

Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor

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 is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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

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, as an option for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) that has not been previously treated with an ALK inhibitor in adults. It is recommended only if the company provides brigatinib according to the [commercial arrangement](#).

Why the committee made these recommendations

People with ALK-positive advanced NSCLC who have not had an ALK inhibitor before are usually offered alectinib. If a person's ALK status is not known at diagnosis, crizotinib is offered after chemotherapy. Brigatinib may be offered as an alternative to these treatments.

Clinical evidence shows that brigatinib is more effective than crizotinib at delaying disease progression. It suggests that brigatinib extends life more than crizotinib, but this is uncertain. There is no clinical trial evidence directly comparing brigatinib with alectinib. An indirect comparison suggests that brigatinib is as effective as alectinib in delaying disease progression, including in the central nervous system. However, although it appears that brigatinib could extend life as much as alectinib, there is uncertainty because of a lack of long-term data.

Despite the uncertainty, the most likely cost-effectiveness estimates for brigatinib are within what NICE considers an acceptable use of NHS resources. So, brigatinib is recommended.

2 Information about brigatinib

Marketing authorisation indication

- 2.1 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 (NSCLC) previously not treated with an ALK inhibitor'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price of brigatinib is £4,900.00 (excluding VAT; BNF accessed November 2020) for the:

- starter pack (7 tablets at 90 mg plus 21 tablets at 180 mg)
- 28-tablet pack at 180 mg.

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](#) considered evidence submitted by Takeda, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- it was appropriate to consider alectinib as the main comparator in the appraisal (issue 1, see technical report, page 2)
- use of time on treatment to inform duration of treatment was appropriate (issue 5, see technical report, pages 8 to 9)
- partitioning disease by central nervous system (CNS) progression to account for the effect of CNS involvement was appropriate (issue 6a, see technical report, pages 9 to 10).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed the following issues (issues 2, 3, 4 and 6b; see technical report, pages 3 to 10), which were outstanding after the technical engagement stage.

Treatment pathway and comparator

A new treatment option would benefit people with ALK-positive advanced NSCLC that has not been treated with an ALK inhibitor

- 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. Approximately 40% to 50% of all people with NSCLC develop CNS metastases, which can reduce quality of life and how long people live. The patient and clinical experts explained that there are very few treatments available for untreated ALK-positive advanced NSCLC. Most

people diagnosed with ALK-positive NSCLC will be offered treatment with alectinib, a second-generation tyrosine kinase inhibitor. The patient and clinical experts further explained that compared with alectinib, brigatinib has a reduced treatment burden (1 tablet per day compared with 8 tablets per day). They noted that in clinical practice, people having alectinib can experience side effects such as sun sensitivity, fatigue and gastrointestinal issues, which can substantially affect their quality of life. The committee concluded that there was a need for more treatment options for people with ALK-positive advanced NSCLC.

Alectinib is the most appropriate comparator for this appraisal, but crizotinib is also considered

3.2 The clinical experts advised that they routinely offer alectinib for untreated ALK-positive advanced NSCLC in line with [NICE's technology appraisal guidance on alectinib](#). [NICE also recommends ceritinib and crizotinib](#) for this indication. The clinical experts and the company explained that ceritinib is used for only 1% to 2% of people with ALK-positive NSCLC in the NHS, because CNS metastases have limited response to it. Crizotinib is primarily offered to people with ALK-positive NSCLC who do not have an ALK status at diagnosis, who are a minority. The clinical experts explained that at least 90% of people who receive ALK status at diagnosis will have alectinib. The committee concluded that first-line treatment with alectinib was the most appropriate comparator for this appraisal.

Clinical-effectiveness evidence

Brigatinib is more effective than crizotinib, but there is uncertainty on how much brigatinib extends overall survival

3.3 The main evidence for brigatinib came from ALTA-1L, an open-label phase 3 randomised controlled trial that compared brigatinib (n=137) with crizotinib (n=138) in adults with untreated ALK-positive advanced or metastatic NSCLC. The ALTA-1L trial showed that brigatinib statistically significantly extends progression-free survival compared with crizotinib. The ERG considered that the best overall survival hazard ratio for

brigatinib was 0.87 (95% confidence interval [CI] 0.40 to 1.80). This suggested that brigatinib is more effective than crizotinib. However, the ERG noted that because of the immaturity of data and the high level of crossover from the crizotinib arm to the brigatinib arm in the trial (see [section 3.5](#)), there is uncertainty about the precise improvement in overall survival with brigatinib compared with crizotinib.

There is no direct evidence for brigatinib compared with alectinib but there is suitable indirect evidence using data from the ALTA-1L and ALEX trials

- 3.4 Because there was no evidence directly comparing brigatinib with alectinib, the company did an indirect treatment comparison that included data from the ALEX trial, an open-label phase 3 randomised controlled trial. ALEX compared alectinib (n=152) with crizotinib (n=151) in adults with untreated ALK-positive advanced NSCLC. The company excluded the ALESIA trial, a randomised, open-label phase 3 study comparing alectinib and crizotinib, from the indirect treatment comparison. This was because it only included people from Asian countries (China, South Korea and Thailand) so was not considered generalisable to the UK. The ERG considered that the ALESIA study should be included. It noted that the European Public Assessment Report for brigatinib states that it is possible to extrapolate clinical-effectiveness data from a population of Asian family origin to a population of mainly European family origin. The clinical experts explained that they did not expect ethnicity to affect clinical outcomes. However, they noted that the ALESIA trial predominately included people from China, who are likely to be offered different subsequent treatments and have access to a healthcare system that is different to the NHS in England. The committee noted that the ALTA-1L and ALEX trials were well-done studies that were more generalisable to the NHS. Considering this, the committee agreed that it was suitable to exclude the ALESIA trial from the indirect treatment comparison and to use data only from the ALTA-1L and ALEX trials.

The unanchored matched-adjusted indirect comparison is not acceptable for decision making

3.5 The studies used in the indirect treatment comparison had some key baseline differences. For example, a higher proportion of patients in the ALEX trial had CNS involvement at baseline for both the alectinib and crizotinib arms compared with those in the ALTA-1L trial. Also, the ALTA-1L study included patients who had previously had at least 1 full cycle of chemotherapy (26% of patients in the brigatinib arm and 27% of patients in the crizotinib arm). The ALEX trial did not include patients who had chemotherapy before. Because of these differences, the company used matching-adjusted indirect comparisons (MAICs) to compare the efficacy of brigatinib with alectinib. Three methods of indirect treatment comparison (ITC) were used:

- unanchored MAIC
- anchored MAIC
- unweighted Bucher ITC.

The unanchored MAIC ignored the crizotinib arms of the ALTA-1L and ALEX trials and considered the brigatinib and alectinib data as if they were from 2 single-arm studies. The anchored MAIC used crizotinib (the common treatment arm) as an anchor. The unweighted Bucher ITC was included as a baseline reference. All 3 ITC methods resulted in similar progression-free survival results. The hazard ratios were close to 1, showing that brigatinib and alectinib both extend the time before disease progression for a similar amount of time. The ITC results for overall survival varied and had wider confidence intervals than the results for progression-free survival (see [section 3.6](#)). The anchored MAIC and unweighted Bucher ITC were adjusted for different crossover scenarios using rank-preserving structural failure model methods to generate additional overall survival results. Because there was high crossover (99%) from the crizotinib arm to the brigatinib arm in the ALTA-1L study on disease progression, the company believed that the anchored MAIC results could potentially be influenced by bias. So, the company chose to use the unanchored MAIC for its base case. However, the committee noted that the [NICE Decision Support Unit technical support document 18](#) states that when connected evidence with a common comparator is available, only anchored

forms of population adjustment may be used. Unanchored population adjustment may only be considered in the absence of a connected network of randomised studies, or when there are only single-arm studies. Also, the ERG explained that reliable unanchored MAIC results rely on the assumption that all prognostic factors and treatment effect modifiers are accounted for, and that this assumption was not considered to have been met in the company's ITCs. The committee concluded that the unanchored MAIC results were not acceptable for decision making.

There is uncertainty about whether brigatinib produces similar overall survival compared with alectinib

3.6 Hazard ratio results from the company's anchored MAICs, unanchored MAICs and unweighted Bucher ITC for overall survival ranged between 0.83 and 1.36 and had wide confidence intervals. The ERG considered all the indirect treatment comparison overall survival results to be uncertain because of the immaturity of the data. It considered the best available overall survival result to be from the anchored MAIC with rank-preserving structural failure time model adjustment for all people who switched treatments during the trials without re-censoring (hazard ratio 1.15; 95% CI 0.62 to 2.12). The overall survival data from the ALTA-1L trial were immature and median overall survival was not reached in either treatment arm. Also, the committee recognised that overall survival data were confounded by the high proportion of people who crossed over from the crizotinib arm to the brigatinib arm during the study (see [section 3.5](#)). The clinical experts commented that, although the survival data were very immature, they would expect to see an increase in survival over time with brigatinib, in the absence of confounding. They noted that brigatinib is a second-generation tyrosine kinase inhibitor with the same mechanism of action as alectinib and that both technologies have shown pre-clinical activity against several ALK mutations. Both brigatinib and alectinib showed an improved efficacy as measured by progression-free survival compared with crizotinib in the ALTA-1L and ALEX trials, respectively. Also, the company's 3 ITCs all suggested that brigatinib and alectinib led to similar progression-free survival (see [section 3.5](#)). Considering the biological and pharmacological similarity of alectinib and brigatinib, and their experience with both technologies in clinical practice, the clinical experts were confident that overall survival with

brigatinib could be expected to be similar to alectinib. Also, the committee noted that the 5-year overall survival outcomes for alectinib exceeded the most optimistic predictions in [NICE's technology appraisal guidance on alectinib](#). The committee accepted that, considering that brigatinib and alectinib have similar mechanisms of action, an increase in progression-free and CNS progression-free survival could plausibly translate to a benefit in overall survival, although uncertainty remains about this. It also accepted that it was plausible for similar overall survival to be seen with brigatinib and alectinib, given the similarities between the 2 treatments.

Economic approach

The CNS-progressed disease utility value of 0.52 is accepted, despite its limitations

3.7 The multiplier used for the CNS health state was based on a utility value of 0.52 from a 2014 abstract (Roughley et al. 2014). The committee noted that this abstract included a small number of people with brain metastases (n=29), and did not report treatment-related adverse events, comorbidities or age. It noted that the limited information prevented the reliability of the data being investigated. Also, the committee considered that since the abstract was published, there have been various changes in how ALK-positive NSCLC is treated. For example, both alectinib and lorlatinib are recommended as first-line and second-line treatment options, respectively (see [NICE's technology appraisal guidance on alectinib](#) and [lorlatinib](#)). The committee recognised that these developments are likely to have affected the quality of life of people with ALK-positive NSCLC with CNS involvement. However, the clinical experts confirmed there are no alternative data to use to measure quality of life in this population. The committee concluded that the CNS-progressed disease utility value of 0.52 was accepted, despite its limitations.

There is not enough evidence to accept a cost comparison with alectinib

3.8 The company included a cost-comparison analysis in its submission to

help with decision making. The company explained that clinical advice suggested that brigatinib would perform similarly to alectinib in a real-world setting. The clinical experts noted that, based on their experience, both brigatinib and alectinib perform similarly in the clinic. Based on this, they considered brigatinib and alectinib to be clinically equivalent and associated with similar long-term outcomes (see [section 3.6](#)). The ERG referred to the wide confidence interval around the overall survival hazard ratios (see [section 3.6](#)) and noted that these can only be interpreted as a measure of uncertainty and not as evidence of similarity. Also, the ERG explained that a lack of statistically significant difference in the company's ITCs is not the same as providing statistical evidence that there is no difference between treatments. The committee concluded that there was not enough evidence to consider brigatinib and alectinib to be clinically equivalent, so a cost-comparison approach with alectinib was not suitable.

Cost-effectiveness results

The company's base-case ICER comparing brigatinib with alectinib is not considered acceptable

3.9 The company's base-case incremental cost-effectiveness ratio (ICER), which did not include the confidential discount for alectinib, showed that brigatinib dominated alectinib (that is, it was more effective and cost less than alectinib). However, this was calculated using the unanchored MAIC overall survival results. The committee recalled that where possible, an anchored MAIC is preferred ([NICE Decision Support Unit technical support document 18](#); see [section 3.5](#)). Having considered the evidence and methodological approach, the committee concluded that an anchored MAIC was feasible for the comparison of brigatinib with alectinib so rejected the company's base case using the unanchored MAIC.

In the company's base case brigatinib dominates crizotinib

3.10 In the comparison of brigatinib with crizotinib, the ERG noted that the ALTA-1L trial results were confounded by crossover. It explained that,

although adjustment methods were implemented correctly, a robust analysis of the effect of crossover was not possible because of the immaturity of the overall survival data and the high level of crossover (99%; see [section 3.5](#)). Because of this, the ERG did not identify a preferred ICER per quality-adjusted life year (QALY) gained for the comparison with crizotinib. When confidential discounts for both brigatinib and crizotinib were included, the ICERs were below what NICE considers cost effective in the company base case and in the ERG's preferred scenarios (including use of time on treatment to model treatment duration, and use of 3-year and 5-year treatment waning for overall survival, progression-free survival and intracranial progression-free survival).

Considering incremental net monetary benefit analyses to compare brigatinib and alectinib is appropriate for decision making

3.11 The company also provided cost-effectiveness results in a net benefit framework. The incremental net monetary benefit of brigatinib was compared with alectinib at threshold values of £20,000 and £30,000 per QALY gained using the confidential discount for brigatinib and list price for alectinib. Using each of the available overall survival results from the anchored MAIC and unweighted Bucher ITC resulted in a positive incremental net monetary benefit at both thresholds of £20,000 and £30,000 per QALY gained, demonstrating cost effectiveness. The ERG considered that the net monetary benefit analyses had been done correctly. It repeated the analyses and included the confidential discount for alectinib, which showed that the net monetary benefit remained positive with all overall survival analyses at the threshold of £20,000 per QALY gained and most overall survival analyses at the threshold of £30,000 per QALY gained. This showed that brigatinib is cost effective compared with alectinib at the range NICE considers an acceptable use of NHS resources. Given the immaturity of the overall survival data and associated uncertainty in the company's base-case analysis, and it being likely that any differences in QALYs between brigatinib and alectinib are small, the committee concluded that net monetary benefit was a useful supplementary analysis to inform the cost-effectiveness of brigatinib compared with alectinib.

Brigatinib is recommended

3.12 The committee considered whether brigatinib would be a cost-effective use of NHS resources for people with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor. Because of the uncertainty about the overall survival benefit of brigatinib (see [section 3.6](#)), the ERG did not identify a preferred ICER compared with alectinib. The company submitted additional cost-effectiveness analyses using overall survival data from the anchored MAICs and unweighted Bucher ITC analyses, with and without adjustment for crossover. Using overall survival data generated from these analyses resulted in scenarios where brigatinib was less effective and less costly than alectinib (incorporating the confidential discount for brigatinib and list price for alectinib). The committee noted that, in situations in which an ICER is estimated for a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. The ERG replicated the company's analyses including the confidential discount for alectinib. Each of the plausible analyses (with 1 exception, in which brigatinib dominated alectinib) resulted in ICERs showing that brigatinib was associated with cost savings per QALY lost (exact ICERs are confidential and cannot be reported here). The committee acknowledged that the overall survival data used to generate these ICERs was uncertain (see [section 3.6](#)). It noted that even if more mature overall survival data became available, uncertainty would remain because of the high level of crossover in the ALTA-1L trial. However, it recalled the clinical experts' comments that overall survival with brigatinib could be expected to be similar to alectinib (see [section 3.6](#)). The committee also considered comments from the clinical and patient experts describing the burden of taking existing treatments and the effect this had on a person's quality of life (see [section 3.1](#)). The committee agreed that extending treatment choices would benefit people. The committee also agreed that brigatinib was a cost-effective use of NHS resources compared with crizotinib for the small number of people who do not have ALK status at diagnosis (see [section 3.10](#)). For the comparison with alectinib, it considered the estimated cost-effectiveness results, results of the net monetary benefit analyses, and the views of clinicians and patients. The committee agreed the likelihood of brigatinib being cost effective was high and that the risk

to the NHS if this decision is incorrect is very small. So, it recommended brigatinib for people with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor.

Other considerations

Equality

3.13 No equality or social value judgement issues were identified.

End of life

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

Innovation

3.15 The company explained that it considered brigatinib to be innovative. The benefits of brigatinib were considered adequately captured in the model.

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 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – a new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 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.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has untreated anaplastic lymphoma kinase-positive advanced 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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