NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Ceritinib for untreated ALK-positive non-small-cell lung cancer

1 Recommendations

1.1 Ceritinib is recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer in adults, only if the company provides it with the discount agreed in the patient access scheme.

Why the committee made these recommendations

Most people with untreated ALK-positive advanced non-small-cell lung cancer are offered crizotinib. Chemotherapy may be offered if the person's ALK mutation status isn't known, and therefore is not a relevant comparator for ceritinib. There are no trials directly comparing ceritinib with crizotinib; the clinical trial compares ceritinib with chemotherapy.

Because the clinical trial has not finished, it is unable to show how much ceritinib prolongs life compared with chemotherapy. But it shows that ceritinib is more effective than chemotherapy at increasing the length of time people live without their disease progressing. An indirect comparison suggests that ceritinib is more effective than crizotinib. Clinical experts support using ceritinib instead of crizotinib.

The most plausible cost-effectiveness estimate for ceritinib compared with crizotinib is around what NICE normally considers acceptable. Therefore ceritinib can be recommended as an option for adults with untreated ALK-positive advanced non-small-cell lung cancer.

2 Information about ceritinib

Marketing authorisation indication	Ceritinib (Zykadia, Novartis) as monotherapy is indicated for 'the first-line treatment of adult patients with anaplastic lymphoma kinase-positive advanced non-small cell lung cancer'.
Dosage in the marketing authorisation	Ceritinib is taken orally, without food, at the same time each day. The recommended dose is 750 mg once daily. The summary of product characteristics recommends that treatment should continue as long as clinical benefit is observed.
Price	A 30-day supply of ceritinib (150 capsules) costs £4,923.45 (excluding VAT; British national formulary [BNF] online [accessed October 2017]). 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, with the discount applied 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 does not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Treatment pathway and relevant comparators

Crizotinib is the only relevant comparator

3.1 The committee understood that the standard of care in England for people with confirmed anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer is crizotinib (a first-generation ALK inhibitor). This is followed, after the disease has progressed, by ceritinib (a second-generation ALK inhibitor). Crizotinib was the only comparator in the company's cost-effectiveness analysis. The company did not compare ceritinib with chemotherapy, stating in its submission that, in current NHS practice, most people with untreated ALK-positive advanced non-small-cell lung

cancer take crizotinib. In written statements clinical experts explained that chemotherapy is offered as the first treatment option only if ALK status has not yet been confirmed. Therefore the committee understood that people with untreated disease having chemotherapy in practice would not be eligible for ceritinib. The committee concluded that crizotinib is the only relevant comparator for ceritinib in people with untreated ALK-positive advanced non-small-cell lung cancer.

Treatment with an ALK inhibitor may continue beyond disease progression

3.2 The summary of product characteristics for ceritinib, and the protocol for the phase 3 clinical trial of ceritinib (ASCEND-4), states that treatment should continue as long as clinical benefit is observed. More than three-quarters of patients in ASCEND-4 had at least 1 dose of ceritinib after disease progression. The clinical experts said that this reflects clinical practice. They explained when it might be appropriate to continue treatment with ALK inhibitors after disease progression, for example if there is evidence of disease progression at only 1 tumour location but otherwise the disease is well-controlled. The clinical experts also explained that they would wait until the disease has progressed at multiple sites before changing treatment, because there are limited alternative options. They said that people taking ceritinib are more likely to continue treatment beyond disease progression than people taking crizotinib. This is because the only option after ceritinib is chemotherapy; there is no clinical evidence to support giving crizotinib after ceritinib, whereas people on crizotinib can switch to ceritinib. The clinical experts suggested that in the future, as more treatment options become available, people might switch to an alternative therapy more quickly. The committee concluded that in current practice treatment with ceritinib, and to a lesser extent crizotinib, continues beyond disease progression.

Clinical effectiveness compared with chemotherapy

Ceritinib improves progression-free survival

3.3 The committee noted that ceritinib improves progression-free survival compared with chemotherapy, and that the difference between treatment arms in ASCEND-4 was statistically significant. The median progression-free survival was 16.6 months with ceritinib and 8.1 months with chemotherapy in ASCEND-4, producing a hazard ratio of 0.55 (95% confidence interval 0.42 to 0.73, p<0.0001). The committee concluded that ceritinib is associated with a significant benefit in progression-free survival compared with chemotherapy.

Survival data from the clinical trial of ceritinib are immature

3.4 The committee was aware that the overall survival data from the trial are immature and that median overall survival was not reached in the ceritinib arm. It also acknowledged the ERG's concerns that the survival results may be biased because:

- Patients were allowed to continue ceritinib after disease progression if clinical benefit was seen.
- Patients whose disease progressed while taking ceritinib could switch to other active treatments (crizotinib, docetaxel or platinum-based chemotherapy).
- Patients randomised to chemotherapy could switch to ceritinib when their disease progressed.

The committee noted that the second-line treatments taken by patients in the trial were different to the treatments available in England, recalling that ceritinib would not be followed by crizotinib (see section 3.2). The committee was therefore concerned that the trial survival results might not be generalisable to current clinical practice. It acknowledged that the trial results appeared promising, noting that the difference between ceritinib and chemotherapy for overall survival was approaching statistical

significance. But it agreed that it was difficult to establish the magnitude of survival benefit for ceritinib because the trial data are immature. The committee concluded that it should account for this uncertainty in its decision-making.

Indirect comparison of ceritinib and crizotinib

Ceritinib appears to be more effective than crizotinib at extending progression-free survival

3.5 Because there were no head-to-head trial data for ceritinib and crizotinib, the company did 2 matching-adjusted indirect comparisons (MAIC) using the results from ASCEND-4. The first MAIC used results from the PROFILE-1014 trial, which compared crizotinib with chemotherapy, and the second MAIC used results from the ALEX trial, which compared crizotinib with alectinib. Both MAICs showed that ceritinib extended progression-free survival compared with crizotinib, and that the difference between treatments was statistically significant, which reflected the clinical experts' expectations. The committee understood that the results of both MAICs were subject to a high risk of bias because there was no common comparator arm in the trials being compared; the committee was aware that the MAIC method is inappropriate without a common comparator. The ERG explained that it could not be certain whether the results from each MAIC are any more reliable than the results of a naive comparison of the unadjusted trial data. The committee was aware of the issues with the MAIC, but concluded that an indirect comparison of individual trial arms was the only way to compare ceritinib and crizotinib.

Clinical evidence in the economic model

Both crizotinib clinical trials are relevant to decision-making

3.6 The company's base-case cost-effectiveness model estimated the relative efficacy of ceritinib compared with crizotinib using hazard ratios from its indirect comparison of ASCEND-4 with PROFILE-1014; hazard ratios

informed by ALEX were included in a scenario analysis. The ERG explained that it had no preference for the results of 1 indirect comparison over the other (that is, whether to consider the results based on PROFILE-1014 or ALEX). The committee was aware that the company had used inappropriate methods in the indirect comparison with PROFILE-1014, because it had matched the whole ASCEND-4 population to the whole PROFILE-1014 population instead of matching only the patients in the ceritinib treatment arms. But the committee considered that results from PROFILE-1014 might be more relevant to clinical practice because patients continued crizotinib treatment beyond disease progression, which was not permitted in ALEX. The committee noted that both indirect comparisons resulted in a similar hazard ratio for progression-free survival and for overall survival. The ERG explained that the company's cost-effectiveness results were very sensitive to small changes in these hazard ratios. The committee concluded that it should consider cost-effectiveness results based on PROFILE-1014 and results from ALEX in its decision-making.

Extrapolating clinical trial data in the economic model

The company's extrapolation of overall survival is appropriate

3.7 The company extrapolated overall survival in its model using the exponential function. The ERG considered that the estimates of long-term survival produced with the exponential curve (which cannot be reported because the company marked them as academic in confidence) were optimistic compared with clinical experience of ALK inhibitors and real-world data on the survival of people who have had crizotinib. The ERG suggested in its report that the Gompertz curve might be more appropriate to model overall survival. This was because it predicted a 5-year survival rate that reflected estimates from its clinical advisers (20%), and estimates from a real-world study of first-line treatment with crizotinib (which cannot be reported because the study authors provided them in confidence). However, the company explained that recently published

data from PROFILE-1014 suggested that 56.6% of patients who had crizotinib would be alive at 4 years and 44% would be alive at 5 years, which supports using the exponential function to extrapolate survival in the model. The clinical experts noted that the survival rates in PROFILE-1014 were higher than in real-world studies. They suggested that this could be because a substantial proportion of people in PROFILE-1014 had subsequent lines of therapy, noting that survival rates have improved considerably in recent years. The clinical experts agreed that the population in PROFILE-1014 was generalisable to clinical practice and, on balance, considered that the survival estimates from PROFILE-1014 could be realistic. The ERG highlighted that all parametric models predicted lower survival rates than the recent PROFILE-1014 data. The committee concluded that, although there is some uncertainty about the long-term prognosis of this population, the exponential function is likely to be the most appropriate way to model overall survival.

Time on treatment should be estimated using patient level data

3.8 In its base-case model, the company estimated the duration of treatment with ceritinib and crizotinib by extrapolating the median duration of treatment from the clinical trial of each drug. The ERG explained that this differed from the company's approach to modelling progression-free survival and therefore assumes no relationship between the 2 outcomes, which is inappropriate. The committee was aware that the company's approach produced unrealistic estimates of treatment duration. The committee concluded that time on treatment should be modelled in the same way as progression-free survival, that is, using patient level data and assuming proportional hazards (that is, a constant relative treatment effect).

Health-related quality of life

The company overestimated quality of life for people with progressed disease

3.9 The company estimated the quality of life associated with progressed disease using published utility values from a real-world study of patients having treatment for advanced non-small-cell lung cancer (Chouaid et al. 2013). The company calculated a weighted average of the utilities reported for people in different health states. The ERG considered that the resulting utility value of 0.641 for progressed disease was too high because the company had included irrelevant patient groups in its weighted average calculation (for example, people having second-line treatment who were progression-free). The committee concluded that the ERG's recalculated utility estimate of 0.56 for progressed disease was more appropriate than the company's estimate.

Quality-of-life estimates should distinguish between people who continue first-line treatment after progression and people who switch treatment

3.10 The committee was aware that, for quality of life, the ERG's alternative base-case cost-effectiveness analysis distinguished between people having first-line treatment after disease progression and people switching treatment after disease progression. To do this, the ERG created an additional health state ('sustained utility on progression'). The utility value in this health state was 0.68, which the ERG calculated by using the midpoint of the progression-free utility (estimated by the company as 0.81) and the ERG's updated utility of 0.56 for the progressed disease health state (see section 3.9). The committee agreed that it was appropriate to assume a better quality-of-life benefit for people continuing treatment after disease progression than those with progressed disease who switched treatment, but noted that the ERG's estimate was not evidence-based. The clinical experts considered that this additional health state was less relevant for people in the crizotinib arm than in the ceritinib arm, because people on crizotinib are more likely to switch treatment after disease progression (see section 3.2). The committee acknowledged this, and the

uncertainty around the utility value for this health state, but considered that the change to utility values in the ERG's alternative base case was appropriate for decision-making.

Costs

It is appropriate to exclude the cost of testing for the ALK mutation

3.11 The company did not include the cost of ALK mutation testing in its analyses because it is part of routine clinical practice at diagnosis. Written statements from experts supported the company's rationale for excluding the cost of the test. The committee concluded that it was appropriate to exclude the cost of the test.

Costs of treatments taken after disease progression should be based on the clinical trial

3.12 The company's base-case cost-effectiveness analysis assumed that 60% of people had second-line systemic treatment, based on feedback from its clinical advisers. This was higher than reported in clinical trials, in which 35% of patients who had first-line ceritinib (in ASCEND-4) and 43% of patients who had first-line crizotinib (in PROFILE-1014) had active second-line treatment after disease progression. The company's justification was that the trials have limited post-progression follow-up time and therefore more patients would have started second-line treatment after the data cut-off for the trials. The clinical experts explained that, in practice, most people would have second-line treatment after stopping ceritinib or crizotinib. One clinical expert suggested that 70–80% of people who have had crizotinib will subsequently have ceritinib. The committee noted that the model did not include third or fourth-line treatments, which it understood would be offered in practice. However, the ERG suggested that it was more appropriate to use data from the clinical trials to estimate the costs of post-progression treatment, to be consistent with the efficacy data in the model. Because there were no scenarios modelling costs and

outcomes relating to treatment sequence, the committee concluded that post-progression treatment costs should be based on the trial data.

Innovation

The benefits of ceritinib are adequately captured in the model

3.13 The clinical experts considered that second-generation ALK inhibitors are an innovative class of drugs. They have a broader spectrum of activity than first-generation ALK inhibitors and may replace crizotinib as the standard of care internationally. Ceritinib is more potent than crizotinib and has a greater binding affinity to its target (the ALK protein). The company stated in its submission that these features allow a reduced dosing frequency and translate into clinically meaningful improvements in progression-free survival compared with crizotinib. 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 quality-adjusted life years (QALYs) and the resulting cost-effectiveness estimates.

Cost-effectiveness estimate

Ceritinib is recommended as a cost-effective treatment

3.14 The committee agreed with all of the changes in the ERG's alternative base-case cost-effectiveness analysis, except the use of the Gompertz model to extrapolate overall survival (see section 3.7). It agreed that the most plausible incremental cost-effectiveness ratio (ICER) was somewhere between the result of the ERG's analysis using PROFILE-1014 to estimate crizotinib's relative efficacy and the scenario based on ALEX (with the exponential model for overall survival). The committee noted that using ALEX increased the ICER for ceritinib compared with crizotinib. When the confidential patient access schemes for both technologies were applied, the ICER for ceritinib was between £20,000 and £30,000 per QALY gained compared with crizotinib, regardless of

whether the PROFILE-1014 or ALEX data were used. NICE cannot report the exact ICERs because the patient access schemes are confidential. The committee concluded that ceritinib is a cost-effective use of NHS resources in people with untreated ALK-positive non-small-cell lung cancer, if it is provided with the discount agreed in the patient access scheme.

Other factors

3.15 No equality or social value judgement issues were identified.

3.16 NICE's advice about life-extending treatments for people with a short life expectancy did not apply.

4 Implementation

4.1 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.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal 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 appraisal determination.

4.3 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 ALK-positive non-small-cell lung cancer and the doctor responsible for their care thinks that ceritinib is the right

treatment, it should be available for use, in line with NICE's recommendations.

4.4 The Department of Health and Novartis have agreed that ceritinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
November 2017

6 Appraisal committee members and NICE project team

Appraisal committee members

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

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.

Sophie Cooper
Technical Lead

Christian Griffiths
Technical Adviser

Kate Moore
Project Manager

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