</p> <p>The company’s model assumed that patients take 82.8% of the licensed dose of ceritinib based on data from ASCEND-1 and ASCEND-2. The Committee concluded that on average in clinical practice, the NHS would not pay for the full dose, but it was likely to pay for more than 82.8% because of wastage. So, the dose intensity in the model should be between 82.8% and 100%.</p>	<p>4.16</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The company used different utility values for ceritinib and best supportive care in the progression-free health state. The Committee concluded that the ERG’s approach (applying the same utility value to both arms of the model) was more appropriate.</p> <p>Clinical experts advised that ceritinib may control brain metastases. The patient expert advised that ceritinib allows people to continue to work and live a more normal life. The Committee concluded that it had not been presented with evidence that these benefits were realised in practice, nor had it seen evidence that these benefits were not captured in the measurement of QALYs.</p>	<p>4.15</p> <p>4.22</p>

Are there specific groups of people for whom the technology is particularly cost effective?	No subgroups were considered.	
What are the key drivers of cost effectiveness?	The key drivers of cost effectiveness were the survival functions used to extrapolate overall survival, assumptions about whether ceritinib treatment continues after disease progression and assumptions about the duration of treatment benefit.	3.30, 3.31
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICER was likely to be greater than £99,700 per QALY gained.	4.18
Additional factors taken into account		
Patient access schemes (PPRS)	None	
End-of-life considerations	The Committee concluded that the life expectancy for people with ALK-positive NSCLC is short and the size of the population is small. It also concluded that although the naive indirect comparison was at high risk of bias because of confounding, it was reasonable to conclude that ceritinib offers an average extension to life of at least 3 months.	4.20, 4.21

<p>Equalities considerations and social value judgements</p>	<p>No equality issues were raised.</p>	
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5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer](#), NICE technology appraisal guidance 347 (2015)
- [Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene](#), NICE technology appraisal guidance 296 (2013)
- [Lung cancer: diagnosis and management](#), NICE guideline CG121 (2011).
- [Pemetrexed for the maintenance treatment of non-small-cell lung cancer](#), NICE technology appraisal guidance 190 (2010)
- [Pemetrexed for the first-line treatment of non-small-cell lung cancer](#), NICE technology appraisal guidance 181 (2009)
- [Bevacizumab for the treatment of non-small-cell lung cancer \(terminated appraisal\)](#), NICE technology appraisal 148 (2008)
- [Pemetrexed for the treatment of non-small-cell lung cancer](#), NICE technology appraisal guidance 124 (2007)

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review by the Guidance Executive when the results of the ASCEND-5 trial are reported (expected to be in the second quarter of 2016). The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Amanda Adler
Chair, Appraisal Committee
January 2016

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital, Cambridge

Professor Ken Stein (Vice Chair)

Professor of Public Health, University of Exeter Medical School

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

National Institute for Health and Care Excellence

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Final appraisal determination – Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer

Issue date: January 2016

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Mr Matthew Campbell-Hill

Lay member

Mr Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Dr Peter Crome

Consultant, Geriatrics

Dr Neil Iosson

Locum GP

Mrs Anne Joshua

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Dr Sanjay Kinra

Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

Professor Ruairidh Milne

Professorial Fellow in Public Health, Wessex Institute, University of Southampton

Mr Christopher O'Regan

Head of Health Technology Assessment & Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Nigel De-Kare Silver

General Practitioner, Imperial College and Gladstone Medical Centre

Marta Soares

Research Fellow, Centre for Health Economics, University of York

David Thomson

Lay member

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Boglarka Mikudina

Technical Lead

Dr Rosie Lovett and Raisa Sidhu

Technical Advisers

Jeremy Powell

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Pink J, Loveman E, Taggart F et al., Lung cancer (non-small-cell, anaplastic lymphoma kinase positive, previously treated) – ceritinib, August 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Novartis

II. Professional/expert and patient/carer groups:

- British Thoracic Society
- Independent Cancer Patients' Voice
- National Lung Cancer Forum for Nurses
- Roy Castle Lung Cancer Foundation
- Royal College of Nursing
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on ceritinib by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Dr Martin Forster, Medical Oncology Consultant, nominated by Novartis – clinical expert
- Ms Rachel Thomas, Lung Cancer Clinical Nurse Specialist, nominated by the National Lung Cancer Forum for Nurses – clinical expert
- Dr Joyce Thomson, Clinical Senior Lecturer and Honorary Medical Oncologist, nominated by Novartis – clinical expert
- Mr Tom Haswell, nominated by Independent Cancer Patients' Voice – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy. They were also invited to comment on the ACD.

- Novartis