NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lorlatinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: January 2020

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using lorlatinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 18 February 2020

Second appraisal committee meeting: TBC

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

1 Recommendations

1.1 Lorlatinib is not recommended, within its marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor
- crizotinib and at least 1 other ALK tyrosine kinase inhibitor.

1.2 This recommendation is not intended to affect treatment with lorlatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Advanced ALK-positive NSCLC is usually first treated with an ALK tyrosine kinase inhibitor (alectinib or ceritinib, or crizotinib followed by either brigatinib or ceritinib). People then have either platinum doublet chemotherapy (PDC) or atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP).

Lorlatinib, another ALK tyrosine kinase inhibitor, has not been compared directly with other drugs. But analyses indirectly comparing lorlatinib with PDC and ABCP suggest that people who take lorlatinib:

- have longer before their disease progresses than people who take PDC
- have longer before their disease progresses and may live longer than people who take ABCP.

The methods and results of the cost-effectiveness modelling are very uncertain, because of limitations in the data and how the treatments are compared indirectly. Lorlatinib meets NICE's criteria to be considered a life-extending treatment at the end of life. But the most likely cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources. So lorlatinib is not

recommended. Lorlatinib does not meet NICE's criteria to be included in the Cancer Drugs Fund.

2 Information about lorlatinib

Marketing authorisation indication

2.1 Lorlatinib (Lorviqua, Pfizer) as monotherapy is indicated for 'the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK TKI'.

Dosage in the marketing authorisation

2.2 The recommended dose is 100 mg lorlatinib taken orally once daily. Treatment with lorlatinib is recommended as long as the patient is benefitting from therapy without unacceptable toxicity.

Price

2.3 The list price of lorlatinib is £7,044.00 per 120-tablet pack of 25 mg tablets, and £5,283.00 per 30-tablet pack of 100 mg tablets (excluding VAT; BNF online accessed January 2020). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with 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:

- Including atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP) as a comparator in the appraisal was appropriate (issue 1, see technical report page 16).
- A hazard ratio of 0.8 was a reasonable estimate of the comparative efficacy between platinum doublet chemotherapy (PDC) and singlet chemotherapy (issue 2, see technical report page 18).
- Of the 6 proposed methods for indirect comparison with PDC, methods 3, 4 and 6 were dismissed by the company and ERG, leaving methods 1, 2 and 5 for committee consideration (issue 3, see technical report page 22).
- The generalised gamma curve was the most appropriate for measuring overall survival on lorlatinib (issue 4, see technical report page 26).
- Treatment of 3.5 months beyond progression with lorlatinib was appropriate (issue 6, see technical report page 33).
- The revised assumptions for proportion and type of subsequent treatment discussed at the technical engagement stage were appropriate:
  - after lorlatinib: 45% of patients have subsequent treatments and the remaining 55% have best supportive care. Of the 45%, 66% have ABCP and 33% have PDC
  - after PDC: 45% of patients have subsequent treatments and the remaining 55% have best supportive care. The 45% have immunotherapies in the proportions in the original company submission (69% atezolizumab, 31% bevacizumab based on NICE's technology appraisal guidance on ABCP)
  - after ABCP: 75% of patients have docetaxel and 25% have best supportive care (issue 7, see technical report page 35)
- The company not making a case for lorlatinib as a candidate for the Cancer Drugs Fund was appropriate because the ongoing lorlatinib clinical trials would not result in the evidence needed to resolve the uncertainties in this appraisal (issue 8, see technical report page 37).

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 3 and 5), which were outstanding after the technical engagement stage.

Clinical need

A third-generation ALK TKI would offer significant benefit to patients

3.1 The patient expert explained that there was a significant unmet need for patients with anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC), even though 4 ALK tyrosine kinase inhibitor (TKI) treatments are available. The committee noted that neither crizotinib nor ceritinib are preferred for untreated disease since the availability of alectinib. Brigatinib has been approved for previously treated disease only after crizotinib. If alectinib's treatment effect wanes the only current option is chemotherapy. ALK TKI treatments are a significant improvement over chemotherapy. People can live relatively normally and do not need to go to hospital for treatment. They do not have distressing symptoms associated with chemotherapy such as hair loss. Also, the patient expert explained that lorlatinib may be better tolerated than other ALK TKIs, appearing to cause less fatigue and fewer sun sensitivity and gastrointestinal problems. The clinical experts confirmed that there was a high unmet need for patients with ALK-positive NSCLC, because there is no cure for metastatic disease. Also, more than 50% of patients with ALK-positive NSCLC develop brain metastases, associated with high morbidity and mortality. Lorlatinib's ability to reach the brain means that patients whose brain tumours respond to treatment may have improved quality of life, allowing them to return to their usual activities. First and second-generation ALK TKIs (alectinib, ceritinib, crizotinib and brigatinib) are associated with the development of drug resistant mutations, leading to disease progression. Brain metastases and drug resistant mutations limit the duration of disease control and benefit from current ALK TKIs. For patients to survive for longer, and to avoid the devastating consequences

of brain metastases, effective treatment that can penetrate the brain and overcome ALK-resistance mutations is needed. The committee noted that lorlatinib would be another line of ALK TKI treatment before a patient has chemotherapy or chemoimmunotherapy. The committee agreed that there was an unmet clinical need in ALK-positive NSCLC and that a third-generation ALK TKI, such as lorlatinib, would significantly benefit patients.

Clinical management

Current treatments after ALK TKIs are not effective for brain metastases

3.2 Current treatment options after ALK TKIs are standard care PDC, ABCP or best supportive care. The clinical experts explained that there was weak evidence for PDC-based regimens for this patient population, with a relative lack of efficacy in patients with brain metastases. The clinical experts explained that ABCP also has poor brain penetration and was not available to NHS patients in England with symptomatically active brain or leptomeningeal (central nervous system) metastases, which are common in ALK-positive NSCLC. In the absence of a third-generation ALK TKI such as lorlatinib, ABCP is expected to be used more in people without symptomatically active central nervous system metastases. The committee agreed that the evidence for the efficacy of current treatments after ALK TKIs was weak in ALK-positive NSCLC and it was unclear how much benefit they had in people with brain metastases.

Clinical evidence

The main clinical evidence comes from a single-arm study

3.3 The main clinical evidence for lorlatinib came from study 1001, a single-arm, open-label, multicentre phase 1 to 2 trial, done in 13 countries but not in the UK. This study investigated the effect of lorlatinib in adults with metastatic (stage 4) ALK-positive NSCLC. It comprised 7 cohorts with 5 (2, 3A, 3B, 4, 5) representing populations having a mix of ALK TKIs and chemotherapy regimens. The company presented evidence for the

combined cohort EXP-3B:5 of 139 patients. This was the pooled cohort whose treatment history most closely resembled that of the patient population covered by the marketing authorisation, with patients relapsing after 1, 2, 3 or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens. Cohort 3B was made up of 28 patients who had had first-line treatment with alectinib or ceritinib, with or without prior chemotherapy. The clinical experts explained that most patients would have alectinib as first-line treatment in the NHS, meaning that this cohort was the closest match to the NHS population. Cohort 4 was made up of 65 patients who had previous treatment with 2 ALK TKIs, with or without prior chemotherapy. Cohort 5 consisted of 46 patients who had previous treatment with 3 or more ALK TKIs, with or without prior chemotherapy. The primary outcome of study 1001 was objective response rate. Secondary outcomes included overall survival and progression-free survival. The results showed an objective response rate of 40.3% (95% confidence interval [CI] 32.1 to 48.9) with lorlatinib. The results also showed a progression-free survival of 6.9 months (95% CI 5.4 to 8.2) and a median overall survival of 20.4 months (95% CI 16.1 to not reached).

Clinical effectiveness evidence in the economic model

The evidence for the PDC arm of the economic model is uncertain

3.4 The clinical effectiveness data for the PDC arm of the economic model was taken from the ALUR and ASCEND-5 trials (for progression-free survival) and the PROFILE 1001 and PROFILE 1005 trials (for overall survival). These trials were used for the matching-adjusted indirect comparison (MAIC, see section 3.7). The ERG emphasised its concerns about the quality and suitability of the data from these trials. This was because most patients in these studies had previously had PDC and crizotinib (most closely matching the treatment history of cohort EXP-3A from study 1001). Also, the patients in the chemotherapy arms of these trials had singlet chemotherapy (pemetrexed, docetaxel) rather than PDC. The committee agreed with the ERG and clinical experts that the

company's assumption of equivalent clinical efficacy between doublet and singlet chemotherapy was not supported by clinical evidence, and that doublet chemotherapy was expected to be somewhat more effective than singlet chemotherapy. The committee noted that adjusting the hazard ratio by 20% to 0.8 to account for the difference in clinical efficacy between PDC and singlet chemotherapy was agreed to be appropriate at the technical engagement stage. The committee agreed that the treatment history differences between the trial populations used for PDC efficacy in the model (ALUR and ASCEND-5 for progression-free survival and PROFILE 1001 and PROFILE 1005 for overall survival) and those of cohort EXP-3B:5 from study 1001 meant that the clinical effectiveness evidence for the PDC arm of the model was uncertain.

Population adjustment for ABCP overall survival is appropriate

3.5 To compare lorlatinib with ABCP, the IMpower150 trial was used to create an unanchored, unadjusted comparison with lorlatinib. A mixed subgroup including patients with epidermal growth factor receptor (EGFR)-positive and ALK-positive NSCLC was the only evidence available on using ABCP in ALK-positive NSCLC. The company applied a population adjustment to reflect that most of the relevant subgroup from IMpower150 had EGFR-positive NSCLC (n=30) rather than ALK-positive disease (n=11). The company claimed that the prognosis for ALK-positive NSCLC was poorer than for EGFR-positive disease, so a failure to adjust would bias the results against lorlatinib. The committee heard that there was a lack of robust evidence to support the company's claim. To do the adjustment, the company compared response to chemotherapy in patients with EGFR-positive disease (using data from the IMPRESS study comparing continued treatment with gefitinib plus chemotherapy with placebo plus chemotherapy after first-line gefitinib in people with EGFR-positive NSCLC) with response to chemotherapy in patients with ALK-positive NSCLC (using data from ALUR and ASCEND-5 for progression-free survival and from PROFILE 1001 and PROFILE 1005 for overall survival). This provided hazard ratios, which were then applied to the fitted log-

logistic and exponential curves in the mixed EGFR-positive and ALK-positive cohort to derive curves for an ALK-positive only cohort. The ERG stated that there was not enough evidence to provide validity for the extent of this adjustment, which shifts both the progression-free survival and overall survival in favour of lorlatinib. As a result, with the −20% hazard ratio adjustment made to the PDC arm data after the technical engagement stage (see section 3.4), the ERG explained that the overall survival curve for ABCP was now almost identical to the curve for PDC in the model, and this lacked clinical plausibility. The company and experts agreed that ABCP would be expected to be more effective than PDC, especially in patients without brain metastases. To correct this, the ERG suggested reducing the company's log hazard ratio adjustment to the ABCP curve for overall survival by 25% to improve clinical plausibility relative to the overall survival curve for PDC. The exact hazard ratios were considered academic in confidence by the company and cannot be reported here. The committee agreed with the ERG that the company's log hazard ratio adjustment of the ABCP curve was uncertain and that the ERG's 25% reduction to this adjustment seemed more clinically plausible for ABCP overall survival relative to PDC overall survival in the model.

Overall survival

10-year survival in this population is uncertain

3.6 To derive long-term overall survival for lorlatinib, parametric curves were fitted to the lorlatinib overall survival data taken from the EXP-3B:5 cohort from study 1001. The exponential curve had the best statistical fit, but the generalised gamma curve was selected as a compromise between the exponential curve and the log-normal curve preferred by the company's clinical experts based on the 10-year survival predictions. The exact overall survival values were considered academic in confidence by the company and cannot be reported here. The clinical expert consulted by the ERG considered that 10% projected survival at 10 years would be too optimistic and 2% would be more plausible. The clinical experts at the

meeting confirmed that predicting 10-year survival in small populations with a very high incidence of brain metastases was highly uncertain because of a lack of reliable evidence. The committee heard that, in the absence of biomarkers for disease progression, brain metastases were the most reliable predictor of survival in patients with advanced ALK-positive NSCLC, and these patients would be expected to survive only for a few months. The committee noted that 66.9% of the pooled cohort EXP-3B:5 from study 1001 and 80.4% of cohort EXP-5 (3 or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens) had brain metastases at baseline. The clinical experts at the meeting agreed that 10% projected survival at 10 years for this population was too high, and that lower values would be more plausible. The committee noted that the incremental cost-effectiveness ratio (ICER) was sensitive to the choice of curve and that using the exponential curve substantially increased the base-case ICER for lorlatinib compared with PDC. It concluded that although the generalised gamma curve had been agreed at the technical engagement stage, projecting 10-year survival in this population remained highly uncertain and it would take this uncertainty into account in its decision making.

Indirect treatment comparisons

The results of the indirect treatment comparisons are uncertain

3.7 The company did an unanchored MAIC (as recommended in the NICE Decision Support Unit technical support document 18), to compare the single-arm trial data for lorlatinib with trial data for PDC. The company chose 4 variables for matching:

- Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 or more than 1)
- brain metastases (yes or no)
- family origin (Asian or non-Asian)
- sex (male or female).

The treatment history of people in the ALUR or ASCEND-5 and PROFILE 1001 or PROFILE 1005 trials was more like that of people in cohort EXP-2:3A from study 1001 than to cohort EXP-3B:5, the target population in the company's submission. The company explained to the committee that in addition to the MAIC it used 2 further approaches for the indirect treatment comparison, giving 6 methods in total:

- hazard ratios estimated using a MAIC with EXP-2:3A (method 1) and EXP-3B:5 (method 2)
- hazard ratios estimated using an unadjusted indirect comparison with EXP-2:3A (method 3) and EXP-3B:5 (method 4)
- direct estimation of progression-free and overall survival by fitting parametric curves to chemotherapy data from the clinical studies (method 5) and the same parametric curves with a population adjustment because the populations in these clinical studies had fewer prior treatments than the EXP-3B:5 cohort (method 6).

The committee noted that methods 3, 4 and 6 had been dismissed at the technical engagement stage. The company's preference was for method 5, mainly because of concerns about whether the assumption of proportional hazards held for the duration of the model with methods 1 and 2. The company said that methods 1 and 2 were also plausible approaches. The ERG had concerns about methods 1, 2 and 5, but considered that they were all plausible, and agreed that method 5 was preferred as the least problematic option. The committee agreed with the ERG that all the proposed indirect comparison methods were highly uncertain, but disagreed that methods 1 and 2 were reliable because of how the company had done the MAIC. The committee agreed that the company's approach of weighting patients in cohorts EXP-2:3A and EXP-3B:5 from study 1001 to match the patient characteristics of the populations from the ALUR or ASCEND-5 and PROFILE 1001 or PROFILE 1005 trials was correct. But it was concerned about how the MAIC had been implemented. The committee noted that matching the

2 pooled cohorts from study 1001 (EXP-2:3A and EXP-3B:5) to the same chemotherapy arm trial populations should have resulted in very similar hazard ratios being generated. Presenting hazard ratios that were not similar (and which resulted in large ICER differences) from the MAIC with EXP-2:3A (method 1) compared with the MAIC with EXP-3B:5 (method 2) showed that the matching adjustments used in the MAIC had failed. This was likely to be because of insufficient covariates being matched. The committee would have preferred a sensitivity analysis around the choice of variables included in the MAIC. The results that used methods 1 and 2 were therefore unreliable and unsuitable for decision making. The committee further discussed the company's rationale for doing the MAIC with both pooled cohorts. In general, the committee felt that using cohort EXP-2:3A for matching with the chemotherapy arm populations was not appropriate because this pooled cohort had a different treatment history and considerably different baseline characteristics to cohort EXP-3B:5. The clinical experts confirmed that cohorts 4 and 5 had already had 2 or 3 lines of treatment and had considerably more brain metastases than cohort EXP-2:3A. But the committee acknowledged that, overall, this was much less important than its fundamental concern that the results of the MAIC were unreliable and could not be considered, leaving only method 5 for consideration. The committee also agreed that the results of the indirect treatment comparison from applying independent curves without population adjustment (method 5) were highly uncertain.

Utility values in the economic model

The committee prefers a utility of 0.65 for progression on treatment and 0.46 for progression off treatment in both arms

3.8 The company did a systematic literature review to identify relevant studies with published utility values for ALK-positive NSCLC. The study by Labbé et al. (2017) was the largest published source of NSCLC ALK-positive EQ-5D questionnaire utility values, and the company selected the value of 0.65 from the study for the progressed disease state in both arms. The

ERG was concerned that this value was likely to represent the health state shortly after progression rather than the whole progressed period and was therefore too high. The committee recalled that the ERG preferred the values from Chouaid et al. (2013) for progressed disease after second-line treatment (0.59) and after third or fourth lines of treatment (0.46). The clinical experts agreed that the population had many previous treatments, and a very high incidence of brain metastases. They said that the best evidence for quality of life in this population was from the QUARTZ study, which looked at the quality of life of patients after treatment for brain metastases. But the population in QUARTZ was considerably less well than the population in study 1001 and had higher levels of comorbidity. So the value of 0.46 was agreed to be too low for progressed disease in the current appraisal. The committee asked the clinical experts which of the 3 options were most clinically plausible:

- a progressed health state utility value of 0.59
- a value of 0.65 for lorlatinib patients in progression on treatment and 0.59 for progressed disease and off treatment in both arms
- a value of 0.65 for lorlatinib patients in progression on treatment and 0.46 for progressed disease and off treatment in both arms.

The committee heard that because the disease and how it affects people varies, both 0.46 and 0.59 were plausible as averages across the progressed disease and off-treatment health state. One clinical expert strongly supported a 2-part utility value for progressed disease, on the basis that disease progression does not immediately correspond to an increase in a patient's symptom burden. But they were uncertain whether the second value should be 0.59 or 0.46. The committee asked the clinical and patient experts how the utility level declines for patients after symptomatic progression to understand which value would better reflect the average utility in progression off treatment with lorlatinib. The clinical experts agreed that some people, particularly with brain metastases, can deteriorate very quickly to a low level of utility with a very high symptom

burden. On balance, given that patients had previously had treatment with surgery (56.1%) and radiotherapy (68.3%) and had a very high incidence of brain metastases (66.9%), the committee concluded that the preferred utility values were 0.65 for lorlatinib patients in progression on treatment and 0.46 for patients who had progressed and were off treatment in both arms.

Results of the cost-effectiveness analysis

The committee has preferred assumptions for decision making

3.9 The committee's preferred assumptions for decision making for PDC were:

- lorlatinib treatment for 3.5 months after progression
- hazard ratio of 0.8 for the relative efficacy of PDC compared with singlet chemotherapy
- MAIC method 5
- progressed disease utility of 0.65 for lorlatinib patients on treatment and 0.46 for lorlatinib patients off treatment, in both arms.

For ABCP:

- company's population adjustment of ABCP overall survival reduced by 25%
- lorlatinib treatment for 3.5 months after progression
- progressed disease utility of 0.65 for lorlatinib patients on treatment and 0.46 for lorlatinib patients off treatment, in both arms.

The range of most plausible cost-effectiveness estimates for lorlatinib is more than £50,000 per QALY gained

3.10 Because lorlatinib and the comparators have commercial arrangements, the exact ICERs are confidential and cannot be reported here. The committee noted that its preferred assumptions produced a range of deterministic ICERs for lorlatinib compared with PDC and ABCP which were more than £50,000 per quality-adjusted life year (QALY) gained.

End of life

Lorlatinib meets the criteria to be considered a life-extending, end-of-life treatment compared with PDC and ABCP

3.11 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. For PDC, average life expectancy was well below 2 years in the company's base case and remained under 2 years across the scenarios assessed. Despite the limitations in the comparative evidence base, it was plausible that lorlatinib treatment would result in a gain in life expectancy of more than 3 months compared with PDC. Although there was some uncertainty around the average life expectancy with ABCP treatment because of the population adjustment applied by the company to the fitted curve, this was also expected to be less than 2 years. Also, life expectancy with ABCP remained under 2 years when the log hazard ratio for the population adjustment of overall survival was reduced by 25%, as agreed by the committee. The survival gains for lorlatinib compared with ABCP remained above 3 months across all scenarios assessed. The committee concluded that lorlatinib met the criteria to be considered a life-extending, end-of-life treatment when compared with both PDC and ABCP.

Lorlatinib is not recommended for routine commissioning

3.12 The committee acknowledged the need for treatment options for people with previously treated ALK-positive advanced NSCLC. But the uncertainty of the evidence presented and the resulting range of plausible ICERs meant that the committee could not recommend lorlatinib as a cost-effective use of NHS resources for previously treated ALK-positive advanced NSCLC.

Cancer Drugs Fund

Lorlatinib is not a candidate for the Cancer Drugs Fund

3.13 The company did not make a case for lorlatinib to be included in the Cancer Drugs Fund. Although there is uncertainty about the comparative clinical effectiveness of lorlatinib, this cannot be reduced by data collection through the Cancer Drugs Fund. The committee heard that lorlatinib's conditional marketing authorisation requires the company to submit the clinical study report for the phase 3 trial (CROWN 1006) comparing lorlatinib with crizotinib for the first-line treatment of advanced ALK-positive NSCLC by December 2021. Because this evidence would be in patients who have not had treatment before, it would not be relevant to this appraisal for previously treated advanced ALK-positive NSCLC. Also, the company has to do a prospective single-arm study investigating the efficacy of lorlatinib in patients whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy. The results from this study would not help to resolve the uncertainties around the comparative effectiveness of lorlatinib and either PDC or ABCP. The committee concluded that lorlatinib was not a candidate for the Cancer Drugs Fund in this indication.

Innovation

The model adequately captures the benefits of lorlatinib

3.14 The company considered lorlatinib to be innovative, highlighting that it was a third-generation ALK TKI that penetrates the central nervous system and is retained in the intracranial space. So it potentially addresses the unmet need for additional treatment options for patients who develop brain metastases. It was specifically designed to inhibit resistant ALK mutations, including the ALKG1202R mutation that increases significantly after treatment with second-generation agents. The clinical experts agreed that lorlatinib was an effective third-generation ALK TKI with good brain penetration and that people would welcome additional

treatment options. The committee concluded that 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 factors

3.15 No equality or social value judgements were identified.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
January 2020

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.

Luke Cowie
Technical lead

Richard Diaz
Technical adviser

Kate Moore
Project manager

ISBN: [to be added at publication]