NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
Published: 22 June 2016

www.nice.org.uk/guidance/ta395

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Ceritinib is recommended, within its marketing authorisation, as an option for treating advanced anaplastic lymphoma kinase positive non-small-cell lung cancer in adults who have previously had crizotinib. The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

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 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 £4,923.45 for a 30-day supply. The summary of product characteristics states that treatment should be continued as long as clinical benefit is seen. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ceritinib at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG). Full details of all the evidence are in the committee papers.

Clinical effectiveness

3.1 The company presented efficacy data from 2 phase 1 or 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 were treated with ceritinib.

3.2 The phase 1 ASCEND-1 study (n=304) enrolled people with a range of treatment histories and explored several different doses of ceritinib. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less and a 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 2 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 3B or 4 NSCLC
- with World Health Organization performance status of 0 to 2
- with a 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	ASCEND-1	ASCEND-2	ASCEND-2
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; n, number; 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)
- had systemic chemotherapy (n=37)
- 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	Ceritinib	BSCOu et al. (2014; n=37)	Pooled results for BSC and systemic chemotherapy
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; n, number; 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 for median overall survival in the ASCEND studies (15.6 months) with the results for the BSC group in Ou et al. (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 a 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 suspected of being 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 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 in 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 the pooled results for overall survival from 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 based on 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 the 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 or 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 £4,100 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 did not adhere to treatment. 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 (now replaced by NICE's technology appraisal guidance on erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy) and on 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 £6,079.40 (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 (see 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	7,203	0.25	–	–	–
Base case: ceritinib	59,155	1.08	51,952	0.83	62,456
Scenario analysis: Treatment with ceritinib for 1.6 months after disease progression	Not reported	Not reported	Not reported	Not reported	76,039
Scenario analysis: Utility values from Chouaid et al. (2013)	Not reported	Not reported	Not reported	Not reported	69,896
Scenario analysis: 100% dose intensity for ceritinib	Not reported	Not reported	Not reported	Not reported	69,896

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 criteria), and it suggested that a log-normal curve should have been used instead (as the ERG did in its scenario analysis). The ERG conducted sensitivity analyses to test the impact of treatment benefits from ceritinib, in terms of overall survival and progression-free survival, stopping at 18 and 24 months from treatment initiation, by switching to the progression-free-survival and overall-survival curves of the BSC arm of the model.

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 did not justify its method in its submission and it 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 (see 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. The ERG scenario that assumed 2 years' duration of treatment benefit reduced the ICER from £79,528 to £76,066 per QALY gained (see table 4). This reduction was mainly driven by lower treatment costs.

Table 4 ERG's exploratory analyses

Scenario	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£)
Company's base case: BSC	7,203	0.25	–	–	–
Company's base case: ceritinib	59,155	1.08	51,952	0.83	62,456
ERG's base case: BSC	7,339	0.27	–	–	–
ERG's base case: 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	Not reported	Not reported	Not reported	76,066

Abbreviations: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life year.

Patient access scheme and updated economic model

3.32 The company submitted a revised economic model after agreeing a patient access scheme, consisting of a simple discount, with the Department of Health (the amount of discount and net price are commercial in confidence). The

company updated its economic model to address the concerns of the committee and the ERG. These updates included all changes done by the ERG outlined in section 3.30. In response to the ERG's comments about the duration of treatment benefits (see section 3.31), the company highlighted that for all scenarios in the model, this had been modelled by extrapolating the Kaplan–Meier curves over a time horizon of 10 years, and this did not imply that the benefits from ceritinib continue indefinitely after stopping treatment. To explore this further, the company provided 2 scenario analyses in which it assumed that the benefits and costs associated with ceritinib (as modelled in the curves for progression-free survival and overall survival) arbitrarily stop either 18 months or 2 years after starting treatment. The company assumed that from those points onwards, treatment benefits no longer follow the ceritinib curves for extrapolated progression-free survival and overall survival, but switch to the respective progression-free-survival and overall-survival curve of the BSC arm of the model. The company highlighted that these scenarios resulted in minimal changes to the ICERs.

3.33 Combining all of the ERG's changes to the parameters described in section 3.30 increased the ICER for ceritinib compared with BSC from £62,456 per QALY gained to £86,364 per QALY gained (not including the patient access scheme discount). But, incorporating the patient access scheme discount reduced the ICER to a level that the company stated was cost-effective compared with current treatment alternatives (the ICER cannot be presented here because the discount is commercial-in-confidence).

3.34 The company did a series of one-way sensitivity analyses, which showed that ceritinib drug costs have the largest impact on the results. The company did not vary estimates of the effectiveness of ceritinib compared with BSC. The company also submitted several scenario analyses and a cost-effectiveness acceptability curve, the details of which are commercial in confidence and cannot be presented here.

4 Committee discussion

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 effect 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, and fatigue, and that complications include chest infections 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 gives 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 through 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 [now replaced by NICE's technology appraisal guidance on crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer]). 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 best supportive care (BSC) is usually 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 people whose disease had progressed after crizotinib. 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 were 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 understood that the results of the ASCEND trials were combined without adjustment, but the ERG did not consider that this greatly

affected the clinical-effectiveness results.

- 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 median 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 results were based on a small sample of patients, and so 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, because these patients had higher Eastern Cooperative Oncology Group (ECOG) values at disease progression than patients in 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 showing statistical significance with a small study population. The committee acknowledged that if those in the Ou et al. study were sicker than those in the ASCEND studies, 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 median 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 people with ALK-positive NSCLC progresses faster or slower than in people 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 having third-line treatment. The committee learned from the company during the third committee meeting that none of the patients in the Shepherd et al. study had previously had treatment with crizotinib. In addition, 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 genetic mutations that differed from the ALK-positive mutation; the proportion of patients with ALK-positive mutation is unknown; and none of the patients had previously had crizotinib. 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 seen. 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 epidermal growth factor receptor [EGFR] inhibitors) and so it would be reasonable to expect ceritinib treatment to continue after progression. The committee was aware from Ou et al. (2014) 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. The committee acknowledged that the control group in the ASCEND-5 trial, having been given chemotherapy rather than BSC, was not consistent with the decision problem for this appraisal. But, the committee concluded that the ASCEND-5 trial may give useful data about the clinical effectiveness of ceritinib to inform the evidence

network.

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 (unadjusted) 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, in which it 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. 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. It noted that the company's revised model had explored 2 scenarios, which reduced the treatment benefit to 18 months or 24 months, and that this had little impact on the company's base-case incremental cost-effectiveness ratio (ICER; see section 3.32). The committee heard from the ERG that this was because most quality-adjusted life year (QALY) benefits and costs are accrued in the first few years of treatment. The committee was not given evidence that the treatment benefit from ceritinib would continue after the end of treatment, but concluded that the company had shown that this had minimal impact on cost effectiveness.

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 (see 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 noted that there was additional uncertainty with the utility value for the progression-free health state because it was derived using a UK-specific algorithm developed in a different disease area (multiple myeloma) and that the value used appeared higher than might be

expected for people with ALK-positive NSCLC. The committee 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 having BSC for the progression-free health state because these patients would not experience adverse events associated with ceritinib. The committee concluded that collecting EQ-5D data from people with ALK-positive NSCLC would be desirable and would address the uncertainties related to the modelled utility values.

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, which 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 agreed 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. 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. The committee noted that the company had taken this into account in its revised analysis (submitted with the patient access scheme discount; see section 3.32) by incorporating a dose intensity of 90%, which the committee accepted.

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. The committee acknowledged that the company had subsequently

included these costs in a revised analysis (see section 3.32 and section 4.18).

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 without the discount resulted in an ICER of £62,500 per 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 noted that the company submitted a patient access scheme and had also revised the model to address some of the committee's key concerns (see section 3.32). The committee recognised that the company had:

- extrapolated overall survival for BSC by using the log-normal normal distribution, as suggested by the ERG (see section 4.12)
- estimated treatment duration and costs by including an extra 1.6 months of time on treatment in line with the trial data (see section 4.8 and section 4.13)
- estimated duration of treatment benefit by assuming that the treatment benefit for ceritinib persists (for progression-free and overall survival) until a patient stops treatment; it presented 2 scenarios that reduced treatment benefits for ceritinib to 18 and 24 months from starting treatment showing minimal impact on the ICER (see section 3.32 and section 4.14)
- modelled utility by updating the model so that the same utility values were used for both ceritinib and BSC in all health states (see section 4.15)
- estimated dose intensity by including a value of 90% for ceritinib, as well as updating costs for giving ceritinib, blood tests and all grade 3 and 4 adverse events, which the company had previously excluded.

  The committee noted that by implementing these changes to the model, the company's base-case ICER without the patient access scheme discount increased from £62,500 to £86,400 per QALY gained. But, including the patient access scheme discount reduced the ICER substantially. The committee accepted the company's changes to the model, although it remained concerned about large uncertainty around some of the parameters in the model. The committee also heard from the ERG that the cost-effectiveness acceptability curve did not reflect this uncertainty and lacked

face validity. It noted that this could be improved with better data. Taking these factors into account, the committee concluded that, on balance, the most plausible ICER was likely to be lower than £50,000 per QALY gained when including the patient access scheme discount and the company's revisions to the model.

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 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 extend life by an additional 3 months, compared with BSC. It was aware that in its submission, the company 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, 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 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 show objectively and robustly 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 providing 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 noted 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, symptoms or quality of life did not

worsen in patients having ceritinib. 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, 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 this appraisal.

4.24 During its third meeting, the committee noted that the company's ICERs for ceritinib now included the patient access scheme discount. Based on the available evidence, the committee considered that although there was some uncertainty, it was satisfied that the end-of-life criteria had been met. The committee noted that when the patient access scheme discount was applied, the ICERs were likely to be within the range usually considered a cost-effective use of NHS resources for an end-of-life treatment. The committee considered that there was a high degree of uncertainty associated with the size of effectiveness of ceritinib compared with BSC because the company based the estimates on a naive indirect comparison with a high risk of bias from confounding (see section 4.6). The committee considered these uncertainties with respect to the small size of the population noting section 6.2.14 of NICE's guide to the methods of technology appraisal, which states that in general, the committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of adopting the technology on NHS resources increases. The committee agreed that although more robust evidence on the clinical and cost effectiveness of ceritinib would be desirable, the impact on NHS resources was not expected to be large. Therefore, because of the large unmet need in the small number of patients, who have a very poor prognosis and for whom no active therapy is available, the committee recommended ceritinib for advanced ALK-positive NSCLC previously treated with crizotinib. The committee also asked that the review date of this guidance be brought forward to address emerging evidence (see section 4.9) and

the conditional nature of the marketing authorisation received from the European Medicines Agency.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced anaplastic lymphoma kinase positive non-small-cell lung cancer previously treated with crizotinib and the healthcare professional responsible for their care thinks that ceritinib is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

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.

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.

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ISBN: 978-1-4731-1948-2