

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Alectinib for untreated ALK-positive advanced
non-small-cell lung cancer**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using alectinib 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, 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 recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see 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 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.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using alectinib in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 26 April 2018

Second appraisal committee meeting: 15 May 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Alectinib is not recommended, within its marketing authorisation, for untreated ALK-positive advanced non-small-cell lung cancer (NSCLC) in adults.
- 1.2 This recommendation is not intended to affect treatment with alectinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with untreated anaplastic lymphoma kinase (ALK)-positive advanced NSCLC are usually offered crizotinib.

The main evidence for alectinib comes from an ongoing clinical trial. This suggests that alectinib is more effective than crizotinib in delaying disease progression, including in the central nervous system. But it is not yet certain whether alectinib prolongs life compared with crizotinib.

Alectinib does not meet NICE's criteria to be considered a life-extending end-of-life treatment. There is concern about some of the assumptions used in the cost-effectiveness modelling, including how much of the medicines is wasted, the types of treatments that people receive after disease progression, and the types of care used to manage disease progression in the central nervous system.

Using the most plausible assumptions, the cost-effectiveness estimates for alectinib compared with crizotinib were above the range that the committee considered to be cost-effective. Therefore alectinib is not recommended for untreated advanced ALK-positive NSCLC.

2 Information about alectinib

Marketing authorisation indication	<p>Alectinib (Alecensa, Roche) as monotherapy is indicated 'for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)'.</p> <p>Alectinib has been available in the UK through the early access to medicines scheme.</p>
Dosage in the marketing authorisation	<p>The recommended dose of alectinib is 600 mg (4×150 mg capsules) taken twice daily with food (total daily dose of 1,200 mg).</p> <p>A validated ALK assay is necessary to identify ALK-positive NSCLC status, which should be established before alectinib therapy starts.</p> <p>Treatment with alectinib should be continued until disease progression or unacceptable toxicity. Management of adverse events may need dose reduction, temporary interruption, or discontinuation of alectinib. The dose of alectinib should be reduced in steps of 150 mg twice daily based on tolerability. Alectinib should be permanently discontinued if patients cannot tolerate the 300 mg twice daily dose.</p>
Price	<p>£5,032.00 per pack of 224×150 mg capsules (British national formulary [BNF] online [accessed February 2018]). Based on the economic model, if the mean treatment duration is 30.8 months, the average cost of a course of treatment is approximately £84,000.</p> <p>The company has agreed a patient access scheme with the Department of Health. If alectinib had been recommended, this scheme would provide a simple discount to the list price of alectinib 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 would not constitute an excessive administrative burden on the NHS.</p>

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Clinical need

A new treatment option would benefit people with untreated ALK-positive advanced non-small-cell lung cancer

3.1 People with ALK-positive non-small-cell lung cancer (NSCLC) tend to be younger and are less likely to have a history of smoking than the wider NSCLC population. As a result, people with ALK-positive disease may be less likely to be included in lung cancer screening programmes. The committee understood that approximately 40% to 50% of all people with NSCLC develop central nervous system (CNS) metastases, which are associated with reduced quality of life and survival prospects. The patient experts submitted comments highlighting that NSCLC has no cure, which can cause physical and psychological distress for people with the disease. The clinical experts welcomed the development of second-generation ALK inhibitors. They said that alectinib appears to demonstrate a benefit in delaying disease progression in the CNS. The committee agreed that additional treatment options for delaying disease progression, particularly CNS disease progression, would benefit people with untreated ALK-positive advanced NSCLC.

Clinical management

Crizotinib is the appropriate comparator for this appraisal

3.2 The clinical experts advised that they routinely offer crizotinib for untreated ALK-positive advanced NSCLC in line with NICE's technology appraisal guidance on [crizotinib](#). The committee was aware that NICE also recommends [ceritinib](#) for this indication. However, it understood that the ceritinib guidance was published in January 2018, and it was not routinely commissioned as a first-line treatment when the NICE scope and company submission for alectinib was written. The committee therefore concluded that first-line treatment with crizotinib was the appropriate comparator for this appraisal.

In clinical practice, treatment with an ALK inhibitor may continue beyond disease progression

3.3 The alectinib summary of product characteristics states that treatment should continue until disease progression or unacceptable toxicity. But the crizotinib and ceritinib summaries of product characteristics do not specify that treatment should stop at disease progression. The clinical experts explained that in clinical practice, people may have an ALK inhibitor beyond disease progression when treatment options are limited to chemotherapy. For example, they explained that if people taking crizotinib (a first-generation ALK inhibitor) as a first-line treatment have disease progression they may switch to ceritinib (a second-generation ALK inhibitor) as soon as possible rather than continuing crizotinib beyond disease progression, which is in line with NICE guidance. In the case of first-line ceritinib, treatment is more likely to continue treatment beyond disease progression because the only available treatment options are chemotherapy for people who are well enough, or best supportive care – in line with [NICE guidance](#). 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. Similarly, the clinical experts said they would prefer to continue alectinib after disease progression (even though this is outside its marketing authorisation and was not how the drug was used for most people in the ALEX trial), because the only treatment options available after alectinib are chemotherapy and best supportive care. They said that another ALK inhibitor would not be given after alectinib in UK clinical practice because there is no clinical evidence to support giving crizotinib after alectinib; the company submission also noted clinical expert concern about use of crizotinib after alectinib given the differences between these first- and second-generation ALK inhibitors. The committee recognised that in clinical practice treatment with alectinib may continue beyond disease progression, but agreed that the appraisal would focus on how the treatment is given according to alectinib's marketing authorisation.

Clinical evidence

The main evidence is from ALEX, an open-label randomised controlled trial

3.4 The main clinical evidence came from an open-label phase 3 randomised controlled trial (ALEX). ALEX compared the efficacy and safety of alectinib (n=152) with crizotinib (n=151) in adults with untreated ALK-positive advanced NSCLC. The primary outcome was investigator assessed progression-free survival, defined as the time from day of randomisation until first documented progression event (determined using Response Evaluation Criteria In Solid Tumors [RECIST] v1.1 criteria) or death from any cause, whichever occurred first. As a secondary outcome, 2 separate independent review committees assessed progression-free survival using RECIST and CNS RECIST criteria. Other secondary outcomes included overall survival, response rates and safety outcomes. Patients had treatment across 98 study sites in 29 countries, including the UK (n=3 patients). On disease progression, people could have subsequent treatment with a different drug (see section 3.12). The committee concluded that ALEX was a well conducted trial which provided high quality evidence that was relevant to the appraisal.

Evidence about CNS progression is relevant to this appraisal

3.5 The company highlighted that alectinib has a potential benefit in delaying or preventing disease progression in the CNS. Because of this, it presented evidence for progression-free survival (that is, survival without any recorded disease progression) and CNS progression-free survival (that is, survival without any disease progression in the CNS). The committee was aware that CNS progression-free survival was not a pre-defined end point in ALEX. However, the clinical experts explained that developing CNS metastases can have a substantial effect on people's prognosis. The committee agreed that it was relevant to consider CNS progression-free survival.

Assessing progression events by independent review committee is appropriate

3.6 The ERG advised that, for consistency, CNS progression-free survival analyses and progression-free survival analyses should use the same measurement criteria. The committee agreed with this approach. In ALEX, progression events were measured by investigators and by 2 independent review committees assessments. The committee understood that the primary outcome of ALEX was investigator assessed progression-free survival, and that independently assessed progression events was a secondary outcome. However, because ALEX was an open-label trial, the committee considered that investigator assessments had a greater risk of bias. It agreed that analyses based on independent assessment of progression events were the most appropriate to use in its decision-making.

Assessing progression events using RECIST criteria is preferable to using a combination of RECIST and CNS RECIST criteria

3.7 In ALEX, 2 separate independent review committees assessed progression events. One independent review committee assessed systemic progression using the RECIST criteria. The other independent review committee assessed intracranial CNS progression events using adapted CNS RECIST criteria. The company's progression analyses were based on events captured using CNS RECIST criteria and RECIST criteria. The ERG was concerned that the CNS RECIST criteria are not routinely used in UK clinical practice, and may be more sensitive than RECIST (meaning that events would be detected earlier than they would in clinical practice). Because of this, the ERG preferred analyses of progression events to use data measured only by the RECIST criteria. The clinical experts confirmed that CNS RECIST is not routinely used in UK clinical practice. The committee concluded that assessing events using only RECIST criteria was more appropriate than assessments based on CNS RECIST and RECIST criteria.

In ALEX, treatment with an ALK inhibitor sometimes continued beyond asymptomatic disease progression, but this reflects clinical practice

3.8 The summary of product characteristics for alectinib states that treatment should continue until disease progression or unacceptable toxicity (see section 3.3). In ALEX, disease progression events could be symptomatic or asymptomatic. However, asymptomatic events were only detected through investigator assessment and not by the independent review committees. Patients with isolated, asymptomatic CNS disease progression could continue on the study treatment (alectinib or crizotinib) if the investigator believed that the patient would benefit. This means that some patients continued with alectinib (n=5) and crizotinib (n=30) after disease progression, contrary to alectinib's marketing authorisation. However, the clinical experts explained that in clinical practice, assessment of progression is typically guided by symptoms in addition to radiographic evidence. Therefore, people with asymptomatic CNS disease progression would not typically be identified in UK clinical practice and therefore would continue on their current treatment until symptoms developed. The committee concluded that although the trial allowed use of an ALK inhibitor after asymptomatic disease progression, this reflected UK clinical practice.

Clinical effectiveness**Alectinib improves progression-free survival compared with crizotinib**

3.9 In ALEX, alectinib statistically significantly improved progression-free survival compared with crizotinib. Median progression-free survival (assessed by investigator) was 11.1 months with crizotinib and was not met for alectinib, producing a hazard ratio (HR) of 0.47 (95% confidence interval [CI] 0.34 to 0.65). There was also a statistically significant difference in median progression-free survival assessed by an independent review committee using RECIST criteria (HR 0.50, 95% CI 0.36 to 0.70); median PFS was 25.7 months for alectinib (95% CI: 19.9, not estimable) compared with 10.4 months for crizotinib (95% CI: 7.7,

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14.6). The committee concluded that alectinib is associated with a substantial benefit in progression-free survival compared with crizotinib.

Alectinib improves CNS progression-free survival compared with crizotinib

3.10 The company presented Kaplan–Meier curves for CNS progression events identified by 2 separate independent review committees (1 committee assessed using CNS RECIST and RECIST criteria, the other used RECIST criteria only). The committee noted that the Kaplan–Meier curves diverged substantially in both analyses. Because of this, the committee concluded that alectinib appears to have a benefit in CNS progression-free survival compared with crizotinib.

ALEX does not provide robust information about whether alectinib prolongs survival compared with crizotinib

3.11 ALEX was not powered to detect a significant difference in overall survival between alectinib and crizotinib. The committee was also aware that the overall survival data from the trial are immature and that median overall survival was not reached in either treatment arm. At the time of the analysis (February 2017 data cut) there was no statistically significant difference in overall survival between alectinib and crizotinib (HR 0.76, 95% CI 0.48 to 1.20), despite the significant difference in progression-free survival. The clinical experts commented that, although the survival data were very immature, they would expect to see an increase in survival over time given the potential benefit of alectinib on CNS progression. The committee concluded that, at this time, there is insufficient evidence to confirm a survival benefit of alectinib compared with crizotinib.

There is substantial uncertainty about the effect of subsequent treatments on overall survival estimates in ALEX

3.12 In ALEX, after patients stopped their study drug they could have subsequent treatment with a different drug. The committee recalled that treatment after progression would be different for those on alectinib or crizotinib in clinical practice in England (see section 3.3). It noted that

subsequent therapy data were only collected for 41% of patients who had progressed and stopped their study drug (see section 3.21). Because subsequent therapies could affect survival outcomes, the ERG were concerned that the missing data could confound overall survival and would need to be taken into account when deriving overall survival estimates. The committee agreed that the extent of the missing data, as well as the uncertainties about the choice and duration of subsequent treatments, could have a large effect on overall survival. The committee agreed that there was substantial uncertainty about the subsequent treatments people had in the trial and their effect on overall survival estimates in ALEX, which would need to be considered in its decision-making.

Cost-effectiveness model structure

Different modelled states for non-CNS and CNS progressed disease are appropriate

3.13 To estimate cost effectiveness, the company used a partitioned survival model with 4 health states:

- progression-free (people with no progression events)
- non-CNS progressed disease (people with progression events outside the CNS)
- CNS progressed disease (people with progression events in the CNS, either with or without progression events elsewhere)
- death.

The company modelled states for non-CNS and CNS progressed disease separately to capture alectinib's benefit in the CNS. The committee recognised that CNS progression was a relevant health outcome for the appraisal (see section 3.5) and accepted this model structure.

It is acceptable for the CNS progressed disease state to include people with or without progression events outside the CNS

3.14 In the CNS progression analysis, the company did not censor patients who had progression events outside the CNS. This meant that the CNS-progressed disease state included people whose first progression event was in the CNS ('primary') and patients who had progression outside the CNS before a CNS progression event ('secondary'). The ERG explained that, although the model did not distinguish between these patient groups, the costs and consequences of a CNS progression event always exceed those of a non-CNS event. Because of this, the ERG were satisfied that the costs and consequences of both primary and secondary CNS progression events were appropriately captured. The committee agreed with the ERG and accepted the company's modelling of the CNS progressed disease state.

Extrapolating clinical trial data in the economic model

It is appropriate to model treatment effects independently and to use the standard RECIST criteria

3.15 The company used extrapolations to model CNS progression-free survival, progression-free survival and overall survival. It assumed non-proportional hazards between the treatments (that is, the effect of alectinib relative to crizotinib changes over time). The company based this assumption on log-cumulative hazard plots for CNS-progression-free survival and progression-free survival from ALEX. The committee agreed that it was appropriate to model the treatment effects independently.

3.16 The company's preferred analyses incorporated events from two independent review committee procedures in ALEX – the main RECIST procedure and a separate procedure based on the modified CNS RECIST – into PFS and CNS PFS (see section 3.10). The ERG preferred the analyses based on standard RECIST only (which were provided as a scenario analysis by the company) because they are likely to be the most

clinically relevant, and more comparable to other trials and NICE technology assessments. The committee accepted that the ERG's approach of basing the analyses on standard RECIST only was more clinically relevant.

The company's estimation of progression-free survival using Kaplan–Meier data from ALEX (measured by independent review committee) and an exponential tail is acceptable

3.17 The company's base-case analysis of progression-free survival for alectinib and crizotinib used Kaplan–Meier data (as measured by independent review committee) from ALEX for the first 18 months, extrapolated with an exponential tail after 18 months. The company chose an exponential tail based on fit, and because it gave conservative estimates compared with the other distributions tested (it was the most conservative for alectinib, second-most for crizotinib). The ERG agreed that the exponential tail for alectinib and crizotinib was conservative, but highlighted that using exponential extrapolations for 2 treatments implicitly assumes proportional hazards between them. The company's analysis had shown that the proportional hazards assumption does not hold for alectinib and crizotinib (see section 3.15). However, the ERG were satisfied that using Kaplan–Meier data for the first 18 months mitigates the problem (although the hazards do become proportional over time). The ERG did consider the 18-month Kaplan–Meier cut-off to be arbitrary, but felt that this would be the case at any cut-off point used to extrapolate the Kaplan–Meier data. The committee agreed with the ERG's comments and considered the company's modelling of progression-free survival to be acceptable.

Extrapolating CNS progression-free survival using a gamma distribution is acceptable, but log normal or log-logistic distributions are preferable

3.18 Although it did not provide the best statistical fit, the company extrapolated CNS progression-free survival using a gamma distribution. It chose the gamma distribution because it was considered to reflect the

plateau in long-term cumulative CNS metastasis incidence reported in the literature. The ERG highlighted that the gamma distribution was one of the worst fitting curves (based on statistical fit), and considered the log normal or log-logistic distributions to be more plausible because they provided a better statistical fit. However, the committee noted that changing to these distributions had a negligible effect on the cost-effectiveness results. It therefore accepted the company's modelling of CNS progression-free survival, but agreed that a log normal or log-logistic extrapolation may have been more appropriate.

The ERG's approach to extrapolating overall survival is the most reasonable

3.19 The company assessed different extrapolations for overall survival for each treatment arm according to statistical and visual fit. It also compared survival estimates for crizotinib with overall survival data from the PROFILE 1014 trial, which compared crizotinib with chemotherapy in the same population. The company used an exponential extrapolation of overall survival for alectinib and crizotinib for their base case, because this was the second best fit to the PROFILE 1014 data and judged by the company to be clinically plausible based on their discussions with clinical experts. In the same way as the progression-free survival analysis (see section 3.16), the ERG highlighted that using exponential extrapolations for both treatments assumes proportional hazards. To address this, and for consistency with the company's modelling of progression-free survival, the ERG preferred to use Kaplan–Meier data for the first 18 months, and then switch to an exponential tail. The committee agreed with the ERG's comments and concluded that the ERG's approach for modelling overall survival was the most reasonable.

Health-related quality of life

The utility value for progressed disease in the CNS is acceptable but the utility value for non-CNS progressed disease may be too high

3.20 The company derived utility values for the progression-free and non-CNS progressed health states using a mixed-effects model based on EQ-5D data from ALEX. The utility values used in the economic model were 0.814 for the progression-free health state and 0.725 for the non-CNS progressed disease health state. The company assumed that the utility for the CNS progressed-disease state was 0.52, which they took from a study abstract by Roughley et al. (2014). The ERG noted that the utilities reported by Roughley et al. were consistently lower than the utilities derived from ALEX (0.65 compared with 0.725). Therefore the ERG preferred to take this into account by applying a percentage decrement ($0.52/0.65$) to the progressed disease utility in ALEX (0.725) which gave an estimated utility of 0.58 for the CNS progressed-disease state. This increased the ICER compared with the company's base case (exact amount cannot be reported because of the confidential patient access schemes in place). The clinical experts stated that the company's utility of 0.52 for the CNS progressed-disease state was reasonable, but the utility for the non-CNS progressed disease state may be an overestimate. The committee recalled that the utility estimates accepted for the recent appraisal of [ceritinib](#) were lower than the values derived from ALEX. The clinical experts highlighted that the utility estimates in ALEX may be affected by the inclusion of people with asymptomatic CNS progressed disease, and by those who were too ill to complete quality-of-life questionnaires. Because of this, the committee accepted the company's chosen health state utility values, but considered that the value for non-CNS progressed disease may be too high.

Resource use and costs

It is reasonable to assume no wastage for alectinib and crizotinib

3.21 The company assumed that a full pack of alectinib or crizotinib would be provided at a lung cancer clinic every 28 days. The company's model incorporated wastage of treatment when a patient died or stopped treatment. The ERG highlighted that a full pack of crizotinib contains 30 days' treatment, whereas a full pack of alectinib contains 28 days' treatment. It considered that the company's model led to 2 days of additional wastage of crizotinib per cycle. The ERG amended the model assumption so that a pack of crizotinib was provided every 30 days. The clinical experts advised that in practice there would be no wastage while a person is on treatment. The committee concluded it was reasonable to assume no wastage for both alectinib and crizotinib as this best reflected clinical practice.

The distribution of subsequent treatments in the company's model does not reflect clinical practice

3.22 Data on the treatments taken after disease progression in ALEX was only captured for 41% of patients. Because of this, the company modelled a 'basket' of subsequent treatments. This was informed by the data available on second- and third-line treatments from patients in ALEX, and reweighted to account for missing data. The company's model assumed that 100% of patients who had disease progression would have subsequent treatment. In the model, 29% of people on alectinib and 72% on crizotinib had a tyrosine kinase inhibitor after progression, and 71% of people on alectinib and 28% on crizotinib had subsequent treatment with a non-tyrosine kinase inhibitor. The clinical experts advised that in routine practice they would expect around 70% to 80% of people on crizotinib to have treatment with ceritinib after progression. They highlighted that ceritinib (as a second-line treatment) may continue after any further disease progression. If people were to stop having ceritinib (as a second-line treatment), the experts estimated that 40% to 50% would have

chemotherapy and 50% to 60% would have best supportive care. The clinical experts also explained that people having alectinib would not have subsequent treatment with a tyrosine kinase inhibitor. They estimated that 50% of people who progressed while taking alectinib would have subsequent chemotherapy, and that the remaining 50% would have best supportive care. Based on the clinical experts' opinion, the committee considered that the distribution of subsequent treatments in the company's model did not reflect UK clinical practice. The committee preferred to assume a distribution that more closely reflects UK clinical practice.

It is appropriate to assume that oncologist visits happen every 4 weeks

3.23 The company's model assumed that patients in the progression-free survival, CNS- progression-free survival and progressed disease states visited an oncologist every 5 to 6 weeks. The ERG consulted clinical experts, who advised them that in clinical practice patients visited an oncologist every 4 weeks. The clinical experts at the meeting agreed that this was reflective of UK clinical practice. The committee concluded that it was appropriate to model oncologist visits every 4 weeks.

The management of CNS progression events is not adequately captured in the model

3.24 The company explored 3 options for managing disease progression in the CNS: steroids, stereotactic radiosurgery and whole-brain radiotherapy. The company's base case assumed that 100% of patients with CNS metastases would have stereotactic radiosurgery and steroids. The company also presented a scenario analysis in which all patients had steroids, 23% of patients had stereotactic radiosurgery and 77% of patients had whole-brain radiotherapy. The company stated that according to the literature, whole-brain radiotherapy is being used less in clinical practice, which is why the company's base case modelled stereotactic radiosurgery only. The ERG preferred the company's scenario analysis to the base case, because the ERG considered that it

was more plausible to assume that 23% of patients would have stereotactic radiosurgery than 100% based on clinical expert opinion. The ERG did question the use of whole-brain radiotherapy in clinical practice, but accepted the company's scenario analysis. The clinical experts explained that treatment of CNS metastases is highly complex. They agreed that steroids would be offered to most people with CNS metastases. The clinical experts estimated that 20% to 25% of people with CNS metastases would have stereotactic radiotherapy, and 25% would have whole-brain radiotherapy, but that these treatments are not mutually exclusive. The clinical experts also suggested that surgical resection is sometimes used to manage CNS metastases. Although the committee recognised that treatment of CNS metastases is a complex area with variation in practice, it considered that the estimates that more closely reflect UK clinical practice (that is, 20% to 25% having stereotactic radiosurgery, 25% having whole brain radiotherapy) were the best assumptions to use in the model.

Cost-effectiveness results

The company's base-case ICER comparing alectinib with crizotinib is greater than £30,000 per QALY gained

3.25 The committee considered the incremental cost-effectiveness ratios (ICERs) from the company's base case, recalculated by the ERG to include the approved, confidential, patient access scheme discounts for alectinib and crizotinib. The company's base-case ICER for alectinib compared with crizotinib was greater than £30,000 per quality-adjusted life year (QALY) gained. The committee concluded that the company's base case was not appropriate for decision-making because of concerns about the following inputs and assumptions in the model:

- the overall survival extrapolation function (see section 3.19)
- the wastage assumption (see section 3.21)
- the distribution of subsequent treatments (see section 3.22) and

- the management of disease progression in the CNS (see section 3.24).

The ERG's preferred assumptions increase the ICER

3.26 The ERG presented a range of its preferred base-case ICERs. Its preferred assumptions included:

- progression events measured by independent assessment using RECIST criteria only (see section 3.7)
- overall survival extrapolated using Kaplan–Meier data and an exponential tail (see section 3.19)
- no wastage (see section 3.21)
- a range of scenarios exploring the proportions of patients from both treatment arms who had subsequent tyrosine kinase inhibitors after disease progression (see section 3.22)
- the company's scenario analysis for managing CNS disease progression (see section 3.24) and
- an increase in the frequency of oncologist visits to every 4 weeks (see section 3.23).

The committee noted that combining the ERG's preferred assumptions substantially increased the ICERs compared with the company's base case. The ERG's preferred base-case ICER for alectinib compared with crizotinib was substantially more than £30,000 per QALY gained.

The most plausible ICER is higher than £30,000 per QALY gained

3.27 Having considered the ICERs using the ERG's preferred assumptions, the committee took into account its preferred assumptions that differed from the ERG's base case:

- subsequent treatment distribution aligned with the clinical experts' opinion (see section 3.22)
- managing CNS metastases in line with the clinical experts' opinion (see section 3.24).

The committee concluded that the most plausible ICER for alectinib compared with crizotinib in people with untreated ALK-positive advanced NSCLC was above £30,000 per QALY gained

End of life

Alectinib does not meet the end-of-life criteria

3.28 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). The company submission stated that alectinib does not meet the end-of-life criteria. The committee considered the clinical evidence and agreed that life expectancy for people with ALK-positive advanced NSCLC having standard care is more than 2 years. Because the ALEX overall survival data were immature, the committee considered that it had not seen robust evidence that alectinib provides an extension to life. The committee therefore concluded that alectinib for untreated ALK-positive advanced NSCLC did not meet the end-of-life criteria.

Innovation

The benefits of alectinib are adequately captured in the model

3.29 The company explained that it considered alectinib to be innovative. The company and the clinical experts highlighted that alectinib has good penetration through the blood-brain barrier. The CNS is a common site of initial progression in ALK-positive NSCLC patients so CNS-active treatments are important targets for development. However, the clinical experts explained that although they consider alectinib to be novel and better at delaying disease progression than current standard care, they considered that alectinib's benefits were captured in the measurement of the QALYs. The committee concluded that alectinib may be innovative, but it had not been presented with any additional evidence of benefits that were not captured in the measurement of the QALYs and the resulting

cost-effectiveness estimates. The committee concluded that alectinib is not a cost-effective use of NHS resources for untreated ALK-positive NSCLC, and is not recommended for routine use.

Cancer Drugs Fund

Alectinib is not recommended for use in the Cancer Drugs Fund

3.30 Having concluded that alectinib is not recommended for routine use, the committee then considered if it could be recommended for treating ALK-positive advanced NSCLC within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the [addendum to the NICE process and methods guides](#). The company did not express an interest in alectinib being considered for funding through the Cancer Drugs Fund. The committee recognised that there was clinical uncertainty about the benefits of alectinib on overall survival because of the immaturity of the data and that more mature data from the ALEX trial would help to resolve this. However, the committee was aware that the company's base-case, ERG's preferred base-case range and committee's preferred base-case all led to ICERs above £30,000 per QALY gained. Given that alectinib does not meet the end-of-life criteria, the committee concluded that alectinib does not have plausible potential to be cost-effective at the offered price, and so could not be recommended for use within the Cancer Drugs Fund.

Other considerations

3.31 No equality/social value judgement issues were identified.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. 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.

Professor Gary McVeigh
Chair, appraisal committee
March 2018

5 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.

Lucy Beggs

Technical Lead

Christian Griffiths

Technical Adviser

Kate Moore

Project Manager

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