NICE National Institute for Health and Care Excellence

NICE guidance

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib

Technology appraisal guidance

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Your responsibility

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

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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

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1 Recommendations

1.1 Brigatinib is recommended, within its marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults who have already had crizotinib. It is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

People with ALK-positive advanced NSCLC that has been treated with crizotinib are currently offered ceritinib as their next treatment.

Clinical evidence based on indirect comparisons of trials suggests that people having brigatinib live longer than those having ceritinib, and that they live longer before their condition worsens. Brigatinib may be more effective for brain metastases and better tolerated than existing treatments.

The cost-effectiveness estimates are uncertain, particularly because of whether brigatinib's treatment benefit continues after stopping treatment. The most plausible estimates for brigatinib compared with ceritinib are around the higher end of what NICE normally considers acceptable for an end-of-life treatment. But the population eligible for brigatinib is small and will decrease because crizotinib is no longer considered first-line treatment for ALK-positive NSCLC. Future treatments will be limited for those who have crizotinib. Taking these exceptional circumstances into account, brigatinib is recommended for ALK-positive advanced NSCLC in adults who have had crizotinib.

2 Information about brigatinib

Marketing authorisation indication	Brigatinib (Alunbrig, Takeda) has a marketing authorisation for 'the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer previously treated with crizotinib'.
Dosage in the marketing authorisation	The recommended starting dosage of brigatinib is 90 mg once daily for the first 7 days, then 180 mg once daily. Treatment should continue as long as there is clinical benefit. If brigatinib treatment is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose. If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered, and the next dose should be taken at the scheduled time.
Price	The proposed list price for brigatinib is: £4,900 for 28×180 mg tablets (the recommended dose), £4,900 for a starter pack (7×90 mg plus 21×180 mg tablets), £3,675 for 28×90 mg tablets, £1,225 for 28×30 mg tablets (company submission). The company has a commercial arrangement. This makes brigatinib 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 5) considered evidence submitted by Takeda 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 ALK-positive advanced NSCLC

3.1 People with anaplastic lymphoma kinase (ALK)-positive advanced 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. The patient experts explained that ALK-positive advanced NSCLC is debilitating, and that people with the condition worry about poor outcomes. They also highlighted that an improved quality of life, better management of symptoms and an increase in how long they live is very important to people with the condition and their families. The clinical experts acknowledged that an additional treatment option would be beneficial if it offered better tolerability than existing treatments. The committee understood that additional options are beneficial for ALK-positive advanced NSCLC, and concluded that brigatinib would be a useful option if it is better tolerated than existing treatments.

Treatment pathway and relevant comparators

Ceritinib is the relevant comparator for this appraisal

3.2 NHS England explained that ALK-status testing is now routine clinical practice, so ALK status is known before starting treatment. Therefore, the committee agreed to focus its discussion on people whose ALK status is known before starting treatment. The committee understood that crizotinib, ceritinib and alectinib are options for people with untreated ALK-positive advanced NSCLC. The clinical experts explained that fewer people are starting treatment on crizotinib because of the availability of ceritinib and alectinib. Therefore, the population eligible for brigatinib after crizotinib is small and will decrease as fewer people start treatment with crizotinib. The committee was aware that NICE has recommended ceritinib as a subsequent treatment option when NSCLC progresses with crizotinib. It therefore concluded that ceritinib was the only relevant comparator for brigatinib in people with ALK-positive advanced

NSCLC who have had treatment with crizotinib.

Clinical evidence

The main evidence for brigatinib is from 2 single-arm studies and is broadly generalisable to UK clinical practice

3.3 There were no studies or clinical trials directly comparing brigatinib with ceritinib. The main clinical evidence for brigatinib came from 2 single-arm studies:

- ALTA, a phase II study including 110 people in the study arm and using the dosage in brigatinib's marketing authorisation.
- Study-101, a phase I and II study including 25 people in the relevant subgroup.

The primary outcome in both studies was investigator-assessed overall response rate, using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Secondary outcomes in the studies included progression-free and overall survival, safety and tolerability and duration of response. The median follow-up in ALTA was 24.3 months and median overall survival was 34.1 months. Objective response rate was 56% in ALTA and 76% in study-101 (investigator-assessed). Median progression-free survival was 16 months in ALTA and study-101 (investigator-assessed). Median duration of response was 14 months (investigator-assessed) and 16 months (independent review committee-assessed) in ALTA and 26 months in study-101 (investigator-assessed). The committee heard that 74% of people in ALTA had previously had chemotherapy and 67% had brain metastases before starting the study. There were no data available on sites of progression for those who progressed during the study. The clinical experts confirmed that the ALTA population broadly reflected people with ALK-positive advanced NSCLC in England. The committee acknowledged that, because there was no head-to-head evidence with the relevant comparator ceritinib, an indirect treatment comparison would be the only way to judge the relative effectiveness of brigatinib compared with ceritinib (see section 3.6). The committee concluded that, although most people in the studies had had previous chemotherapy, ALTA and study-101 provided evidence that was generalisable enough to clinical practice for decision making.

The main evidence for the comparator, ceritinib, comes from ASCEND-2 and ASCEND-5

3.4 The main clinical evidence for ceritinib came from 2 studies:

- ASCEND-2, a single-arm phase II study including 140 people.
- ASCEND-5, a randomised controlled phase III trial including 231 people in the ceritinib arm.

Only 1 arm of the ASCEND-5 study was used in the analysis. This was because its comparator (chemotherapy) was not in the appraisal scope because ALK-status testing is now routine practice in England. The primary outcome in ASCEND-5 was independent review committee-assessed progression-free survival, using RECIST v1.1, and overall survival was included as a secondary outcome. The primary outcome in ASCEND-2 was investigator-assessed objective response rate, using RECIST v1.1. Secondary outcomes in ASCEND-2 included overall and progression-free survival. The committee accepted that ASCEND-2 and ASCEND-5 were appropriate studies to be considered for the comparator in this appraisal.

Treatment with an ALK inhibitor may continue after disease progression

3.5 In ALTA, treatment could continue after disease progression if there was clinical benefit, as determined by the trial investigator. The clinical experts said that this reflects clinical practice in England for both brigatinib and ceritinib. They explained that treatment is continued after disease progression because it might control cancer at sites other than the lungs. The ALTA time on treatment and progression-free survival curves did not support that all people would remain on treatment after progressing. But the committee accepted that it was usual practice in the UK to continue treatment after radiological disease progression in some circumstances.

Indirect comparison of brigatinib and ceritinib

An indirect comparison is appropriate because there are no head-to-head trials comparing brigatinib with ceritinib

3.6 Because there were no head-to-head trials comparing brigatinib with ceritinib, the company did an unanchored indirect treatment comparison (ITC). Results from 4 studies (see section 3.3 and section 3.4) were used and the relevant arms

treated as though they were single-arm studies. There were 2 approaches taken: a naive ITC and a matching-adjusted indirect comparison (MAIC). The MAIC adjusts for differences in baseline characteristics between study populations whereas naive ITC analyses do not. The company presented several analyses using both approaches. For overall survival these were:

- Using combined data for brigatinib (including ALTA and study-101) and using separate data for ceritinib (that is, analyses using either ASCEND-2 or ASCEND-5).
- Using only ALTA data for brigatinib, and using separate data for ceritinib (that is, analyses using either ASCEND-2 or ASCEND-5).

Progression-free survival was not reported as an investigator-assessed outcome in ASCEND-5 or as an independent review committee-assessed outcome in study-101. Therefore, the company presented the results using:

- Combined data for brigatinib (including ALTA and study-101) and using ASCEND-2 data for ceritinib (investigator-assessed progression-free survival).
- Only ALTA data for brigatinib and using separate data for ceritinib (that is, analyses using either ASCEND-2 or ASCEND-5; independent review committee-assessed progression-free survival).

The ERG found the ITC analyses to be broadly appropriate given the available trial data. The ERG agreed with the company that there was broad consistency of the results between the MAIC and naive ITC approaches. The committee concluded that, given the available trial data, the company's approach was appropriate.

Meta-analysis of the indirect treatment comparison results

The meta-analyses gave consistent results that are acceptable for decision making

3.7 For overall survival, the company did 2 meta-analyses to provide estimates of clinical effectiveness:

- It compared pooled brigatinib data (from ALTA and study-101) with ASCEND-2 and ASCEND-5 data (on ceritinib) separately.
- It compared brigatinib data from ALTA only with ASCEND-2 and ASCEND-5 separately.

- The company's preferred approach was to compare pooled ALTA and study-101 data with ASCEND-2 and ASCEND-5 data separately. For progression-free survival, the analysis only included data from ALTA and meta-analysed the results of the ITC against the data from ASCEND-2 with ASCEND-5 separately. This was because data for independent review committee-assessed progression-free survival were not available for study-101, and data for investigator-assessed progression-free survival were not available from ASCEND-5. The ERG was concerned that no adjustment was made to account for the brigatinib data being included twice in the meta-analysis. But overall, it was satisfied that consistent results were produced using each analytical strategy to meta-analyse the ITC results. All approaches taken for the meta-analysis showed that brigatinib extended overall and progression-free survival compared with ceritinib, and that the difference between treatments was statistically significant. The committee noted that the results suggested brigatinib improved overall survival by 16 to 19 months and progression-free survival by 9 to 10 months compared with ceritinib. The committee acknowledged that there was uncertainty with single-arm studies and the results should be interpreted with caution. It concluded that the meta-analyses gave consistent results and were acceptable for decision making.

Clinical evidence in the economic model

The results from the meta-analysis are broadly appropriate to include in the model

3.8 The company's original submission used the results of the MAIC ITC that included ALTA and study-101 data for brigatinib and ASCEND-2 data for ceritinib to estimate the progression-free survival hazard ratio between brigatinib and ceritinib (see section 3.6). The hazard ratio was then applied to the brigatinib data to estimate progression-free survival for ceritinib. The committee noted that ASCEND-5 was a larger trial than study-101 (110 people compared with 25 in study-101) and had reported independent review committee-assessed progression-free survival (see section 3.4). The ERG highlighted that ASCEND-5 was a higher quality trial and a more robust data source. At consultation, the company agreed to use the results of the MAIC that excluded study-101, but for consistency also excluded study-101 for estimating overall survival. The committee agreed that the approach to remove study-101 from both progression-free and overall survival estimates was appropriate.

Extrapolating clinical trial data in the economic model

The company's extrapolation of brigatinib overall survival is appropriate

3.9 At consultation, the company provided an updated model that extrapolated overall survival of brigatinib using the exponential function. This estimated that 29% of people with ALK-positive advanced NSCLC would be alive at 5 years and 2.3% at 10 years. The company explained that this broadly reflected estimates from its clinical advisers. The committee noted the wide range of estimates from the company's advisers. At the appraisal committee meeting, the clinical experts said that it was not possible to accurately estimate the proportion of people with ALK-positive advanced NSCLC who would be alive at specific time points in the future. They explained that overall survival has improved over recent years because of the use of ALK-targeted therapies. The ERG noted that the extrapolation of overall survival was very uncertain because the studies had short follow-ups, making the extrapolation periods relatively long. It highlighted that the conclusions should be treated with caution. The committee noted that the ERG preferred to use the log-logistic distribution to estimate overall survival because it provided a good fit and gave a 10-year survival estimate (4.4% at 10 years) closer to the clinical experts' expectations. The committee concluded that, although there was some uncertainty about the long-term prognosis for this population, both the company's and the ERG's choices of distribution were plausible for modelling overall survival.

The exponential function is more appropriate for extrapolating progression-free survival

3.10 The company extrapolated progression-free survival in its model using the Gompertz function because it provided a reasonable fit to the data and also had both internal and external validity. The committee noted that the ERG's preference for using the exponential function provided a closer fit to both the brigatinib and ceritinib observed data. The committee agreed that both the Gompertz and the exponential functions gave plausible estimates for progression-free survival but considered that the ERG's approach provided a better fit to the available data.

Time on treatment data

Using time on treatment data from the trial is preferred

3.11 The company used progression-free survival plus 1.53 months to estimate time on treatment for both brigatinib and ceritinib. The 1.53 months is the difference between median time on treatment (17.15 months) and median progression-free survival (15.62 months) from ALTA. The ERG was aware that the time on treatment after progression was 3.10 months in ASCEND-2. The clinical experts highlighted that time on treatment after progression could be similar for both brigatinib and ceritinib. They estimated that, in clinical practice, progressed disease could be treated for a further 2 to 3 months (see section 3.5). However, the committee was aware that time on treatment data were available from ALTA and concluded that data from the available evidence were preferred.

Benefit after stopping treatment

The size and duration of any treatment benefit after treatment is stopped is uncertain in the absence of longer-term data

3.12 In its original submission, the company assumed a continued treatment benefit associated with overall and progression-free survival for brigatinib and ceritinib over the full time horizon of the model. Clinical experts explained that it was reasonable to assume that treatment benefit of brigatinib over ceritinib would continue for a few months after stopping treatment, because brigatinib appears to have a deeper response on brain metastases than ceritinib. However, they noted that there is no trial evidence to support a continued survival benefit after treatment stops in people with radiological progression. This benefit of brigatinib over ceritinib may have been captured already in the progression-free survival estimate. The committee was aware of NICE's technology appraisal guidance on ceritinib after crizotinib in which the clinical experts had noted that treatment benefit was unlikely to persist beyond treatment. The committee agreed that the size and duration of any treatment benefit after stopping treatment in people with symptomatic progression was uncertain in the absence of longer-term data.

The ERG's approach of directly linking mortality with time on treatment is preferred

3.13 In response to the committee's concerns that lifetime treatment benefit was not

clinically plausible, the company updated its economic model. The updated model assumed a full treatment benefit for 161 weeks (3.09 years). This included 148 weeks (based on the maximum follow-up in ALTA) plus 13 weeks of continued treatment benefit (based on clinical inputs estimating this to be 2 to 3 months; see section 3.11). After 161 weeks, the brigatinib mortality rate was tapered until week 377 (7.23 years) when only 1% of people remained on treatment. At this point mortality rates for brigatinib and ceritinib were assumed to be the same (hazard ratio of 1). The ERG considered that the company's approach to modelling a loss of treatment effect did not directly link to the length of time on treatment. The ERG also considered that the mortality rate applied for those who were no longer on treatment should be relative to best supportive care rather than to ceritinib. The ERG's updated model adjusted the mortality rates for both brigatinib and ceritinib during the extrapolated period (after week 161) from ALTA, which therefore kept a direct link between the time on treatment and the time at which loss of effect begins. After this period the ERG applied an estimated mortality rate for best supportive care for those who stop treatment with either brigatinib or ceritinib. Although the committee acknowledged that there was uncertainty with both the company's and the ERG's approaches to modelling treatment benefit after stopping treatment because of a lack of longer-term data, the committee preferred to retain a link between time on treatment and the time at which loss of effect begins.

Health-related quality of life

The utility value for pre-progressed disease is acceptable

3.14 The company derived the utility value of 0.793 for pre-progressed disease from ALTA. The clinical experts confirmed that this utility value was reasonable. They explained that people with ALK-positive advanced NSCLC are well, even at the end of treatment. The committee concluded that the utility value of 0.793 for pre-progressed disease was appropriate.

The utility values for people with progressed disease on or off treatment are acceptable

3.15 The company estimated the quality of life associated with progressed disease using published utility values. In the original submission, the company used a utility decrement of 0.15 from Chouaid et al. (2013), giving a utility estimate of

0.643 for progressed disease. The committee accepted the 0.15 utility decrement and the 0.643 utility value for those who have progressed on treatment, but did not consider 0.643 appropriate for progressed disease once patients are no longer taking treatment. This was in line with the clinical experts, who felt that it was unlikely that this value would remain constant throughout progression. The company revised the utility values, creating a separate value for progression on and off treatment. The progressed on-treatment value (0.732) was derived from ALTA, and was for patients who had just progressed (both on and off treatment). The company then applied the utility decrement of 0.15 from Chouaid et al. to the progressed on-treatment value, giving a utility estimate of 0.582 for progressed disease off treatment. The committee concluded that the company's updated utility values were reasonable.

Resource use and costs

Drug wastage for brigatinib and ceritinib is adequately captured

3.16 The company's original submission assumed that there was no drug wastage (that is, the NHS would save all costs associated with the reduced dose intensity seen in the studies). A written statement from NHS England confirmed that there was likely to be more drug wastage with ceritinib than brigatinib. The clinical experts explained that dose reduction is common with ceritinib because of toxicity but dose reduction with brigatinib is uncommon. The company revised its submission in response to consultation, to reflect the committee's preference for the ERG's model assumption to use half the difference between the observed and expected dose for each treatment. The committee accepted the company's amendments to the model.

It is reasonable to include drug administration and delivery costs

3.17 The company included administration costs for both brigatinib and ceritinib in its model (£526 for the first cycle and £217 for subsequent cycles). At the first committee meeting, the Cancer Drugs Fund clinical lead explained that most trusts use a third-party dispenser for oral chemotherapy, which incurs a cost for home delivery. He also suggested that a delivery cost would be applied about 70% of the time. The Cancer Drugs Fund clinical lead also explained that, because brigatinib is a high-cost chemotherapy, the oral chemotherapy administration tariff (£120) should have been used in the company's model and

included as a cost per item per cycle. In response to the comments, the company noted that the resource use inputs for dispensing, administration, dose changes and monitoring, as well as administration and dispensing costs for each cycle, were already included in the administration costs used in the model. NHS England confirmed that £217 was more than the current oral administration tariff and it was content that the appropriate costs were contained within the model, as long as they were applied to both treatments. The committee concluded that the administration costs were suitably captured within the model.

Cost-effectiveness results

The company's probabilistic base-case ICER comparing brigatinib with ceritinib is above £50,000 per QALY gained

3.18 The committee considered the incremental cost-effectiveness ratios (ICERs) from the company's base case, recalculated by the ERG to include the approved patient access scheme discounts for brigatinib and ceritinib (which are confidential so the ICERs cannot be reported here). The company's base-case probabilistic ICER for brigatinib compared with ceritinib was above £50,000 per quality-adjusted life year (QALY) gained. The committee considered that the company's base case was not appropriate for decision making because of concerns about the uncertainty about continued treatment benefit beyond 3 months used in the model (see section 3.12).

The ERG's preferred assumptions increase the ICER

3.19 The ERG's preferred assumptions about clinical benefit after treatment stopped included:

- Starting mortality rate decline from week 161 (similar to the company's approach).
- Using data from the ALTA Kaplan–Meier plot to estimate time on treatment instead of using progression-free survival plus 1.53 months, thereby maintaining a direct link between time on treatment and progression-free survival.
- Using mortality rates for those no longer on treatment with either brigatinib or ceritinib based on best supportive care (applying a hazard ratio of 0.75 between best supportive care and ceritinib).

- Using an exponential distribution for progression-free survival and a log-logistic distribution for overall survival.

The committee noted that combining the ERG's preferred assumptions increased the ICERs compared with the company's base case. The ERG's base case with its preferred assumptions gave an ICER for brigatinib compared with ceritinib that was more than £50,000 per QALY gained. The committee noted that the ERG's base case may have underestimated the time on treatment for ceritinib (around 3.7 months compared with a median of 5.5 months in the company model). The ERG explored scenarios that adjusted the hazard ratio for time on treatment for brigatinib compared with ceritinib, some of which gave time on treatment estimates that were more consistent with ASCEND-5. Some of these scenarios decreased the ICER to below £50,000 per QALY gained. The committee agreed with the ERG's general approach and preferred the hazard ratios that gave a median time on treatment for ceritinib of between 6.4 and 7.4 months, which was consistent with ASCEND-5 (which had a median time on treatment of about 7 months in the published results).

Changes to clinical practice mean that the population eligible for brigatinib after crizotinib is decreasing, with limited future treatment options

3.20 The committee was aware that crizotinib was no longer standard care for ALK-positive NSCLC because most people now start treatment with alectinib. The committee considered that future treatment options for people who start treatment with crizotinib will probably be limited. Also, the committee was aware that the population eligible for brigatinib after crizotinib is small (less than 50 people) and will decrease as fewer people start treatment with crizotinib (see section 3.2). Therefore, the committee recognised that there was a need for effective and well tolerated treatments for this small and diminishing group of people who started treatment with crizotinib and who are affected by this change in treatment pathway. The committee concluded that these were exceptional circumstances, which should be taken into consideration in its decision making.

End of life

Life expectancy for people with ALK-positive advanced NSCLC is considered to be less than 24 months

3.21 The committee considered advice about life-extending treatments for people

with a short life expectancy in NICE's guide to the methods of technology appraisal. The company considered that the life expectancy of people with ALK-positive advanced NSCLC would be less than 24 months, which meets the first criterion for an end-of-life treatment. Median life expectancy reported in ASCEND-2 was 14.9 months and in ASCEND-5 it was 18.1 months. Mean overall survival was not reported in ASCEND-2 and ASCEND-5. The company's model predicted a mean overall survival of 22 months for people with ALK-positive advanced NSCLC. The committee concluded that the life expectancy of people with ALK-positive advanced NSCLC having ceritinib is less than 24 months.

Brigatinib extends life by at least 3 months

3.22 The company estimated a mean life extension of 21 months with brigatinib compared with ceritinib, which meets the second criterion for an end-of-life treatment. The committee understood that estimating overall survival for this population was very uncertain (see section 3.9). The ERG highlighted that the data used to estimate the extension to life were not robust but extension to life was likely to be at least 3 months. The committee concluded that brigatinib for ALK-positive advanced NSCLC would likely extend life by at least 3 months.

Brigatinib meets the criteria for end-of-life treatments

3.23 The committee concluded that, although the most plausible estimate of life expectancy for people with previously treated ALK-positive advanced NSCLC was less than 24 months, the potential life extension benefit of brigatinib was proportionally substantial. It was therefore satisfied that brigatinib met the criteria for end-of-life treatments.

Innovation

The benefits of brigatinib are adequately captured in the model

3.24 The company considered brigatinib to be innovative because it offers meaningful extension to life and longer progression-free life. The clinical experts explained that brigatinib has a lower toxicity than ceritinib and so is better tolerated. They said that brigatinib treatment is not a step change but is innovative because it is well tolerated. The committee agreed that the benefits of brigatinib over ceritinib in the central nervous system were adequately

captured in the analysis through health-related quality of life. It concluded that although brigatinib may be innovative, it had not been presented with any additional evidence of benefits that were not captured in the economic model and resulting cost-effectiveness estimates.

Conclusion

Brigatinib after crizotinib is recommended for people with ALK-positive advanced NSCLC

3.25 The committee considered the strengths and weaknesses of the company's and the ERG's base cases, noting the overall uncertainty in the results from both approaches. Having considered the ICERs from both approaches, the committee agreed that the most plausible ICER for brigatinib compared with ceritinib in people with ALK-positive advanced NSCLC was around the higher end of what would normally be considered cost effective for an end-of-life treatment. The committee also considered that the population was small and decreasing over time, with limited future treatment options for people who started treatment with crizotinib. It also considered that brigatinib is a treatment option that could offer benefits in terms of progression-free and overall survival as well as better tolerability than ceritinib. Although the most plausible ICER was around the higher end of what NICE normally considers cost effective for an end-of-life treatment, the committee agreed that there were exceptional circumstances for this population that should be taken into account (see section 3.5 and section 3.20). Therefore, the committee concluded that brigatinib was recommended for routine use in the NHS for ALK-positive advanced NSCLC after crizotinib.

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

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.

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