NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

1.1 Alectinib is recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults. It is recommended only if the company provides alectinib according to the commercial arrangement (see section 2).

Why the committee made these recommendations

People with untreated 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. There is not enough evidence to tell how long alectinib prolongs life compared with crizotinib.

There is uncertainty about how treatments after disease progression affect people's quality and length of life. But using the most plausible assumptions and with the commercial arrangement, the cost-effectiveness estimates for alectinib compared with crizotinib are within the range NICE normally considers acceptable. Therefore, alectinib is recommended for untreated advanced ALK-positive NSCLC.

Issue date: June 2018

2 Information about alectinib

Marketing authorisation indication	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)'. Alectinib has been available in the UK through the early access to medicines scheme.
Dosage in the marketing authorisation	The recommended dose of alectinib is 600 mg (4×150 mg capsules) taken twice daily with food (total daily dose of 1,200 mg). A validated ALK assay is necessary to identify ALK-positive NSCLC status, which should be established before alectinib therapy starts. 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.
Price	£5,032.00 per pack of 224×150 mg capsules (British national formulary [BNF] online [accessed February 2018]). Based on the company's economic model, if the mean treatment duration is 32 months, the average cost of a course of treatment is approximately £87,000 using the list price for alectinib. The company has a commercial arrangement (simple discount patient access scheme). This makes alectinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 6) 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 anaplastic lymphoma kinase (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 can reduce 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. In particular, they said that alectinib appears to show 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 ceritinib was not routinely commissioned as a first-line treatment when the NICE scope and company submission for alectinib were written. The committee therefore concluded that first-line treatment with crizotinib was the appropriate comparator for this appraisal.

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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 continue to have an ALK inhibitor beyond disease progression when the only other treatment option is chemotherapy. For example, if people having 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; in line with NICE guidance. If people are having first-line ceritinib, treatment is more likely to continue beyond disease progression because the only available treatment options are chemotherapy for people who are well enough, or best supportive care. 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 not how the drug was used for most people in the ALEX trial), because the only 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 evidence to support giving crizotinib after alectinib, and ceritinib is not licensed for use after alectinib. The committee recognised that in 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 the first documented progression event (determined using Response Evaluation Criteria In Solid Tumors [RECIST] v1.1) 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. 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 potential benefit in delaying or preventing CNS disease progression. 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 disease progression by independent review committee is appropriate

3.6 The ERG advised that, for consistency, the analyses of CNS progression-free survival and progression-free survival should use the same measurement criteria. The committee agreed with this approach. In ALEX, progression events were assessed by investigators and by 2 independent review committees. 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. But 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 disease progression using RECIST is preferable to using both RECIST and CNS RECIST

3.7 In ALEX, 2 separate independent review committees assessed progression. One of these committees assessed systemic progression using RECIST. The other committee assessed intracranial CNS progression using the adapted CNS RECIST. The company's initial analyses of disease progression were based on events captured using CNS RECIST and RECIST. The ERG was concerned that CNS RECIST is 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 to use RECIST data only. The clinical experts confirmed that CNS RECIST is not routinely used in UK clinical practice. After consultation, the company provided progression analyses based on events captured using RECIST only. The committee agreed that the company's revised analyses were more appropriate than analyses based on CNS RECIST and RECIST.

In ALEX, an ALK inhibitor is sometimes continued after 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 meant that 5 patients continued with alectinib and 30 with crizotinib 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 as well as radiographic evidence. Therefore, people with asymptomatic CNS disease progression would not usually be identified and 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, February 2017 data cut) 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 (HR 0.50, 95% CI 0.36 to 0.70); median progression-free survival was 25.7 months for alectinib (95% CI 19.9 to not estimable) compared with 10.4 months for crizotinib (95% CI 7.7 to 14.6). After consultation, the company

provided investigator assessed progression-free survival results from a more recent data cut; these results are academic in confidence. The committee concluded that alectinib was 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, the other used RECIST only). The committee noted that the Kaplan–Meier curves diverged substantially in both analyses; the exact analyses are commercial in confidence. Because of this, the committee concluded that alectinib appears to have a benefit in CNS progression-free survival compared with crizotinib.

There is uncertainty about the extent to which 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 were immature and that median overall survival was not reached in either treatment arm. At the first committee meeting, the company presented results from the February 2017 data cut. These results did not show a statistically significant difference in overall survival between alectinib and crizotinib (HR 0.76, 95% CI 0.48 to 1.20), despite the statistically 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. After consultation, the company provided overall survival results from an updated data cut; these results are academic in confidence. The committee accepted that an increase in progression-free and CNS progression-free survival could plausibly translate to a benefit in overall survival, but considered that uncertainty remained about the extent of any

such benefit. The committee concluded that there was insufficient evidence to confirm how much alectinib prolongs survival 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 treatment data were only collected for 41% of patients who had progressed and stopped their study drug (see section 3.22). Because subsequent therapies could affect survival outcomes, the ERG was concerned that the missing data could confound overall survival and would need to be taken into account in the 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. It 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 was 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

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 changed 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.

Basing the analyses of disease progression on RECIST is preferred

3.16 The company's initial analyses incorporated events from 2 independent review committee assessments in ALEX into progression-free survival and CNS progression-free survival analyses (see section 3.10); a main RECIST analysis and a separate analysis based on the adapted CNS RECIST. The ERG preferred the analyses based on RECIST only (which were provided as a scenario analysis by the company) because they were likely to be the most clinically relevant, and more comparable to other trials and NICE technology appraisal assessments. After consultation, the company did an updated analysis in which disease progression was modelled using events captured by RECIST only. The committee accepted that this revised approach was more clinically relevant.

The company's progression-free survival modelling using the ALEX Kaplan–Meier data (independent review) 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 and the second most conservative 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 was satisfied that using Kaplan–Meier data for the first 18 months offsets the problem (although the hazards do become proportional over time). The ERG considered the 18-month Kaplan–Meier cut-off to be

arbitrary, but felt that this would be the case for 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

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 most recent data on overall survival from ALEX are the best available for estimating cost effectiveness

3.19 After the first committee meeting, the company provided additional overall survival evidence based on a later data cut from ALEX; this evidence is academic in confidence. The company used these data as part of a scenario analysis. The ERG included this updated overall survival data in its own cost-effectiveness estimate for alectinib. The committee recognised that an inherent uncertainty remained in the ALEX overall survival data because of its immaturity and because of potential confounding from subsequent treatments (see sections 3.11 and 3.12). However, the committee concluded that the updated data cut was the best available data for estimating alectinib's potential survival benefit and cost effectiveness.

Extrapolating overall survival using Kaplan–Meier data from the most recent ALEX data cut and an exponential tail is acceptable

3.20 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's initial model used an exponential extrapolation of overall survival for alectinib and crizotinib for the base case, because this was the second best fit to the PROFILE 1014 data and the company judged it to be clinically plausible based on its discussions with clinical experts. As with 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, the company's revised model extrapolated overall survival using Kaplan–Meier data (from the February 2017 data cut) for the first 18 months, and then switched to an exponential tail. After consultation, the company also presented a scenario analysis which extrapolated survival using Kaplan–Meier data from the updated data cut. Aware of the inherent uncertainty in the ALEX overall survival data (see section 3.11), the committee preferred the analysis based on the more mature overall survival data. The committee concluded that extrapolating overall survival using Kaplan–Meier data from ALEX (measured using the most recent data cut) and an exponential tail was acceptable.

Resource use and costs

It is reasonable to assume no wastage for alectinib and crizotinib

3.21 The company's initial model assumed that a full pack of alectinib or crizotinib would be provided at a lung cancer clinic every 28 days and 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 because this best reflected clinical practice. After consultation, the company updated its analysis in line with the committee's preferred assumption.

The distribution of subsequent treatments in the company's model reflects clinical practice

3.22 Data on the treatments taken after disease progression in ALEX was only captured for 41% of patients. 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. After consultation the company submitted a revised analysis, which assumed a subsequent treatment distribution based on the clinical experts' estimates. The company modelled second-line subsequent treatments, followed by best supportive care. Although the clinical experts' estimates had included some third-line treatment with ceritinib, the ERG advised that limiting the analysis to second-line treatments helped to contain the uncertainty caused by the high proportion of missing data in ALEX (see section 3.12). The committee considered that the distribution of subsequent treatments in the company's updated model sufficiently reflected UK clinical practice.

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

3.23 The company's initial 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. Clinical experts advised the ERG that in practice patients visited an oncologist every 4 weeks. The clinical experts at the meeting agreed that this reflected UK clinical practice. The committee concluded that it was appropriate to model oncologist visits every 4 weeks. After consultation, the company updated its modelling of oncologist visits in line with the committee's preference.

The management of CNS progression events is adequately captured in the model

3.24 In its model, the company explored 3 treatment options for managing disease progression in the CNS: steroids, stereotactic radiosurgery and whole-brain radiotherapy. The company's initial 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 clinical experts explained that treating CNS metastases is highly complex, and that the choice of treatment would depend on a variety of factors (such as age, health and prognosis). They advised 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 radiosurgery, and 25% would have whole-brain radiotherapy, but that some people may have both. 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 and 25% having whole-brain radiotherapy) were the best assumptions to use in the

model. After consultation, the company submitted a revised analysis based on the clinical experts' estimated distributions of treatment for CNS metastases.

Health-related quality of life

It is preferable to model the role of subsequent treatments on quality of life

3.25 In its initial model, 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 (from a study abstract by Roughley et al. 2014). After consultation, the company did an updated analysis which modelled different subsequent treatment distributions for alectinib and crizotinib in line with clinical practice (see section 3.22). The ERG highlighted that although the company's updated model took into account the costs of subsequent treatments, it did not model the effect of the different subsequent treatments on utilities. The ERG's preferred analysis modelled both the costs of the subsequent treatments and their effects on quality of life. The committee considered that it was good practice for cost-effectiveness analyses to capture quality of life when possible. Therefore, the committee concluded that it was preferable to model the role of subsequent treatments on costs and quality of life.

It is acceptable for post-progression utility values to reflect differences in subsequent treatment distribution

3.26 The subsequent treatment distributions in the company's revised model differed between the alectinib and crizotinib treatment arms. To capture this in the modelling of quality of life, the ERG weighted the utility values according to the subsequent treatment distributions. In line with the company's revised analysis (see section 3.22), the ERG assumed that

people in the alectinib arm did not have second-line treatment with tyrosine kinase inhibitors, and that people in the crizotinib arm did not have second-line treatment with chemotherapy. People who did not have second-line treatment (50% of the alectinib arm and 30% of the crizotinib arm) or who progressed on second-line treatment had best supportive care, which was assumed to have a utility of 0.47. The resulting weighted utilities were 0.565 for second-line treatment with chemotherapy, 0.649 for second-line treatment with a tyrosine kinase inhibitor, and 0.47 for best supportive care. The committee agreed that it was realistic to weight utilities to reflect subsequent treatment distribution.

It is acceptable for post-progression utilities to reflect the site of disease progression

3.27 Although the ERG was in favour of modelling the role of subsequent treatments on quality of life, it highlighted that utilities based only on subsequent treatment would not capture the differences in quality of life between people with CNS and non-CNS progressed disease. Because of this, the ERG's preferred analysis accounted for the site of the disease progression. Utility values were weighted to reflect the different distributions of subsequent treatments between alectinib and crizotinib (see section 3.22). However, people with CNS-progressed disease were assumed to have the CNS-progressed disease utility (0.52 in the company's model) regardless of subsequent treatment. From the clinical experts' evidence at the first meeting, the committee was aware of the importance of site of disease progression on quality of life. The committee therefore concluded that it was acceptable for post-progression utilities to reflect this.

A CNS-progressed disease utility value of 0.52 is preferred

3.28 Not enough data were collected in ALEX to estimate the utility value for the CNS-progressed disease state. Because of this, the company used a utility value taken from a study by Roughley et al. (0.52; see section 3.25). The ERG noted that the utilities reported by Roughley et al. for non-CNS

progressed disease were consistently lower than the utilities derived from ALEX (0.65 compared with 0.725). Because of this, the ERG was concerned that the utility value for the CNS-progressed disease state taken from Roughley et al. (0.52) was lower than if it had been derived from ALEX. The ERG accounted for this by applying a percentage decrement (0.52/0.65) to the non-CNS progressed disease utility in ALEX (0.725) which gave an estimated utility of 0.58 for the CNS-progressed disease state. The committee was aware of the differences between the utilities reported in ALEX and Roughley et al., but also that in the first committee meeting it had accepted 0.52 as the CNS-progressed disease utility. The committee considered scenario analyses based on utilities with and without the Roughley et al. decrement. It noted that applying the decrement for people having chemotherapy after alectinib led to a utility value for CNS-progressed disease (0.58) that was higher than the utility value for non-CNS progressed disease (0.565; see section 3.26), which the committee considered to be clinically implausible. Because of this, the committee concluded that the CNS-progressed disease utility value of 0.52 was preferable.

Cost-effectiveness results

The company's base-case ICER comparing alectinib with crizotinib is lower than £20,000 per QALY gained

3.29 The committee considered the incremental cost-effectiveness ratios (ICERs) from the company's base case, recalculated by the ERG to include the confidential commercial arrangements for alectinib and crizotinib. The company's base-case ICER for alectinib compared with crizotinib was lower than £20,000 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 modelling of the role of subsequent treatments on quality of life (see section 3.25.

The ERG's preferred assumptions increase the ICER

3.30 The ERG accepted the company's revised modelling of wastage, oncologist visits and the management of CNS metastases. The ERG also agreed with the company's updated approach of capturing progression events using RECIST only. The ERG's additional preferred assumptions were:

- progressed disease utility values to be related to progression site (see section 3.27)
- utilities weighted to reflect subsequent treatment distributions in each treatment arm (see section 3.26)
- CNS-progressed disease utility value to be adjusted using the decrement from Roughley et al., increasing from 0.52 to 0.58 (see section 3.28)
- cost-effectiveness modelling based on updated ALEX data cut of overall survival (see section 3.19).

The committee noted that combining the ERG's preferred assumptions increased the ICER compared with the company's base case. When the confidential discounts from the commercial arrangements for both technologies were applied, the ERG's preferred base-case ICER for alectinib compared with crizotinib was between £20,000 and £30,000 per QALY gained.

The most plausible ICER is between £20,000 and £30,000 per QALY gained

3.31 The committee largely agreed with the ERG's preferred assumptions. Although it was aware of the uncertainties about overall survival benefit and subsequent treatment in the appraisal, the committee concluded that the most plausible ICER for alectinib compared with crizotinib in people with untreated ALK-positive advanced NSCLC was between £20,000 and £30,000 per QALY gained. The committee agreed that alectinib, with the discount agreed in the commercial arrangement, was a cost-effective use

of NHS resources for adults with untreated ALK-positive advanced NSCLC and was therefore recommended for routine use in the NHS.

Innovation

The benefits of alectinib are adequately captured in the model

3.32 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.

Other considerations

3.33 No equality or social value judgement issues were identified.

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. Because alectinib has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after 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 document.

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 untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer and the doctor responsible for their care thinks that alectinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Date for review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
June 2018

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.

Lucy Beggs
Technical Lead

Christian Griffiths
Technical Adviser

Kate Moore
Project Manager

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