

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ceritinib in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ceritinib in the NHS in England.

For further details, see the Guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 27 October 2015

Second Appraisal Committee meeting: 11 November 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

## **1 Appraisal Committee's preliminary recommendations**

- 1.1 Ceritinib is not recommended within its marketing authorisation, that is, 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, which reduces cell proliferation and tumour development.
- 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 observed. 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 through 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. People continued treatment with ceritinib until unacceptable toxicity, disease progression, or they and their clinician decided to stop.
- 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 safety.

- 3.4 The phase II ASCEND-2 study enrolled 140 patients previously treated with crizotinib. 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.
  - Who had progressed disease despite therapy 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 from the blinded independent review committee assessments in ASCEND-1 and ASCEND-2. The pooled median progression-free survival was 7.0 months and the pooled median overall survival was 15.64 months.

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

	<b>ASCEND-1 investigator assessment (n=163)</b>	<b>ASCEND-1 BIRC assessment (n=163)</b>	<b>ASCEND-2 investigator assessment (n=140)</b>	<b>ASCEND-2 BIRC assessment (n=140)</b>
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]
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]
OS: median [95% CI], months	16.72 [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. The company submission did not give the actual scores, nor did it state the time point at which the summary of results was calculated.

### ***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 did a literature search to identify evidence of outcomes for patients who have BSC. It then conducted 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 are not relevant to the appraisal. The company deemed that the appropriate comparison included both BSC and chemotherapy. 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**

	<b>Ceritinib ASCEND-1 (n=163)</b>	<b>Ceritinib ASCEND-2 (n=140)</b>	<b>BSC Ou et al. (2014) n=37</b>	<b>Pooled results for BSC and systemic chemotherapy Ou et al. (2014) n=74</b>
OS: Median [95% CI], months	16.7 [14.8, NE]	14.9 [13.5, NE]	2.2 [1.1–3.8]	3.9 [2.7–5.1]
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 prior lines of therapy),

although the company noted that patients in Ou et al. had a slightly higher ECOG status at baseline. By comparing the pooled results of the ASCEND studies (median overall survival 15.64 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 about 10 months.

3.10 To assess whether ceritinib delays disease progression, the company compared the ASCEND-1 and ASCEND-2 studies with 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 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 was 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 serum hepatic transaminase (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 prior 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 For BSC, the company took overall survival data from Ou et al. (2014) and progression-free survival data from Shepherd et al. (2005). As for ceritinib, for BSC the company chose a Weibull curve for overall survival and a log-logistic curve for progression-free survival.

- 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 occurred 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 serum alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase).
  - 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 approximately £4100 per month. This included 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. The company assumed that there were no administration costs for ceritinib. In the base case, patients continued treatment until their disease progressed. In sensitivity analyses the company used full doses (100% dose intensity) for ceritinib and, separately, assumed that ceritinib was continued for a median of 1.6 months after disease progression based on ASCEND-2.

- In the base case, the company assumed that BSC generated 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 would be 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 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 submission only presented baseline patient characteristics for the combined BSC and chemotherapy subgroups in Ou et al., 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 the company's indirect comparison of the ASCEND studies, Ou et al. (2014) and Shepherd et al. (2005) did not adjust for differences in baseline patient characteristics, so the model results relied on the assumption 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 prior 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 trial populations, the ERG noted that 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. 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. So 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 For extrapolating overall survival with BSC beyond that observed in Ou et al. (2014), the ERG noted that the company's choice of a Weibull curve was the worst-fitting curve, and it stated that a log-normal curve should have been used instead (this was done in the ERG's 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 advised 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 submission in the utility values for the progression-free health state. The company submission stated that the same utility value was used for both ceritinib and BSC. However, the ERG advised that, in the model, a weighted average utility value 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 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 experience the adverse events 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 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.
- 3.30 The ERG made the following changes to 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 observed in ASCEND-1 and ASCEND-2.
- For ceritinib, included costs of 2 blood tests and 2 outpatient visits for managing lab abnormalities.
- 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 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 the log-normal curve was used to model overall survival with BSC and because the costs of ceritinib treatment after disease progression were included.

- 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 symptoms are persistent cough, chest pain, breathlessness, chest infections,

fatigue and metastases in the brain and elsewhere. It also heard that currently there is no targeted treatment available for ALK-positive NSCLC after the disease progresses after crizotinib. The patient expert explained that ceritinib had the potential to extend life, improve quality of life and provide people with hope for the future. 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 (that is, the treatments that people would otherwise have in the NHS). It heard from the clinical experts that most people with advanced or metastatic ALK-positive NSCLC first have platinum-based chemotherapy. People whose disease progresses, and who have a confirmed ALK mutation, may have crizotinib which is only available via the Cancer Drugs Fund (NICE [Technology appraisal 293](#) does not recommend crizotinib). The Committee noted that the population relevant to this appraisal was people with 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 these people are usually offered best supportive care (BSC). 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. The Committee concluded that the relevant comparator for ceritinib was BSC.

4.3 The Committee discussed whether ALK mutation testing is established practice within the NHS. It heard from the clinical experts that currently there are differences across the country and not all people are tested. It understood that the summary of product

characteristics for ceritinib states that, before starting treatment , clinicians should assess the person's ALK status. It also noted that, according to the marketing authorisation, ceritinib can only be used after crizotinib, which is another ALK inhibitor. The Committee was aware that ALK mutation testing would be done before starting crizotinib, so the relevant population for this appraisal would already have been tested. It concluded that consideration of the costs and availability of ALK mutation testing was beyond the scope of the 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. (meaning the comparison was not adjusted for differences in patient or study characteristics between the studies).
- 4.5 The Committee discussed whether differences in outcomes between ceritinib and BSC could be attributed to differences between studies rather than wholly to the benefit of treatment with ceritinib itself. Specifically, the Committee discussed the risk of confounding in the overall survival analysis by considering whether people included in the ceritinib studies had a different risk of dying than people in the BSC study. It was aware that in Ou et al. (2014) treatment was determined by clinician choice and therefore people who were offered BSC may have been more unwell than those who

had ongoing crizotinib or systemic chemotherapy. The Committee understood that the BSC group in Ou et al. may therefore have been sicker than patients in the ASCEND studies, which would under estimate the effectiveness of BSC for the population of interest. The Committee heard at the meeting that the company had not identified any 'significant differences' in certain baseline characteristics (age and Eastern Cooperative Oncology Group [ECOG] performance status) between Ou et al. and the ASCEND-1 and ASCEND-2 studies, but the Committee was aware that the small numbers of patients in Ou et al. could mean that statistical testing could miss important differences. The Committee heard from the company that because of data limitations it could not compare the studies with respect to other potential confounders, such as disease burden, which the clinical experts noted would reasonably be associated with mortality. The Committee therefore concluded that the results of the naive indirect comparison were uncertain because there was a high risk of bias due to confounding.

4.6 The Committee discussed the evidence presented by the company about the clinical effectiveness of ceritinib compared with BSC.

- It was aware that median overall survival with ceritinib was 16.7 months in ASCEND-1 (data cut-off April 2014) and 14.9 months in ASCEND-2 (data cut-off August 2014). The Committee considered the number of patients these data were based on 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 and therefore uncertain. The Committee was aware that median overall survival with BSC was 2.2 months in Ou et al. (2014). However, the BSC data were based on a very small sample of patients and therefore these results were also uncertain. Moreover, the comparison

between ceritinib and BSC was at risk of bias (see section **Error! Reference source not found.**).

- The Committee noted that median progression-free survival with ceritinib was 6.9 months in ASCEND-1 and 7.0 months in ASCEND-2. For comparison, median progression-free survival with BSC was 1.8 months in Shepherd et al. (2005). The Committee noted that Shepherd et al. included patients with all types of NSCLC, and it did not include only people having third-line treatment. The Committee heard from the clinical experts that ALK-positive NSCLC may have a natural history that differs from other types of NSCLC. Therefore it concluded the comparison of progression-free survival between Shepherd et al. and the ASCEND studies was at risk of bias due to confounding.

The Committee concluded that ceritinib was likely to prolong life and delay disease progression compared with BSC, but the extent of treatment benefit was 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 a small subgroup of patients from ASCEND-1, but that the clinical experts felt that they represented the relevant population in England. The Committee was aware that only a few patients from Ou et al. (2014) were included in the analysis, making it difficult to determine whether they represented the relevant population in England. The Committee also heard from the clinical experts that Shepherd et al. (2005) enrolled patients with all types of NSCLC; about one-quarter of whom had EGFR-positive advanced NSCLC, which is a different genetic mutation to ALK. 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 discussed whether, in clinical practice in England, people are likely to continue ceritinib after disease progression. It heard from the clinical experts that they did not know whether clinicians would continue ceritinib after disease progression, but that this was done for other targeted treatments for NSCLC (such as EGFR inhibitors). The Committee noted that, in ASCEND-2, ceritinib was taken for a median of 1.6 months after disease progression. 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 ongoing ASCEND-5 randomised controlled trial is comparing ceritinib with chemotherapy (pemetrexed or docetaxel) in people with ALK-positive NSCLC previously treated with crizotinib. The Committee noted that ASCEND-5 would not provide data about the effectiveness of ceritinib against the relevant comparator of best supportive care, but nonetheless it is a randomised trial in the relevant patient population. 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 should provide useful data about the clinical effectiveness of ceritinib.
- 4.10 The Committee discussed the adverse events associated with ceritinib. It noted that in the ASCEND studies, all patients experienced adverse events and many patients had a dose reduction or an interruption to treatment. It also considered the comments from the patient and clinical experts (both in their

submissions and during the meeting) that the adverse events associated with ceritinib are tolerable and manageable. The Committee concluded that, although many people experienced adverse events with 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 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 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

fitted the data better whereas the Weibull curve gave results that better reflect clinical experience. It therefore 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 progression, whereas the ERG assumed a median of 1.6 months of treatment after progression based on ASCEND-2. The Committee had 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 provide a benefit beyond the end of treatment, and if it did, it would not be as long as 2 years. The Committee was not provided with evidence that the treatment benefit from ceritinib would continue after the end of treatment, and concluded that it was not appropriate to model a 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, specifically, that using the same utility value would have been more appropriate and that the company's choice was not justified in its submission (section 3.28). The Committee concluded that the ERG's approach was more appropriate and 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 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 therefore 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. In addition, the Committee heard from the clinical experts that people who stop ceritinib because of adverse effects cannot return unused tablets to the NHS. Based on this advice, the Committee concluded that in clinical practice the NHS would not pay for the full dose on average, 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 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). The Committee was aware that decreasing the duration of treatment benefit with ceritinib to 2 years increased the ERG's ICER to £99,700 per QALY gained; however, it had agreed that it is unlikely that ceritinib would provide a benefit beyond the end of treatment, and it noted that this would increase the ICER further. The Committee acknowledged the uncertainty associated with the effectiveness of ceritinib compared with BSC, but nonetheless it concluded that all of the ICERs estimated by the company and the ERG fell substantially above the range normally considered cost effective; that is, £20,000 to £30,000 per QALY gained.

4.18 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with 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.

- 4.19 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 surrounding 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. It noted the company's assumption that about 120 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.
- 4.20 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 had concluded that this comparison was at high risk of bias because of confounding. It was also aware that 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 concluded that, while it was possible that ceritinib offers an average extension to life of at least 3 months, the data were too uncertain to consider that this criterion had been met objectively and robustly.

4.21 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. 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 QALYs.

4.22 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 for the consideration of the cost effectiveness of ceritinib.

4.23 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 was uncertain whether ceritinib met the criteria for end-of-life consideration. However, the Committee agreed that, even if the end-of-life criteria had been met, 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-positive non-small-cell lung cancer	Section
<b>Key conclusion</b>		
	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.	1.1
	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.	4.6
	The Committee noted that the company’s incremental cost-	4.23

<p>effectiveness ratios (ICERs) for ceritinib were above the range usually considered a cost-effective use of NHS resources and the Evidence Review Group's (ERG's) ICERs were even higher. Based on the available evidence, the Committee was uncertain whether ceritinib met the end-of-life criteria. However, even if the end-of-life criteria had been met, 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>		
<p><b>Current practice</b></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>	<p>4.2</p>
<p><b>The technology</b></p>		
<p>Proposed benefits of the technology</p>	<p>Ceritinib has the potential to extend life, improve quality of life and provide people with hope for the future.</p>	<p>4.1</p>
<p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</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>4.21</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, and who have a confirmed ALK mutation, may have crizotinib which is only available via the Cancer Drugs Fund (NICE <a href="#">Technology appraisal 293</a> does not recommend crizotinib). Ceritinib would be used after the disease progresses following crizotinib.</p>	<p>4.2</p>
<p>Adverse reactions</p>	<p>The Committee concluded that, although many people experienced adverse events with ceritinib, these events were manageable.</p>	<p>4.10</p>
<p><b>Evidence for clinical effectiveness</b></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. (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.</p>	<p>4.4</p>

<p>Relevance to general clinical practice in the NHS</p>	<p>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 type of NSCLC, rather than ALK-positive NSCLC.</p>	<p>4.7</p>
<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>Regarding overall survival, the data for ceritinib were immature and the data for best supportive care came from only 37 patients. 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>4.5, 4.6</p> <p>4.6</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 and 14.9 months in ASCEND-2. 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 and 7.0 months in ASCEND-2. The median progression-free survival with best supportive care was 1.8 months in Shepherd et al. (2005).</p>	<p>4.6</p>
<p><b>Evidence for cost effectiveness</b></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>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) fitted the data better whereas the Weibull curve (chosen by the company) gave results that better reflect clinical experience. It therefore considered both in its decision</p>	<p>4.12</p>

	<p>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>4.13</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 a benefit beyond stopping treatment with ceritinib.</p>	<p>4.14</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 in clinical practice the NHS would not pay for the full dose on average, 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>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>4.15</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>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>4.21</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No subgroups were considered.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<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.</p>	<p>3.30, 3.31</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The company's base case gave an incremental cost-effectiveness ratio (ICER) of £62,500 per quality-adjusted life year (QALY) gained. The ERG's preferred parameters gave an ICER of £79,500 per QALY gained, rising to £99,700 when the duration of treatment benefit with ceritinib was decreased to 2 years.</p>	<p>4.17</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>None</p>	
<p>End-of-life considerations</p>	<p>The Committee concluded that the life expectancy for people with ALK-positive NSCLC is short and the size of the population is small. It further concluded that, while it was possible that ceritinib offers an average extension to life of at least 3 months, the data were too uncertain to consider that this criterion had been met objectively and robustly.</p>	<p>4.19, 4.20</p>
<p>Equalities considerations and social value judgements</p>	<p>No equality issues were raised.</p>	

## 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).
- 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).
- Lung cancer: The diagnosis and treatment of lung cancer, NICE Clinical Guideline 121 (2011).

## 7 Proposed date for review of guidance

- 7.1 NICE proposes that the guidance on this technology is 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). NICE welcomes comment on this proposed date. 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  
September 2015

## **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

#### **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



**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 General Practitioner

**Mrs Anne Joshua**

NHS 111 Pharmacy Lead, Patients and Information, NHS England

**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

**Mr Christopher O'Regan**

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

**Dr Sanjeev Patel**

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

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**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**

Technical Adviser

#### **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 are 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 Novartis – clinical expert
- Mr Tom Haswell, nominated by Independent Cancer Patient's 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.

- Novartis