

Lorlatinib for ALK-positive advanced non-small-cell lung cancer that has not been 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.

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Contents

1 Recommendation.....	4
What this means in practice.....	4
Why the committee made these recommendations.....	4
2 Information about lorlatinib	6
Marketing authorisation indication	6
Dosage in the marketing authorisation	6
Price.....	6
Carbon Reduction Plan	6
3 Committee discussion	7
The condition.....	7
Clinical management.....	7
Clinical effectiveness.....	10
Economic model.....	14
Severity	25
Cost-effectiveness estimates.....	26
Other factors	28
Conclusion	29
4 Implementation.....	30
5 Evaluation committee members and NICE project team.....	31
Evaluation committee members	31
Chairs	31
NICE project team	31

This guidance replaces TA909.

1 Recommendation

- 1.1 Lorlatinib can be used as an option for ALK-positive advanced non-small-cell lung cancer in adults who have not had an ALK inhibitor. Lorlatinib can only be used if the company provides it according to the [commercial arrangement](#).
- 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 must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Lorlatinib must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that lorlatinib provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced [tools and resources to support the implementation of this guidance](#).

Why the committee made these recommendations

This evaluation reviews the evidence for lorlatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor (NICE technology appraisal guidance 909). This does not include everyone who it is licensed for. 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 first-line treatment in the NHS for ALK-positive advanced non-small-cell lung cancer is alectinib or brigatinib. Crizotinib is also available but is 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 people live longer when they have lorlatinib compared with alectinib and brigatinib as a first-line treatment option.

Because there are uncertainties in the clinical evidence, the cost-effectiveness analyses are also uncertain. But, when considering all the available evidence and economic analyses, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, lorlatinib can be used.

2 Information about lorlatinib

Marketing authorisation indication

- 2.1 Lorlatinib (Lorviqua, Pfizer) 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 July 2025).
- 2.4 The company has a [commercial arrangement](#). This makes lorlatinib available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

- 2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on [Pfizer's website \(PDF only\)](#).

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 a later diagnosis than 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 normally must 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 first-line treatment: alectinib, brigatinib, ceritinib and crizotinib. The clinical experts explained that crizotinib and ceritinib are rarely used in the NHS since alectinib and brigatinib, which are 'second-generation' ALK TKIs, became available. 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 CDF lead said that about twice as many people have alectinib than have brigatinib. 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](#); from here, TA628). But the clinical experts and the CDF lead agreed that fewer than half of people in the NHS who have alectinib or brigatinib at first line go on to have second-line treatment with lorlatinib. Chemotherapy is usually used as the last line of treatment because of side effects and toxicity. The committee concluded that current NHS practice for untreated ALK-positive advanced NSCLC is alectinib or brigatinib at first line, followed by lorlatinib or chemotherapy at second line, then chemotherapy or best supportive care at third line. In this evaluation, the company positioned lorlatinib as a first-line treatment. So, the committee concluded that alectinib and brigatinib were the relevant comparators for this appraisal; crizotinib and ceritinib were not considered comparators because they are rarely used in the NHS. The committee considered that the relative use of alectinib and brigatinib should be reflected in the modelling of the comparators, and that the proportion of people in the NHS who use each treatment should be used to weight the cost-effectiveness estimates.

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 from those of alectinib and brigatinib. They described adverse effects including weight gain, neuropathy and mood disturbance. In the same way that lorlatinib may be more effective against CNS metastases, it also has greater potential for causing CNS-related 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, although adverse effects can substantially affect quality of life, they are often manageable with supportive care or by dose reductions. The committee cautioned that the CNS adverse effects from lorlatinib may be less important for

people having second-line treatment than people having first-line treatment, because people having second-line treatment typically have worse health and may already be experiencing adverse effects from CNS metastases. The committee further noted that, although dose reductions may effectively manage lorlatinib's adverse effects, it was uncertain how this would influence efficacy. The committee was also concerned that managing adverse events based on prior experience may mean that there is varied care across NHS centres.

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 have first-line lorlatinib, they could not have a second-line ALK TKI (including lorlatinib again). This is because alectinib and brigatinib do not have a marketing authorisation for second-line treatment after first-line lorlatinib. The clinical experts 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 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 people benefit most from the technology, and
- whether there are subgroups of people for whom the effectiveness evidence suggests differential cost effectiveness or cost savings.

The committee considered whether, 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 because the marketing authorisation for alectinib does not permit second-line treatment after lorlatinib. 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 option (unless, in rare cases, crizotinib was the first-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, treatment after progression was allowed if a person was still experiencing clinical

benefit, but only 7% of people continued treatment. Committee recalled that alectinib and brigatinib do not have a marketing authorisation in the UK for second-line treatment after first-line lorlatinib. So, the treatment sequences in CROWN do not align with NHS practice. The EAG thought that overall survival in CROWN could be confounded, that is overall survival in the lorlatinib arm may have been increased by second-line use of alectinib or brigatinib, which would not typically be available for people 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 said 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 for overall survival aimed to account for this by using data from other sources. The company also highlighted that these treatment sequence issues were present in trials of the comparators. The committee noted that treatment sequences are typically determined by the licences given to new medicines, and by clinical evidence on best practices. It also noted that the treatment sequences used in clinical practice are subject to change as more treatments are licensed and new evidence becomes available. The committee decided that the comparator, the lack of treatment after progression and the second-line treatments used 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 uncertainty 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 (43% of the total 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, BICR-assessed progression-free survival was significantly longer for lorlatinib than crizotinib (hazard ratio [HR]

0.27, 95% confidence interval [CI] 0.18 to 0.39). BICR was 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, investigator-assessed progression-free survival was significantly longer for lorlatinib 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 than for 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 planned 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 a further data cut is planned at 70% of overall survival events, and that CROWN is estimated to finish by December 2028. But the company could not estimate when 70% of the 198 overall survival events needed for the next analysis will happen. 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 an 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 compared with crizotinib. The committee concluded that it was unclear if lorlatinib extends overall survival compared with crizotinib because the overall survival data was immature and may be biased by treatments given after disease progression.

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 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 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, and 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 highly 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 In its original submission, 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 first progressed disease and second progressed disease. 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, so requested that the company provide a 4-state model structure. For the second meeting, the company updated its model to include the requested first progressed-disease and second progressed-disease health states. The EAG thought that the company had done this appropriately. The committee concluded that the 4-state model better reflected NHS treatment sequences and should be used for decision making.

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 its assessment of 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 alive and progression-free 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, 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.

Relative treatment effect waning

3.12 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. And 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 used lorlatinib as the reference arm. The EAG also applied 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.

Modelling approach for post-progression survival

3.13 In the original 3-health-state model (see [section 3.10](#)), 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, in which estimates of survival over time determined 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 CROWN overall survival data pooled with an external source (Study 1001, see [section 3.14](#)), with the death state occupancy calculated as 1 minus overall survival. 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 one health state to another in each model cycle. Importantly, this approach used data from 2 external sources (Study 1001 and PROFILE 1001 and 1005; see [section 3.14](#)) to estimate post-progression survival in the model.

The EAG noted that using different modelling approaches in the lorlatinib and comparator arms was inconsistent. 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 was immature and had limited generalisability to the NHS, the advantages of a partitioned survival model may have been limited. The EAG explained that the main advantages of the state-transition model were greater emphasis on progression-free survival, which had more mature evidence, and that it allowed the use of external data. The main disadvantages were 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 said that, on balance, the state-transition approach would better suit the available data. So, the EAG used a state-transition approach in both the lorlatinib and comparator arm in its model. The committee agreed that a consistent approach should be used across the model. At the second meeting, the company applied the state-transition approach to both arms of the new 4-state model. The committee concluded that the company's updated modelling approach was appropriate for decision making.

Additional sources used for modelling post-progression health states

3.14 Given the immaturity of the CROWN overall survival data, the company used supplementary data sources in its analyses. In the original 3-state model, data from Study 1001 was combined with the CROWN data to inform long-term overall survival estimates for the lorlatinib arm. Study 1001 was a single-arm, open-label, phase 1 and 2 trial of lorlatinib. 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 PROFILE 1001 and 1005: 2 single-arm, open-label, phase 1 and 2 trials. The EAG explained that there were multiple limitations with both Study 1001 and PROFILE 1001 and 1005. It noted that because they were single-arm studies, the data was not randomised. It also noted that the treatments used in the studies did not align with NHS practice.

For the second meeting, the company used some different evidence sources to inform the new 4-state model. To model time to second progression for people who had chemotherapy as a second-line treatment after lorlatinib, alectinib or brigatinib, the company used data from CROWN. To model time to second progression for people who had lorlatinib as a second-line treatment after either alectinib or brigatinib, the company used data from Study 1027. Study 1027 was a phase 4, single-arm trial of 71 people who had lorlatinib after 1 previous ALK TKI. Most of the people in Study 1027 had alectinib as a first-line treatment, so the company thought that it better reflected NHS treatment sequences than the data from Study 1001. To model post-second progression survival, the company used data from TA628. For people who had lorlatinib, alectinib or brigatinib at first line, chemotherapy at second line and best supportive care at third line, the company used the second-line chemotherapy post-progression survival estimates from TA628. For people who had alectinib or brigatinib at first line, lorlatinib at second line and chemotherapy at third line, the company used post-progression survival from people in Study 1001. Overall survival was derived from the sum of progression-free survival, time to second progression and post-second progression survival.

The EAG agreed that using time to second progression data from CROWN and Study 1027 was appropriate, but disagreed with the company's extrapolation of Study 1027 (see [section 3.15](#)). It noted that the new structure and sources meant

that the suboptimal data from PROFILE 1001 and 1005 was no longer used in the model. Overall, the EAG thought that the new model better reflected NHS treatment sequences and reduced some of the uncertainty. But, it repeated its concerns that the model used several external non-randomised sources to estimate overall survival. It highlighted that each of the evidence sources came from different patient populations, under different study conditions, and this meant there was inherent uncertainty in combining the results of each. The committee accepted that the company had attempted to address the immaturity of the CROWN overall survival data by using additional data sources. But, the committee concluded that this approach introduced uncertainty, which would be taken into account in its decision making.

Time to second progression extrapolation

- 3.15 In the company's new 4-state model, data from Study 1027 was used to estimate time to second progression for people who had alectinib or brigatinib at first line followed by lorlatinib at second line (see [section 3.14](#)). The company selected the exponential curve for its base case. The EAG noted that using the exponential curve implied that time to second progression was shorter with second-line lorlatinib than with second-line chemotherapy, which it thought was not clinically plausible. Instead, the EAG preferred the gamma extrapolation for its base case. The committee concluded that the gamma extrapolation was more appropriate to extrapolate time to second progression with lorlatinib.

Proportion starting second-line lorlatinib

- 3.16 In its submission, the company assumed that 86.8% of people who had alectinib or brigatinib at first line, and survived their first cancer progression, would then have lorlatinib at second line. Clinical advice to the EAG had suggested that this was appropriate. At the first meeting, the CDF lead noted that NHS England figures showed that only approximately 40% people who had alectinib or brigatinib at first line started second line lorlatinib. The CDF lead reasoned that this lower proportion reflected the negative effect of ALK-positive advanced NSCLC on a person's health. The clinical experts also explained that suboptimal NHS care may have an impact on second-line lorlatinib uptake. To account for

lower uptake, for the second meeting, the EAG updated its base case so that 40% of people who had first-line alectinib or brigatinib went on to have second-line lorlatinib. Also at the second meeting, the National Speciality Advisor for Cancer Drugs presented data from the entire 4.5-year period that all 3 treatments had been available in the NHS. This data showed that about 42.2% of people who had alectinib or brigatinib at first line then had lorlatinib at second line. The company said that the relatively low uptake of lorlatinib may be because of a time lag in people moving to second-line treatment, and that this percentage would be expected to increase over time. The National Speciality Advisor for Cancer Drugs confirmed that the 42.2% was in alignment with clinical advice that they had received, and was stable over time. So, the committee concluded that the model should assume that 42.2% of people who have alectinib or brigatinib first line should start lorlatinib second line.

Treatment after progression

- 3.17 The company's original model assumed that people having alectinib and brigatinib would have treatment until (but not after) progression. This was because the time-on-treatment data from the pivotal alectinib and brigatinib trials overlaid progression-free survival almost exactly. 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 to be continued after progression. The company said the higher rate of adverse events with lorlatinib may mean people stop treatment before progression. The EAG received clinical advice that suggested that 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 noted that the company's model predicted an implausible 12-month gap between stopping treatment and cancer progression. 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. The clinical experts explained that treatment continuation after progression would be expected for many people on ALK TKIs. They said treatment would continue until there was a loss of clinical benefit. They noted

that clinicians aim to maximise the benefit gained from each treatment before switching, while treating any specific sites of progression with radiotherapy. The CDF lead confirmed that this aligned with how alectinib, lorlatinib and brigatinib are commissioned in the NHS. The committee noted that treatment being continued after progression was included in previous appraisals for ALK TKIs (such as TA909 and TA628). They concluded that alectinib, brigatinib and lorlatinib are regularly continued after progression in the NHS.

Treatment after progression for first-line ALK TKI treatments

3.18 Having concluded that ALK TKIs are continued after progression in the NHS (see [section 3.17](#)), time on treatment was considered. To align with the committee's preferences from the first committee meeting, the updated company model assumed that 75.6% of people taking an ALK TKI as first-line treatment continued treatment for 3.5 months after progression. This was based on figures used in previous NICE appraisals (TA909 and TA628). During consultation, the EAG cited clinical advice that suggested that treatment after progression would be longer and more frequent for lorlatinib than for alectinib or brigatinib. This is because lorlatinib is available as a second-line treatment for people who have alectinib or brigatinib, so people would prefer to start second-line lorlatinib as soon as possible. But people who have first-line lorlatinib do not have the option of a second-line ALK TKI, so they would continue treatment with lorlatinib to avoid the toxicity associated with chemotherapy. The EAG also cited TA909, in which the committee's preference was that treatment after progression was longer for lorlatinib (5.7 months) than for the comparators (3 months). So, the EAG's updated base case included 5.7 months of treatment after progression for 75.6% of people having first-line lorlatinib and 3.5 months of treatment after progression for 25% of people having first-line alectinib or brigatinib. The EAG also provided a scenario in which 54.2% of people having first-line alectinib or brigatinib continued treatment after progression. This figure was an average of the company (75.6%) and EAG (25%) base-case assumptions, weighted by the proportion of people having each second-line treatment. This was to reflect the smaller proportion of people who were modelled to move to second-line lorlatinib in the EAG's updated base case (see [section 3.16](#)), reasoning that people may be more likely to continue on alectinib or brigatinib if they are not moving to lorlatinib.

The committee noted that time on treatment had a substantial impact on costs. It thought that it was plausible that more people would continue treatment after progression with lorlatinib than with alectinib or brigatinib. It noted the company's concerns that this was a conservative assumption for lorlatinib, given that the CROWN trial had shown that time on treatment was consistently lower than progression-free survival. But it recalled the clinical expert advice that there is increasing NHS experience with managing toxicity caused by lorlatinib. On balance, the committee concluded that the TA909 assumption of 5.7 months of treatment after progression with lorlatinib for 75.6% of people was most likely in the NHS context. For the comparators, the committee thought that the EAG base case 25% proportion was likely too low, especially when considering the lower second-line lorlatinib uptake figures from the CDF lead (section 3.16). So, the committee concluded that the EAG's scenario of 3.5 months of continued treatment after progression for 54.2% of people was most appropriate. The committee also acknowledged that any treatment after progression may lead to better clinical outcomes. But, the model only captured the costs of treatment after progression and not any clinical benefits. It noted that this further contributed to uncertainty.

Treatment after progression for second-line lorlatinib

- 3.19 The committee noted that neither the company's nor the EAG's model contained continued treatment after progression for people having second-line lorlatinib. Alectinib and brigatinib are not available as second-line treatments for this population on the NHS. The clinical experts said that treatment after progression would typically be for a shorter period when using second-line lorlatinib than when using first-line lorlatinib. This is because of a lower expected benefit of continued treatment with second-line lorlatinib, more aggressive resistance and greater adverse effects in a patient population with poorer health. The committee recalled TA628, in which 3.5 months of continued treatment after progression was assumed for second-line lorlatinib. So, the committee concluded that the model should include continued treatment after progression of 3.5 months for 75.6% of people who have second-line lorlatinib.

Utility values

3.20 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 ([alectinib for untreated ALK-positive advanced non-small-cell lung cancer \[TA536\]](#) and [brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor \[TA670\]](#)). 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 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. It also disagreed with separating progression-free utility values into on or off treatment. Treatment can be stopped while still in the progression-free state 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's 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 noted that the additional adverse effects associated with lorlatinib at first line would be unlikely to confer a utility benefit over alectinib or brigatinib. The committee concluded that the EAG's approach was the better of the 2 presented.

For the second meeting, the company used a 4-state model structure (see [section 3.10](#)). This included a new health state for second progressed disease. The company sourced a value of 0.46 from TA628 and applied it to all people in the second progressed-disease health state, regardless of whether they were having treatment. The EAG noted that 0.46 likely underestimated the utility of people in this health state who are having chemotherapy, considering that the company's model predicted that these people would live for more than 1 year. So, it applied the same 0.62 utility that was applied to people in the first progressed-disease health state on chemotherapy. The clinical expert thought that a value between these figures would be more appropriate, citing that while people may appreciate that they are still having treatment, chemotherapy has many adverse effects that impair quality of life. The committee agreed that a value between those presented would be more plausible. It noted that the [Chouaid et al. \(2013\) study](#) from which the 0.46 value was taken also reported the utility of people who had progressed disease after second-line treatment. The committee concluded that this value (0.59) was most clinically plausible and aligned with the clinical advice that it had received, reflecting the average utility over time for people in this health state.

Implementation of lorlatinib discount

- 3.21 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 apply only 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's 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 thought that the new PAS should be applied to both the intervention and the comparator arms. 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. That is, 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 for NICE to formally publish 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 was applied to the intervention arm and the current PAS to the comparator arm, was appropriate for decision making.

Severity

3.22 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 quality-adjusted life years (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

3.23 [NICE's manual on health technology evaluations](#) notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per 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. At the first meeting, 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 new overall survival 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](#))
- the 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 3.14](#))
- continuing treatment after progression assumptions added to the cost of each treatment but did not add to the efficacy ([section 3.18](#)).

At the second meeting, the committee acknowledged the efforts of the company to address these uncertainties. The committee thought that the new 4-state model had reduced the uncertainty around non-NHS treatment

sequences, and that it used some conservative assumptions. But the committee thought that several uncertainties remained:

- Overall survival data from CROWN was immature and new data, beyond that considered in TA909, was not available ([section 3.8](#)). This created significant uncertainty because the new model predicted a large overall survival benefit for lorlatinib, despite no direct evidence from CROWN to confirm it.
- Non-randomised external sources were used to model time to second progression and post-second progression survival (Study 1001 and 1027; [section 3.14](#)).
- Continuing treatment after progression assumptions captured the expected costs of treatment after progression but not the expected health effects ([section 3.18](#)).

In light of the reduction of some uncertainty, the committee increased the acceptable ICER at which lorlatinib would be considered cost effective. But, it concluded that an acceptable ICER would still 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

3.24 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:

- Using lorlatinib as the reference arm to which hazard ratios are applied to model progression-free survival for the comparators ([section 3.11](#)).
- Using the 36-month piecewise Gompertz curve to extrapolate lorlatinib progression-free survival ([section 3.11](#)).
- Waning the progression-free survival hazard rates to the hazard rates of alectinib after 10 years ([section 3.12](#)).
- Using a state-transition approach for post-progression survival in both the

lorlatinib and comparator arms ([section 3.13](#)).

- Using the gamma curve to extrapolate time to second progression from Study 1027 ([section 3.15](#)).
- Using 42.2% as the proportion of people starting second-line lorlatinib in the model ([section 3.16](#)).
- For all treatments in the model, using time on treatment equal to progression-free survival plus continuing treatment after progression of:
 - lorlatinib first line: 5.7 months for 75.6% of people ([section 3.18](#))
 - lorlatinib second line: 3.5 months for 75.6% of people ([section 3.19](#))
 - alectinib and brigatinib first line: 3.5 months for 54.2% of people ([section 3.18](#)).
- Aligning health-state utility values with the company's updated base case, including a utility value of 0.59 for people in the second progressed-disease health state who are on chemotherapy ([section 3.20](#)).
- Applying the new conditional PAS discount for lorlatinib to only the intervention arm of the model ([section 3.21](#)).
- Weighting the ICER by relative NHS use of alectinib and brigatinib ([section 3.2](#)).

The ICER produced by the committee's preferred assumptions was below its acceptable ICER threshold. The committee decided that it had enough evidence to conclude that lorlatinib was a cost-effective option.

Other factors

Equality

- 3.25 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, because it is available in Scotland. The committee noted that geographic location is not a protected characteristic and it could not address this through its recommendation. 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

- 3.26 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

- 3.27 The committee noted the uncertainty in the clinical evidence and economic modelling for lorlatinib, and the lack of evidence that lorlatinib prolongs life. But it also recognised the company's efforts to reduce uncertainty with its revised modelling approach. It also noted comments from patient and professional groups that cited lorlatinib's highly clinically significant progression-free survival benefit, and the unmet need that people with advanced ALK-positive NSCLC have. When the committee's preferred assumptions were applied, the ICER for lorlatinib was within the range it considered to be a cost-effective use of NHS resources. The committee concluded that lorlatinib can be used for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor.

4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.
- 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 patient has untreated ALK-positive advanced non-small-cell lung cancer and the healthcare professional responsible for their care thinks that lorlatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Chairs

Megan John and Amanda Adler

Chair and 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 and Lorna Dunning

Associate directors

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