NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909)

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 evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: April 2025

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using lorlatinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 2 May 2025
- Second evaluation committee meeting: 9 July 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Lorlatinib should not be used for untreated ALK-positive advanced non-small-cell lung cancer in adults who have not had an ALK 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 healthcare professional consider it appropriate to stop.

What this means in practice

Lorlatinib is not required to be funded in the NHS in England for untreated ALK-positive advanced non-small-cell lung cancer. It should not be used routinely in the NHS in England.

This is because there is not enough evidence to determine whether lorlatinib is value for money.

Why the committee made these recommendations

This evaluation reviews the evidence for lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (NICE technology appraisal guidance 909).For this review, the company provided 2 extra years of evidence on how long people have before their cancer gets worse, but no new evidence on how long people live.

Usual treatment for untreated ALK-positive advanced non-small-cell lung cancer is alectinib or brigatinib. Crizotinib is also available, but rarely used in the NHS. Lorlatinib is already used after alectinib or brigatinib. It is now being evaluated as a first treatment, as an alternative to alectinib or brigatinib.

Clinical trial evidence shows that, compared with crizotinib, lorlatinib increases how long people have before their cancer gets worse. But, crizotinib is not usually used

as a first treatment for this condition, so the trial results do not reflect what happens in the NHS. An indirect comparison suggests that lorlatinib increases how long people have before their cancer gets worse compared with alectinib and brigatinib. But, it is uncertain whether lorlatinib makes people live longer compared with alectinib and brigatinib.

Because there are uncertainties in the clinical evidence, the cost-effectiveness analyses are also uncertain. Taking into account the available cost-effectiveness estimates, and the additional evidence needed to inform decision making, the committee could not conclude that lorlatinib was a cost-effective use of NHS resources. So, lorlatinib should not be used in the NHS.

2 Information about lorlatinib

Marketing authorisation indication

2.1 Lorlatinib (Lorviqua) is indicated 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 or whose disease has progressed after prior treatment with an ALK inhibitor.'

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for lorlatinib.

Price

2.3 The list price of 30 lorlatinib 100-mg tablets and 90 lorlatinib 25-mg tablets is £5,283 (excluding VAT; BNF online; accessed March 2025).

2.4 The company has a commercial arrangement for lorlatinib as a second-line treatment. This makes lorlatinib available to the NHS with a discount. The company proposed a new discount for lorlatinib for this evaluation. This new discount would have applied to both first-line and second-line lorlatinib had it been recommended at first line. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 About 5% of people with non-small-cell lung cancer (NSCLC) have mutations in the anaplastic lymphoma kinase (ALK) gene. People with ALK-positive advanced NSCLC tend to be younger and are less likely to have a history of smoking than the wider NSCLC population. The patient and clinical experts explained that ALK-positive NSCLC is associated with late diagnosis compared with other types of NSCLC, so people often have advanced cancer, and some also have metastases to the central nervous system (CNS). The patient experts described how the symptoms of ALK-positive advanced NSCLC can be debilitating, and the prognosis is poor. They also explained that CNS metastases substantially affect quality of life. When a person is diagnosed with CNS metastases, they typically have to surrender their driving licence, which has a significant impact on independence and family life. The patient experts also spoke of the worry of developing CNS metastases, and the resulting toll on mental health. The committee concluded that ALK-positive advanced NSCLC has a substantial impact on both quality and length of life.

Clinical management

Current treatment and comparators

3.2 Treatment for ALK-positive advanced NSCLC usually includes ALK tyrosine kinase inhibitors (TKIs). There are 4 ALK TKIs available for untreated NSCLC: alectinib, brigatinib, ceritinib and crizotinib. The clinical experts explained that since the availability of alectinib and brigatinib, which are 'second-generation' ALK TKIs, crizotinib and ceritinib are rarely used in the NHS. NHS England's Cancer Drugs Fund (CDF) clinical lead (from here, CDF lead) noted that alectinib is used more often than brigatinib as a first-line treatment. The committee understood that

lorlatinib is a third-generation ALK TKI. It is already used for treating ALK-positive advanced NSCLC in adults whose cancer has progressed after other ALK TKIs (see NICE's technology appraisal guidance on lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer). But the clinical experts and the CDF lead agreed that only a minority of people have second-line treatment with lorlatinib in the NHS. Chemotherapy is usually used as the last line of treatment because of toxicity. The committee concluded that current NHS practice for untreated ALK-positive advanced NSCLC is alectinib or brigatinib in the first-line setting, followed by lorlatinib at second line, then chemotherapy at third line. It noted that crizotinib and ceritinib are rarely used in the NHS. In this evaluation, the company positioned lorlatinib as a first-line treatment. So, the committee concluded that alectinib and brigatinib are the relevant comparators for this appraisal.

Unmet need

3.3 The clinical experts noted that lorlatinib would be a useful addition to first-line treatment options, particularly given its potential effect on intracranial outcomes: they explained that lorlatinib may penetrate the blood–brain barrier better than other ALK TKIs. The clinical and patient experts noted that lorlatinib has a different toxicity profile to those of alectinib and brigatinib. They described adverse effects including weight gain, neuropathy, and mood disturbance. In the same way that lorlatinib may have more efficacy against CNS metastases, it also has greater potential for causing CNS adverse effects. But the clinical experts also explained that healthcare professionals in the NHS have experience of managing these adverse effects when using lorlatinib at second line. So, while adverse effects can substantially affect quality of life, they are often manageable with supportive care or by dose reductions. But, the committee cautioned that the CNS adverse effects from lorlatinib may be less important for people on second-line treatment, as these people typically have worse health and may already be experiencing adverse effects from CNS metastases. The committee further noted that while dose reductions may effectively manage lorlatinib's adverse effects, it was

uncertain how this would influence efficacy.

The clinical experts explained that if lorlatinib were available, it would likely become the first-line treatment of choice for younger people and for those with CNS metastases. But, they noted that uptake would probably be lower in older people and people who are at risk of mental health issues. They also explained that people who have alectinib or brigatinib as a first-line treatment have the option of second-line lorlatinib. But, if people had first-line lorlatinib, they could not have a second-line ALK TKI (including lorlatinib again). This is because alectinib and brigatinib are not indicated for second-line treatment after first-line lorlatinib. They thought that this may affect the uptake of lorlatinib as a first-line treatment because people would have fewer second-line options. The committee concluded that lorlatinib would be a useful addition to first-line treatment options for untreated ALK-positive advanced NSCLC in the NHS, but that alectinib or brigatinib would continue to be offered.

Subgroups

3.4 The committee also considered the relevant population for this appraisal within the marketing authorisation. NICE's manual on health technology evaluation notes that the committee will consider:

- which individuals benefit most from the technology, and
- whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost effectiveness or cost savings.

The committee considered that, because lorlatinib may be particularly effective for intracranial outcomes (see section 3.3), it may be appropriate to consider the clinical and cost effectiveness of lorlatinib in a subgroup of people with CNS metastases. But it had not seen any cost-effectiveness evidence for lorlatinib in people with CNS metastases. Also, the committee understood that there is variation in identifying CNS metastases at diagnosis in the NHS. So, it was unable to consider this subgroup further.

Clinical effectiveness

CROWN trial and its generalisability to the NHS

3.5 The main evidence for lorlatinib came from CROWN. This is an ongoing, open-label, phase 3, superiority, randomised controlled trial comparing lorlatinib (n=149) with crizotinib (n=147). It includes adults with untreated ALK-positive advanced or metastatic NSCLC who have not had systemic treatment for metastatic cancer, including previous ALK TKIs. The primary outcome of CROWN is progression-free survival assessed using blinded independent central review (BICR). Key secondary outcomes include overall survival, progression-free survival by investigator assessment, intracranial outcomes, adverse effects, and quality of life. CROWN is a multinational study with 104 study sites in 23 countries, including 3 sites in the UK.

As described in section 3.2, crizotinib is rarely used in the NHS, so is not a relevant comparator for this appraisal. Also, the EAG explained that the treatment sequences (the order in which people have treatment) in CROWN do not represent current NHS practice. For example, 43% of people randomised to lorlatinib whose cancer progressed had a further line of treatment with an ALK TKI, most commonly alectinib. But, this would not typically happen in the NHS. Similar issues applied to the crizotinib arm of CROWN. Of the people randomised to crizotinib whose cancer progressed, 4% had lorlatinib at second line, and 81% had alectinib or brigatinib. In the NHS, people whose cancer progresses on a first-line ALK TKI do not have alectinib or brigatinib as a second-line treatment. Their options would be lorlatinib or chemotherapy. The clinical experts also said that in the NHS, people would typically continue taking lorlatinib for about 3 to 6 months after their cancer has progressed. In CROWN, continuing treatment after progression was allowed if a person was still experiencing clinical benefit, but only 7% of people did so. As the treatment sequences in CROWN did not align with NHS practice, the EAG considered that overall survival in CROWN could be confounded. For example, overall survival in the lorlatinib arm may have been increased by

second-line use of alectinib or brigatinib, which would not typically happen in the NHS. The EAG was concerned that this would substantially limit the applicability of the evidence from CROWN to NHS clinical practice. The clinical experts confirmed that subsequent treatments in clinical trials often have a confounding effect on overall survival. But they also explained that, for the lorlatinib arm, there was no certain evidence that using additional ALK TKIs after lorlatinib would have any meaningful effect on overall survival. The company acknowledged these issues with the second-line treatments in CROWN and highlighted that its modelling approach aimed to account for this by including data from additional sources. The company also highlighted that these treatment sequence issues were present in trials of the comparators. The committee considered that the comparator in CROWN and the second-line treatments in both arms did not represent NHS practice. This meant that there was a high level of uncertainty in the clinical evidence after cancer progression. The committee concluded that it would take this into account in its decision making.

Progression-free survival

3.6 The primary outcome of CROWN was progression-free survival assessed using BICR. An interim analysis, done after 75% of the expected progression or death events, was reported in March 2020. Formal statistical testing for progression-free survival ended after this interim analysis, but CROWN continued to report further post hoc analyses of progression-free survival at 3 years and 5 years of follow up. At the September 2021 data cut, after a median of 36.7 months of follow up for lorlatinib, lorlatinib was associated with significantly longer BICR-assessed progression-free survival than crizotinib (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.18 to 0.39). BICR stopped after 3 years, but the company kept collecting progression-free survival as assessed by the investigators. At the October 2023 data cut, after a median of 60.2 months follow up for lorlatinib, lorlatinib was associated with significantly longer investigator-assessed progression-free survival than crizotinib. Median progression-free survival by investigator assessment was not

reached for lorlatinib (95% CI 64.3 months to not estimable) and was 9.1 months (95% CI 7.4 to 10.9 months) for crizotinib (HR 0.19, 95% CI 0.13 to 0.27). The submission from the British Thoracic Oncology Group said the progression-free survival benefit observed for lorlatinib is 'one of the most pronounced and impressive seen in solid tumours'. The EAG agreed with the company and experts that the progression-free survival benefit was highly clinically significant. But, the EAG also cautioned that, because CROWN is an open-label trial in which the investigators know which treatment participants are assigned to, there is a risk of bias in investigator-assessed outcomes. The committee noted that the investigator-assessed progression-free survival was more favourable to lorlatinib than the BICR. But, the committee concluded that the progression-free survival benefit for lorlatinib was clinically significant.

Time to intracranial progression

3.7 Evidence from the October 2023 data cut of CROWN also showed that time to progression of intracranial disease was significantly longer for lorlatinib compared with crizotinib. The median time was not estimable in the lorlatinib arm and was 16.4 months (95% CI 12.7 to 21.9 months) in the crizotinib arm. This difference was statistically significant (HR 0.06, 95% CI 0.03 to 0.12). The committee agreed with the EAG and the company that these results were clinically significant, but recognised that the open-label design of CROWN may have biased investigator-assessed outcomes.

Overall survival

3.8 The CROWN trial protocol specified 3 overall survival analyses: 1 coinciding with the final progression-free survival analysis (if statistically significant), another at 70% of overall survival events, and a final overall survival analysis. Data on overall survival was provided only from the first of these, the March 2020 data cut, after a median of 20.0 months of follow up for lorlatinib. So no additional data was available on overall survival since NICE considered this topic previously (NICE technology appraisal guidance 909 [TA909]). The company explained that this was because

overall survival analyses are event driven, and too few events had occurred to trigger further analyses. Evidence from the March 2020 cut suggested that lorlatinib reduced the risk of death compared with crizotinib, but the difference was not statistically significant (HR 0.72, 95% CI 0.41 to 1.25), and the Kaplan–Meier curves were overlapping. Median overall survival was not estimable in either treatment arm. The EAG highlighted that the data on overall survival from CROWN was immature because of the limited number of deaths. The company cited clinical advice that suggested the observed progression-free survival benefit would translate into longer overall survival. The EAG agreed this was plausible, but said no robust conclusions could be drawn from CROWN about overall survival. The company explained that further cuts are planned at 70% and 100% of overall survival events, and that CROWN is estimated to finish by December 2028. But the company could not estimate when the analysis at 70% of overall survival was likely to occur. The committee was disappointed that the company had decided to not amend the study protocol to allow for earlier analyses of overall survival. The committee recalled its discussions from section 3.5 that second-line treatments may have confounded the overall survival data from CROWN. The committee noted that lorlatinib did not show an overall survival benefit compared with crizotinib in the March 2020 data cut. And, with no further data cuts, there was no evidence that the progression-free survival benefit would translate into overall survival benefit. The committee further noted that crizotinib is not the relevant comparator for this appraisal, and that in other trials, alectinib has been shown to have a statistically significant overall survival benefit over crizotinib. The committee concluded that the overall survival data was immature and may be biased by treatments given after disease progression. So, it was unclear if lorlatinib extends survival compared with crizotinib.

Network meta-analysis

3.9 Because the comparator in CROWN was not relevant to NHS clinical practice, the company did a Bayesian network meta-analysis (NMA) to compare first-line lorlatinib with alectinib and brigatinib. The company

identified 4 trials relevant to the decision problem: CROWN (lorlatinib), ALEX and ALESIA (alectinib), and ALTA-1L (brigatinib). All trials used crizotinib as the comparator. The EAG agreed that the selection of trials was appropriate. Results of the NMA suggested that lorlatinib was associated with benefits in progression-free survival (both BICR- and investigator-assessed) and intracranial progression compared with alectinib and brigatinib. Crossover-adjusted results from the NMA suggested that lorlatinib was associated with a shorter overall survival than either alectinib or brigatinib, but this difference was not statistically significant. Similar to the issues with CROWN discussed in section 3.5, the EAG noted that the treatment sequences in the comparator trials did not represent current NHS practice. Only a small proportion (up to 5%) of people continued treatment after progression with alectinib, brigatinib or crizotinib, and only a minority (up to 30%) had lorlatinib as a second-line treatment after progression on alectinib, brigatinib or crizotinib. The EAG reasoned that the lack of second-line lorlatinib use in the crizotinib arm of CROWN, and in both arms of the comparator trials, could have resulted in lower overall survival than would be expected in the NHS. In addition, the EAG cautioned that the proportional hazards assumption was likely violated for CROWN, ALEX and ALTA-1L, which may have invalidated the derived hazard ratios for progression-free survival. These issues, in addition to the immaturity of the CROWN overall survival data (see section 3.8), meant that the EAG thought the overall survival results from the NMA were very uncertain. It said that no definitive conclusions could be drawn from the analysis and that there was no evidence to support an overall survival benefit for lorlatinib over alectinib or brigatinib. The committee concluded that the overall survival results of the NMA were very uncertain because of the treatment sequence issues in all trials, violation of the proportional hazards assumption, and the immaturity of the overall survival data from CROWN.

Economic model

Model structure

3.10 The company used a 3-state model to evaluate the cost effectiveness of lorlatinib. The 3 mutually exclusive health states were progression free, progressed disease, and death, the absorbing state. The EAG noted that the company's 3-state structure may have been unable to account fully for the impact of second-line treatments. To address this, the EAG suggested a 4-state structure, in which the progressed disease health state would be split into progression after first-line treatment and progression after second-line treatment. The EAG proposed that this 4-state structure would better differentiate the costs and benefits of second-line lorlatinib compared with other second-line treatments. It would also impose a structural relationship between a person's health state and how long they had treatment, which was a key influencer of cost. The committee agreed with the EAG that a 4-state structure would better reflect NHS treatment sequences. It concluded that it would need to consider a model with a 4-state structure to inform decision making. So, the committee asked the company to provide a 4-state model.

Progression-free survival extrapolation

3.11 The company's model used a time horizon of 30 years, which exceeded the length of the trials. So, to extrapolate beyond the end of the trials, the company modelled progression-free survival for lorlatinib by fitting parametric curves to the 5-year investigator-assessed progression-free survival data from CROWN. The company selected a 3-year piecewise Weibull curve based on statistical goodness-of-fit, visual inspection, and clinical advice. The company also fitted parametric curves to the crizotinib data on progression-free survival from CROWN. For consistency with the lorlatinib extrapolation, the company chose a Weibull curve, extrapolated over the entire time horizon. Then, the company applied the hazard ratios for progression-free survival from the NMA to the crizotinib curve to model progression-free survival for alectinib and brigatinib.

The EAG noted that most of the company's survival projections led to clinically implausible long-term predictions. This included the company's preferred 36-month piecewise Weibull model, which predicted that more

than 10% of people would remain progression free and alive at 20 years. The only extrapolation curve that the EAG considered was a good fit to the observed data and produced clinically plausible predictions was the 3-year piecewise Gompertz model. The EAG acknowledged that this model provided the most conservative predictions, but given the high uncertainty surrounding long-term survival, it considered that this was the most reasonable approach. The EAG also questioned the company's approach to extrapolating crizotinib. The EAG thought it was inconsistent to use a piecewise approach for lorlatinib and at the same time a full extrapolation for crizotinib. Further, the Weibull curve had the worst fit to the crizotinib data of all the models, and it was the most pessimistic curve, contributing to the model underpredicting progression-free survival for alectinib and brigatinib compared with the respective trials. For these reasons, and those detailed in section 3.12, the EAG instead used lorlatinib as the reference curve to which the EAG applied the hazard ratios for alectinib and brigatinib. The committee concluded that the EAG's approach to progression-free survival extrapolation was more appropriate than the company's approach.

Additional sources used to model post-progression survival

3.12 Given the immaturity of the CROWN overall survival data, the company used supplementary data from Study 1001 in its analyses. This was a single-arm, open-label, phase 1 and 2 trial of lorlatinib. There were several patient cohorts in Study 1001. Of interest in this evaluation, the EXP1 cohort included 30 people who had lorlatinib as a first-line treatment and were followed up for a median of 73 months. The company combined the data from the EXP1 cohort with the CROWN data to inform long-term overall survival estimations for the lorlatinib arm. But, the EAG explained that the design of Study 1001, and its differences to CROWN, meant that the value of pooling the results of both studies was unclear. The company also used 2 external data sources to model survival after cancer progression for alectinib and brigatinib. Cohorts 3B to 5 from Study 1001 included people who had lorlatinib as a second-line treatment after progression on 1 or more ALK TKIs. This was used to model post-

progression survival for people who had lorlatinib as a second-line treatment after progression on alectinib or brigatinib in the comparator arm. To inform post-progression survival outcomes for people having second-line chemotherapy after progression on first-line alectinib or brigatinib, the company used data from a retrospective analysis of 2 single-arm, open-label, phase 1 and 2 trials, PROFILE 1001 and 1005. The EAG explained that the issues with CROWN necessitated using external data to inform survival predictions, but that there were multiple limitations with both Study 1001 and PROFILE1001 and 1005. It noted that because they were single-arm studies, the data were not randomised. It also noted that the treatments used in the studies did not align with NHS practice. The committee accepted that the company had attempted to address the immaturity of the CROWN overall survival data by using imperfect external data. But, the committee concluded that this approach introduced considerable uncertainty, which would be taken into account in its decision making.

Modelling approach for post-progression survival

3.13 The company applied different modelling approaches in each arm to model survival after progression. In the lorlatinib arm, the company used a partitioned survival model, where estimates of survival over time determine state occupancy. The company determined the proportion of people in the progression-free state by fitting curves to the progression-free survival data from CROWN. Overall survival was determined by fitting curves to pooled overall survival data from CROWN and Study 1001 EXP1, with the death state occupancy calculated as 1 minus overall survival. Occupancy of the progressed disease health state was then calculated as the difference between the proportion of people in the death state and the proportion in the progression-free state. In the comparator arm, to address issues with treatment sequences in the comparator trials, the company used a state-transition approach to model post-progression survival. A state-transition approach defines explicit transition probabilities that quantify the risk of moving from 1 health state to another in each model cycle. Importantly, this approach used data from Study 1001 and

PROFILE1001 and 1005 to estimate post-progression survival in the model.

The EAG noted that using different modelling approaches in the lorlatinib and comparator arms was inconsistent. It explained that, while both approaches are commonly used and widely accepted, partitioned survival models and state-transition models use fundamentally different assumptions and produce different results. The EAG summarised that the main advantage of a partitioned survival model was that the treatment comparisons were based on randomised evidence. But, given that the CROWN data were immature and had limited generalisability to the NHS, the advantages of a partitional survival model may have been limited. The EAG explained that the main advantage of the state-transition model was that there was greater emphasis on progression-free survival, which had more mature evidence, and that it permitted use of external data. The main disadvantage was that modelled overall survival would not be based on randomised evidence, and that the identified external studies to inform post-progression survival did not fully reflect the modelled pathway. The EAG concluded that, on balance, the state-transition approach would better suit the available data. So, in the EAG's model, it used a state-transition model in both the lorlatinib and comparator arm, with post-progression survival for lorlatinib informed by PROFILE1001 and 1005. The committee agreed that the immature CROWN overall survival data meant that a partitioned survival model was less appropriate. It concluded that a consistent approach should be used across the model. So, it decided that a state-transition approach in both arms of the model would be its preferred approach.

Time on treatment and treatment after progression

3.14 Time on treatment had a substantial impact on costs. The company modelled time on treatment for the comparators using data from the respective trials. The company observed that the time-on-treatment data from the pivotal alectinib and brigatinib trials overlayed progression-free survival almost exactly. So, the company model assumed that people

having alectinib and brigatinib would have treatment until progression. For lorlatinib, the company noted that in CROWN, time on treatment was on average shorter than progression-free survival. This was despite the treatment protocol permitting treatment after progression. The company explained that this was because of the long treatment duration observed with lorlatinib – twice or longer than that observed with alectinib or brigatinib. So, people on lorlatinib had a higher chance of stopping lorlatinib before progression, for reasons such as the higher rate of adverse events. The EAG disagreed with the company's assumptions about time on treatment, noting that the company's model predicted an implausible 12-month gap between stopping treatment and cancer progression. The EAG received clinical advice that suggested people in the NHS would continue treatment for longer than observed in CROWN. This was because CROWN permitted second-line treatment with ALK TKIs, which is not usual practice in the NHS (see section 3.2), where the sole second-line treatment available after lorlatinib would be chemotherapy. The EAG also noted that healthcare professionals now have more experience of managing lorlatinib's adverse effects (which would translate to longer time on treatment) and are more aware of its benefits. Considering these factors, the EAG thought that people in the NHS would prefer to stay on lorlatinib for as long as possible. The EAG also cited TA909, in which the company's base case included 5.7 months of treatment after progression for 75.6% of people on lorlatinib. This was based on an analysis of treatment after progression in Study 1001. The company's base case in TA909 also included 3 months of treatment after progression with alectinib and brigatinib. But, the EAG reasoned that treatment after progression would be less likely with alectinib and brigatinib because people having these treatments have the option of second-line lorlatinib, and may prefer to switch upon progression. So, the EAG's base case assumed that time on treatment would be equal to progression-free survival for all treatments in the model but also included 5.7 months of treatment after progression for 75.6% of people on lorlatinib.

The clinical experts explained that treatment after progression would be expected for many people on ALK TKIs, usually for around 3 to 6 months. The CDF lead confirmed that this aligned with how alectinib and brigatinib are commissioned. The committee understood the company's position that the higher rate of adverse events with lorlatinib may mean people stop treatment before progression. So, it thought that there was uncertainty in the modelling of time on treatment and treatment after progression. The committee also acknowledged that any treatment after progression may lead to better clinical outcomes. But, it highlighted that this would not be captured in the model's estimates of clinical effectiveness, and so further contributed to uncertainty. The committee acknowledged the importance of using data on costs and effectiveness from the same source, if possible. The committee considered that neither the company's nor the EAG's modelling approaches were appropriate. Instead, because of the uncertainties around treatment after progression, the committee thought that it was likely to be most appropriate to assume equal treatment after progression for each treatment. The committee recalled the preferred assumptions of NICE's technology appraisal guidance 628, in which 3.5 months of treatment after progression was assumed for lorlatinib. The committee therefore asked the company to update its model to assume that, for all treatments, time on treatment was equal to PFS with 3.5 months of treatment after progression for 75.6% of people.

Relative treatment effect waning

3.15 The company acknowledged that the long-term treatment effect was uncertain for all treatments in the model. To account for this, it assumed that the benefit of treatment waned after 10 years, where the hazard rates for all treatments waned to the hazard rates of crizotinib. The EAG agreed that waning should be implemented, but disagreed with the company's method. As noted in section 3.11, the lorlatinib estimations of progression-free survival without waning were very optimistic. Further, progression-free survival after 10 years depended on the choice of crizotinib

extrapolation. The EAG explained that different crizotinib curves led to very different lorlatinib survival estimates after 10 years, and thought that the company's choice of the Weibull model for crizotinib ensured that lorlatinib progression-free survival was more closely aligned with clinical expectations. The EAG commented that the function of waning should be to reflect uncertainty in the durability of the treatment effect, not as a correction to otherwise clinically implausible extrapolations. To remove crizotinib entirely from the model, the EAG chose to use lorlatinib as the reference arm. The EAG also chose to apply waning to alectinib hazards after 10 years. The committee concluded that it preferred the EAG's approach to the company's approach to model waning of the relative treatment effect.

Utility values

3.16 Health-related quality-of-life data was collected in CROWN. The company used a mixed-effects regression model and treatment-specific utility values to generate utility values for the progression-free and progressed disease health states. In the progression-free health state, the company generated separate utility values based on whether people were on or off lorlatinib. Progression-free utility values for alectinib and brigatinib were sourced from their respective NICE technology evaluations (TA536 [alectinib] and TA670 [brigatinib]). As in TA909, despite having collected them, the company did not use the post-progression utility values from CROWN; these showed only a small decrease from the pre-progression utility values, and the company said they lacked face validity. Instead, it sourced post-progression utility values from TA670. To account for CNS progression, the company applied a multiplier derived from a literature source to the progressed disease utility. The company applied the resulting disutility in the model for 24 months (in addition to a one-off cost) to people who experienced CNS disease progression.

The EAG disagreed with using treatment-specific utility values in the progression-free state, noting that this approach was inconsistent with that taken in TA909, TA536 and TA670. The EAG also noted that the

progression-free utility derived for lorlatinib from CROWN was too high because it was similar to that expected in the general population. The EAG also disagreed with separating progression-free utility values into on or off treatment. Stopping treatment while still in the progression-free state can be done to manage adverse events. So, applying separate on- or off-treatment values, and disutilities for specific adverse events, may have double counted the effect of adverse events on quality of life. The EAG base case therefore applied the progression-free utility value from TA670 to the progression-free health state, irrespective of type of treatment, or whether on- or off-treatment. In the progressed disease health state, the EAG agreed with using the values from TA670, given the issues with the CROWN data. But the EAG thought that separate on- or off-treatment utility values in the progressed disease state would be appropriate. This was because using second-line lorlatinib may confer a utility benefit. So, the EAG base case included separate on- or off-treatment utility values in the progressed-disease health state, with the progressed on-treatment value approximately midway between the progression-free and progressed off-treatment values. The committee preferred the EAG's approach, concluding that the EAG's amendments to the company's utility values were appropriate.

Implementation of lorlatinib discount

3.17 Lorlatinib as a second-line treatment is available to the NHS with a patient access scheme (PAS) discount ('current PAS'). In this evaluation, the company offered to increase the PAS discount for lorlatinib (that is, a lower price) if NICE were to recommend lorlatinib as a first-line treatment ('new PAS'). If NICE were to recommend first-line lorlatinib, this new PAS would apply to both first-line and second-line lorlatinib use. The company explained that the comparator arm represented current treatment in the NHS. So, it considered that the current PAS should apply in the comparator arm. It said the new PAS should only apply in the intervention arm, because this reflected the cost for lorlatinib if it were recommended for first-line use. The EAG argued that it was inappropriate to introduce a temporal 'before versus after' aspect to the decision problem. Instead, the

decision should reflect a single point in time. The EAG argued that the company approach would render the estimates of cost effectiveness invalid upon positive guidance, because as soon as positive guidance were published, the new PAS would apply to second-line lorlatinib, and the comparator arm would become cheaper. It considered that the new PAS should be applied to both the intervention and the comparator arm. The NICE technical team noted that NICE's manual on health technology evaluations did not specify the approach that the committee should take in these circumstances. The NICE technical team also acknowledged that there were potential limitations associated with both approaches. But it advised that applying the new PAS in the intervention arm only appropriately reflected the decision problem. Using the current PAS in the comparator arm reflected the cost of current care, and what would be the case if first-line lorlatinib were not recommended, and hence represented the displaced scenario. The committee noted that it would be helpful if NICE formally published advice on this issue for when it arises in future. Taking into account NICE's advice and the specific circumstances affecting the PAS in this appraisal, the committee concluded that the company's approach, in which the new PAS is applied to the intervention arm and the current PAS to the comparator arm, was appropriate for decision making.

Severity

3.18 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The estimates did not meet the criteria for applying a severity weight.

Cost-effectiveness estimates

Acceptable ICER

3.19 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- treatment sequences used in CROWN did not represent current NHS practice (section 3.5)
- overall survival data from CROWN was immature and that new data, beyond that considered in TA909, was not available (section 3.8)
- trials of the comparators were biased by treatment sequences that would not be used in the NHS (section 3.9)
- results of the NMA were uncertain because of the issues with treatment sequences in all trials, the immaturity of the overall survival data from CROWN, and the possible violations of the proportional hazards assumption (section 3.9)
- the 3-state model structure may have been too simplistic to differentiate the benefits of second-line treatment (section 3.10)
- non-randomised external sources were used to model post-progression survival (Study 1001, and PROFILE 1001 and 1005) (section 3.12)
- treatment after progression assumptions added to the cost of each treatment but did not add to the efficacy (section 3.14).

So, the committee concluded that an acceptable ICER would be towards the lower end of the range that NICE usually considers to be a cost-effective use of NHS resources.

Committee's preferred assumptions

3.20 Because of confidential commercial arrangements for lorlatinib and the comparators, the exact cost-effectiveness estimates are confidential and cannot be reported here. The committee's preferred assumptions were:

- Lorlatinib should be used as the reference arm to which hazard ratios are applied to model progression-free survival for the comparators (section 3.11).
- The 36-month piecewise Gompertz curve should be used to extrapolate lorlatinib progression-free survival (section 3.11).
- The model should use a state-transition approach for post-progression survival in both the lorlatinib and comparator arms (section 3.13).
- Time on treatment should, for all treatments in the model, be equal to progression-free survival with treatment after progression of 3.5 months for 75.6% people (section 3.14).
- Progression-free survival hazard rates should be waned to the hazard rates of alectinib after 10 years (section 3.15).
- Health state utility values should align with the EAG's approach (section 3.16).
- The new conditional PAS discount for lorlatinib should apply only to the intervention arm of the model (section 3.17).

The committee was not presented with a scenario that included its preferred assumptions about treatment after progression or a 4-state model structure. But it did have a scenario that included all the other preferred assumptions. The ICER produced by this scenario was above what the committee considered a cost-effective use of NHS resources (see section 3.19).

Taking into account the available cost-effectiveness estimates, and noting its preferred assumptions for which estimates were not available, the committee considered that it did not have evidence to conclude that lorlatinib was a cost-effective option. So, lorlatinib could not be

recommended for routine use. The committee asked the company to present additional information to inform decision making:

- a 4-state model structure that differentiates first progression from second progression (section 3.10).
- an updated base case with the committee's preferred assumptions, including that on treatment beyond progression (section 3.14).

Managed access

3.21 Having concluded that lorlatinib should not be used routinely in the NHS, the committee then considered if it could be used during a managed access period. The committee heard from the CDF lead that because many people would continue to be offered alectinib and brigatinib even if NICE were to recommend lorlatinib, the NHS would generate observational data on both the intervention and comparators. The committee noted that a period of managed access may allow for the collection of more mature overall survival data from CROWN. But, the company could not state when it expected to do the planned analysis for 70% (or 100%) data maturity. Further, the company had not presented the committee with a managed access proposal, so it could not assess whether managed access would help resolve the remaining clinical uncertainties. The committee requested that the company consider making a managed access proposal when responding to consultation.

Other factors

Equality

3.22 The company stated that some underserved communities and ethnic or socioeconomic groups are diagnosed later and have worse outcomes, and that this likely includes those with ALK-positive advanced NSCLC. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not a potential equalities issue that it could address. The patient organisations also noted that there is inequitable access to lorlatinib across the UK, as it is

available in Scotland. It noted that geographic location is not a protected characteristic. The committee concluded that the recommendations would not have a different effect on people protected by equality legislation than on the wider population.

Uncaptured benefits

3.23 The committee considered whether there were any uncaptured benefits of lorlatinib. It did not identify additional benefits of lorlatinib not captured in the economic modelling. So, the committee concluded that the modelling accounted for the benefits of lorlatinib.

Conclusion

Recommendation

3.24 The committee concluded that lorlatinib should not be used for untreated ALK-positive advanced NSCLC in adults. It noted the high degree of uncertainty in the clinical evidence and economic modelling for lorlatinib, and the lack of evidence that lorlatinib prolongs life. When most of the committee's preferred assumptions were applied, the ICERs for lorlatinib were substantially above the level it considered to be a cost-effective use of NHS resources, and the committee noted that analyses based on its preferred assumptions for duration of treatment and a 4-state model were not available. It requested further evidence on those assumptions to inform decision making.

4 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Amanda Adler

Interim vice chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Tom Palmer

Technical lead

Alex Sampson

Technical adviser

Kate Moore

Project manager

Ian Watson

Associate director

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