NICE National Institute for Health and Care Excellence

NICE guidance

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer

Technology appraisal guidance
Published: 12 July 2023

www.nice.org.uk/guidance/ta909

Your responsibility

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

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

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

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

Contents

1 Recommendations

1.1 Lorlatinib is not recommended, within its marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

People with ALK-positive advanced NSCLC who have not had an ALK inhibitor before usually have alectinib or brigatinib in NHS practice. Ceritinib and crizotinib are also available but are rarely used. Lorlatinib is already used after alectinib or brigatinib. It is now being proposed as an alternative to alectinib or brigatinib as a first treatment.

Clinical trial evidence suggests that lorlatinib improves the amount of time people have before their condition progresses compared with crizotinib. But crizotinib is not usually used as a first treatment for this condition, so the trial results are not generalisable to the NHS. An indirect comparison suggests that lorlatinib may increase how long people live before their condition gets worse compared with alectinib and brigatinib, but this is uncertain. Also, because the clinical trial is ongoing, it is not possible to conclude whether this difference will continue and whether lorlatinib will increase how long people live.

Because there are many uncertainties in the clinical evidence, the company's economic analyses are also uncertain. The cost-effectiveness estimates are also all above the range NICE considers an acceptable use of NHS resources. So, lorlatinib is not recommended for routine use in the NHS.

Collecting more data through managed access may resolve some of the uncertainties in the clinical evidence. But, because all the cost-effectiveness estimates are above the range NICE considers an acceptable use of NHS resources, lorlatinib does not have the likely possibility to be cost effective at its current price at the end of the managed access

period. So, lorlatinib cannot be recommended for use with managed access.

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'.

2.2 Lorlatinib is also indicated for previously treated ALK-positive advanced NSCLC (see NICE's technology appraisal guidance on lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer).

Dosage in the marketing authorisation

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

Price

2.4 The list price of lorlatinib 30x100 mg and 90x25 mg tablets is £5,283 (excluding VAT; BNF online accessed March 2023).

2.5 The company has a commercial arrangement. This makes lorlatinib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The 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.

Clinical management

Clinical need

3.1 People with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) tend to be younger and are less likely to have a history of smoking than the wider NSCLC population. The condition is associated with late diagnosis, so people can often present with advanced disease. One patient expert explained that there remained a significant unmet need for people with ALK-positive NSCLC. There are 4 ALK tyrosine kinase inhibitor (TKI) treatments available for untreated NSCLC, alectinib, brigatinib, ceritinib and crizotinib. But, since the availability of second-generation ALK TKIs alectinib and brigatinib, crizotinib and ceritinib are rarely used. The patient and clinical experts explained that people with ALK-positive NSCLC often have advanced disease at diagnosis, with some also having central nervous system (CNS) metastases. They explained that CNS metastases have a substantial effect on morbidity and quality of life. The committee understood that lorlatinib is a third-generation ALK TKI. It has been approved for second-line use in the NHS for ALK-positive advanced NSCLC in adults whose cancer has progressed after other ALK TKIs in NICE's technology appraisal guidance on lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer. The clinical experts explained that lorlatinib may offer improved blood-brain barrier penetration compared with other ALK TKIs because of its underlying mechanism. They added that the second-generation ALK TKIs may be associated with intracranial responses, but that whether this is because of blood-brain barrier penetration is unclear. They noted that lorlatinib would be a useful addition to first-line treatment options for untreated ALK-positive advanced NSCLC, particularly because it may be effective

for intracranial outcomes. Both the clinical and patient experts noted that lorlatinib tends to be well tolerated but may be more toxic than alectinib and brigatinib. They also noted that it can have significant side effects, including neuropathy and mood disturbance, which can negatively affect quality of life. But the clinical experts also noted that clinicians in the NHS have experience of managing these side effects when using lorlatinib second line. They added that some potential side effects can substantially affect quality of life, but are often manageable with additional supportive care or dose reductions. The committee was aware that lorlatinib may have a different side effect profile to other ALK TKIs. For example, a patient expert commented they have had less fatigue and a better quality of life when having lorlatinib than they did when taking alectinib. But they noted that some people may have a better quality of life when having alectinib or brigatinib than when having lorlatinib (see section 3.11). The committee agreed that there are unmet needs in people with ALK-positive advanced NSCLC, and that lorlatinib would be a useful addition to first-line treatment options.

Proposed positioning of lorlatinib and comparators

3.2 The committee was aware that the company proposed lorlatinib as a first-line treatment option for ALK-positive advanced NSCLC. It noted that the comparator crizotinib in the CROWN trial is rarely used in the NHS. The EAG commented that current NHS practice would be to use alectinib or brigatinib first line, then lorlatinib second line and chemotherapy third line. The clinical and patient experts confirmed the EAG's view that some people may continue on lorlatinib after progression. This is because it is the last available targeted TKI treatment before moving to chemotherapy (see section 3.18). For people who have lorlatinib first line, chemotherapy would be used second line. The committee was aware that chemotherapy is usually used as the last line of treatment because of the toxicity associated with it. The committee concluded that the company's positioning of lorlatinib as a first-line treatment option was appropriate, and that alectinib and brigatinib were the relevant comparators for this appraisal. The committee also considered the relevant population for this appraisal. 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 effective for intracranial outcomes (see section 3.1), 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, so it was unable to consider this population further.

Clinical evidence

The CROWN trial

3.3 The main evidence for lorlatinib came from CROWN. This is an ongoing open-label phase 3 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 disease, including previous ALK TKIs. It is a multinational study with 104 study sites in 23 countries, including in Japan (17 sites), China (9 sites), Taiwan (4 sites), Hong Kong (3 sites), Russia (4 sites) and the UK (3 sites).

Generalisability of CROWN to the NHS

3.4 The EAG noted that the baseline characteristics in CROWN are well balanced between the 2 trial arms. But it explained that CROWN includes very few people with an Eastern Cooperative Oncology Group (ECOG) performance status of 2, and that 96% of people have an ECOG of 0 or 1. It noted that this contrasted with the company's estimate that 25% to 30% of people with ALK-positive NSCLC would be expected to have an ECOG of 2 in clinical practice. The EAG commented that that the ECOG performance status is considered to be a prognostic variable and could affect progression-free and overall survival. It suggested that it was possible that lorlatinib may be more or less effective in the subgroup of

people with an ECOG of 2, but that there was a lack of evidence about this. The clinical lead for the Cancer Drugs Fund noted that it is common that clinical trials recruit people with an ECOG of only 0 or 1. This is because recruiting people to clinical trials is usually selective. Also, people with an ECOG of 2 often do not fulfil the trial recruitment criteria or choose not to participate in the trial if this might delay starting treatment. They also noted that it was likely that lorlatinib was less effective in people with an ECOG of 2, but that this could be the same for the comparator arm in the trial. The clinical experts noted that most people with an ECOG of 2 would respond quickly to treatment, resulting in an ECOG performance status improvement. The committee noted that the proportion of people with an ECOG of 0 or 1 in clinical trials of alectinib (ALEX) and brigatinib (ALTA-1L) was very similar to that in CROWN. It also noted that lorlatinib's marketing authorisation is not restricted by ECOG performance status. The EAG further explained that many of the CROWN study sites are in Asia. This means that the proportion of people from an Asian family background is much higher in CROWN than would be seen in clinical practice in the UK. On the possibility of family background being an effect modifier, the company cited an analysis of lorlatinib pharmacokinetics. In this analysis, no inherent differences in lorlatinib pharmacokinetics between people with Asian and non-Asian family backgrounds were found. Considering the lack of evidence in people with an ECOG of 2, the committee concluded that the evidence from CROWN may be applicable to people with an ECOG of 2 in the NHS, but that this was uncertain. It also agreed that, considering the available evidence, the case for family background being a treatment-effect modifier in ALK-positive NSCLC was not compelling.

Subsequent treatments

3.5 CROWN compares lorlatinib with crizotinib, which was the most relevant comparator when the trial was designed. But crizotinib is rarely used in clinical practice in the UK (see section 3.1). The subsequent treatments in CROWN include second-generation ALK TKIs, such as alectinib and brigatinib, and chemotherapy. The EAG commented that there was no crossover to lorlatinib in the CROWN trial. At the September 2021 data cut, a relatively large proportion of people (data deemed confidential and not reported here) in the crizotinib arm of CROWN had had a subsequent

second-generation ALK TKI. The same was true for the lorlatinib arm, although fewer people went on to have a subsequent treatment compared with the crizotinib arm. The EAG noted that current NHS practice is alectinib or brigatinib as first-line treatment, followed by lorlatinib at second line and chemotherapy at third line (see section 3.2). Brigatinib is also recommended second line in the UK after crizotinib, but crizotinib is rarely used. The EAG highlighted that the treatment sequences in CROWN do not align with those currently used in the NHS. So, the EAG considered that overall survival in CROWN could be confounded or driven by subsequent use of second-generation ALK TKIs. The EAG was also concerned that the trial's treatment sequences substantially limit the applicability of the evidence from CROWN to UK clinical practice. The clinical experts confirmed that subsequent treatments in clinical trials often have a confounding effect on overall survival results. They explained that, for the lorlatinib arm, there was no evidence that using second-generation ALK TKIs after third-generation lorlatinib would have any meaningful effect on overall survival, but that this is uncertain. The committee considered that the comparator in the trial and subsequent treatments in both arms do not represent NHS practice, meaning a high level of uncertainty in the clinical evidence from CROWN. The committee concluded that it would take this into account during decision making.

Progression-free and overall survival data

3.6 The primary outcome of CROWN was progression-free survival assessed using blinded independent central review. Evidence at the planned September 2021 data cut showed that lorlatinib was associated with longer progression-free survival compared with crizotinib. The differences were statistically significant (data deemed confidential so not reported here). Data on overall survival was less mature because of the limited number of events, and was taken by the company from an earlier data cut-off point of March 2020. Evidence suggested that lorlatinib reduced the risk of death compared with crizotinib, but the difference was not statistically significant (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.41 to 1.25). For overall survival, the committee also noted that the Kaplan–Meier curves diverged, suggesting an advantage for lorlatinib, but then later reconverged (data deemed confidential and not

reported here). The EAG highlighted that the data on progression-free and overall survival from CROWN was immature because of the limited number of events. The EAG noted that it was plausible that longer progression-free survival could lead to increased overall survival with lorlatinib, but that no robust conclusions could be drawn about overall survival from CROWN. The company explained that data on overall survival was not available from September 2021 because of a lack of death events. It also explained that further data cuts from CROWN are planned for 2025 and 2028. The committee was aware that the trial is still ongoing, that the median follow-up times (data deemed confidential and not reported here) were short for progression-free and overall survival outcomes when the analyses were done, and that the data was immature. At the first committee meeting, the committee considered that the immaturity of data was associated with a high level of uncertainty in the evidence, and concluded that it would take this into account during its decision making. In response to the draft guidance consultation document, the company stated that the immaturity of the data, with median progression-free survival having not yet been met, shows the efficacy of lorlatinib at preventing progression. It also noted that early data suggests that lorlatinib reduces the risk of death compared with crizotinib. The EAG explained that the available data supports a progression-free survival benefit for lorlatinib relative to alectinib and brigatinib. But it noted the magnitude of that benefit was uncertain. The committee concluded that lorlatinib was likely associated with a progression-free survival benefit compared with alectinib and brigatinib. But it thought that the magnitude of the benefit and the associated effect on overall survival was very uncertain. It concluded that it would continue to take this into account during its decision-making process.

Intracranial time to progression

3.7 Evidence from CROWN also showed that intracranial time to progression (referred to as time to CNS progression for the remainder of this document) was longer in the lorlatinib arm compared with the crizotinib arm. The difference was statistically significant (HR 0.08, 95% CI 0.040 to 0.174). But the EAG noted that the company only counted the first progression events in these analyses. The EAG was also concerned that there was no data from CROWN on people who had a non-CNS

progression and then had a CNS progression. In response to the draft guidance consultation document, the company noted that overall progression and CNS progression were independent events. It also stated that, in CROWN, people who had CNS or non-CNS progression could continue on the same treatment, or could start a new anticancer treatment. People who started a new anticancer treatment were censored. But data is available for people who had non-CNS progression, who continued on the same treatment and then had CNS progression (data deemed confidential so not reported here). The company noted that, after 36.7 months of follow up in CROWN, 6.0% of people having lorlatinib had CNS progression compared with 34.7% of people having crizotinib. It also noted that additional data on CNS progression would be collected in the ongoing CROWN trial. The committee noted that the number of people who had CNS progression at least 7 days after 'overall progression or death' was very small (data deemed confidential and not reported here). So, the data is very uncertain. The committee concluded that the effect of lorlatinib on preventing CNS progression was uncertain. It also concluded that it would continue to take this into account during its decision-making process.

Network meta-analysis

3.8 Because the comparator in CROWN is not relevant to UK clinical practice, the company did a Bayesian network meta-analysis (NMA) to compare the clinical effect of lorlatinib with alectinib and brigatinib. The results of the NMA suggested that lorlatinib was associated with an improvement in progression-free survival. Because of the immaturity of the data, no conclusions could be drawn from the NMA for overall survival. The company initially identified 10 studies for inclusion in the NMA, 6 of which were found to be irrelevant to the decision problem. The company then further excluded the ALESIA trial comparing alectinib and crizotinib after a feasibility assessment. The company explained that its decision to exclude this trial was because it only included people of Asian family background. Also, it was excluded from the NMA done to inform NICE's technology appraisal guidance on brigatinib for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor. In that appraisal, the committee had noted that the ALESIA trial mainly included sites in China. So, differences in healthcare systems and subsequent

treatment options meant that ALESIA is not as applicable to the UK population as the ALTA-1L and ALEX trials are. The EAG explained that it did not agree that it was appropriate to exclude ALESIA from the company's NMA in the current evaluation. It suggested that, if clinical trials were excluded based only on this criteria, most other trials in the NMA would also have to be considered inapplicable to the UK population. The committee noted that CROWN only included 3 UK sites out of a total of 104, including 9 study sites from China (see section 3.3). At clarification, the EAG asked the company to do an NMA including ALESIA. The company maintained its view that ALESIA was not appropriate for its base-case analysis. But it did an NMA for progression-free survival including ALESIA as a scenario analysis to provide a global perspective on the effectiveness of lorlatinib against alectinib. The EAG considered that the NMA for the progression-free survival outcome that included ALESIA (alectinib) is the most appropriate. This was because its inclusion provided a more complete data set for the comparison of alectinib with lorlatinib. The EAG also noted that including ALESIA in the NMA was associated with a minor reduction in lorlatinib's treatment effect on progression-free survival relative to alectinib. The committee noted that CROWN included sites in Asia and a higher proportion of people from an Asian family background than would be expected in the NHS (see section 3.4). Considering all the evidence and on balance, it agreed with the EAG that including ALESIA in the NMA for progression-free survival increased the sample size for the analysis. It concluded that it preferred using the results from the global NMA, including data from the ALESIA trial. In response to the draft guidance consultation document, the company revised its base case to include the results from the global NMA, including ALESIA. The committee concluded that the company's revised approach was appropriate for decision making.

Identifying CNS metastases at diagnosis

3.9 The EAG explained that the clinical trials for alectinib and brigatinib included in the company's NMA recruited more people with CNS metastases at baseline than were recruited in CROWN. In CROWN, the lorlatinib arm had 26% and the crizotinib arm had 27%. In ALEX, the alectinib arm had 42% and the crizotinib arm had 38%. In ALTA-1L, the brigatinib arm had 29% and the crizotinib arm had 30%. The clinical

experts explained that, in clinical practice, symptomatic or prognostic CNS metastases could have a substantial effect on the quality of life of people with ALK-positive NSCLC (see section 3.1). They noted that there are considerable variations in identifying and monitoring CNS metastases in the NHS in people with untreated advanced ALK-positive NSCLC. This is because brain imaging or MRI is not available in all NHS hospitals at diagnosis. Also, the proportion of people with or without CNS metastases at diagnosis remains unknown. Some people would not know whether or not they have CNS metastases until they have symptoms. They explained that people could have minor lesions that would not immediately affect prognosis or quality of life. One patient expert also explained that not everyone would like to have a brain scan at diagnosis if there are no symptoms related to CNS metastases. This is because identifying minor lesions that would otherwise be undetectable could have a negative effect on their usual activities and quality of life (for example, if they were no longer legally permitted to drive a car). The committee understood that, in the NHS, there is variation in identifying CNS metastases at diagnosis.

The effects of CNS metastases

3.10 The EAG was concerned that CNS metastases at baseline could be associated with a poorer prognosis or a reduced treatment effect associated with ALK TKIs, compared with advanced NSCLC without CNS metastases. It explained that the lower proportion of people with CNS metastases in CROWN compared with ALEX and ALTA-1L (see section 3.9) could potentially have created a bias in treatment effect in the NMA. But it also noted that, because of the small sample sizes, no stratified subgroup analysis could be done to meaningfully inform whether baseline CNS metastases are a treatment-effect modifier for lorlatinib when compared with other ALK TKIs. Referring to other published NMAs for lorlatinib, both the EAG and company noted that published literature suggested that there was no strong evidence that baseline CNS metastases affected progression-free survival in comparison with alectinib. But lorlatinib was seen to be more effective than brigatinib in people without CNS metastases. This improvement compared with brigatinib was not seen in people with CNS metastases. The company acknowledged that the proportion of people with CNS

metastases was lower in CROWN. It suggested that the differences were unlikely to affect observed relative treatment effects, but did not provide evidence to support this. The EAG explained that clinical advice and published evidence suggested that CNS metastases are associated with a poorer prognosis and significant morbidities. But it thought that whether it is a treatment-effect modifier was unclear. The committee understood that baseline CNS metastases may affect prognosis and modify treatment effect, but that the lack of evidence meant that this was uncertain. It concluded that it would take this uncertainty into account in its decision making.

Adverse events

3.11 The company noted that CROWN recorded a higher incidence of grade 3 or 4 adverse events in the lorlatinib arm than in the crizotinib arm. The company did not provide an indirect treatment comparison assessing lorlatinib's treatment effect on grade 3 or 4 adverse events compared with other ALK TKIs, as had been requested by the EAG. The EAG explained that, in published NMAs, evidence showed that lorlatinib was associated with an increased risk of grade 3 and above adverse events compared with alectinib or brigatinib. The company agreed with the EAG that the range and severity of adverse reactions are different for lorlatinib compared with those of other ALK TKIs. The company highlighted that data on stopping treatment from CROWN showed that these adverse events are tolerable and are often resolved through dose reductions. The clinical experts explained that a simple comparison of the number of grade 3 and 4 adverse events between lorlatinib and other ALK TKIs could be potentially misleading. This is because it is important to account for the nature of the adverse events, and the likely effect they have on quality of life. For example, a rise in cholesterol levels would not have an immediate effect on quality of life. But a grade 3 or 4 neurological adverse event could significantly affect someone's quality of life. Also, clinical advice to the EAG suggested that lorlatinib has a different side effect profile to alectinib and brigatinib, and that this is an important consideration for people with ALK-positive NSCLC. The clinical experts suggested that the treatment decision inevitably involves a discussion on the trade-off between the likely better progression-free survival outcomes with lorlatinib (that might or might not translate into

better overall survival), and the different safety profiles of alectinib and brigatinib. The patient experts agreed that the different side effect profiles are important for people with NSCLC to consider. They explained that some people found their quality of life to be better on lorlatinib than on alectinib or brigatinib, while others found the reverse to be true. The patient experts explained that some side effects associated with alectinib are not found with lorlatinib. People taking lorlatinib may have less fatigue compared with other ALK TKIs. But some people may have more debilitating effects with lorlatinib such as diarrhoea. The committee understood that lorlatinib may be associated with a higher risk of adverse events compared with other ALK TKIs. It also recalled that the data on lorlatinib's treatment effect on progression-free survival and overall survival was immature (see section 3.6). At the first committee meeting, the committee concluded that a comparative analysis of grade 3 and 4 adverse events with lorlatinib compared with other ALK TKIs would help its decision making. In response to the draft guidance consultation document, the company did not provide a comparative analysis of grade 3 and 4 adverse events. The committee considered that the safety profile of lorlatinib relative to other ALK TKIs was uncertain. It concluded that it would take this into account in its decision making.

Economic approach

The company's original economic model

3.12 In its original evidence submission, the company presented a 4-state (progression free, non-CNS progressed disease [PD], CNS PD and death) partitioned survival model. The model assessed the cost effectiveness of lorlatinib compared with alectinib or brigatinib in untreated ALK-positive NSCLC. Health states were determined from a set of non-mutually exclusive survival curves using an area under the curve approach. Although partitioned survival models are commonly used when appraising cancer medicines, the EAG did not consider this model to be methodologically robust in this particular instance. This was because the model lacked transparency and the flexibility to explore alternative extrapolations of trial data. The model also resulted in projections that

were incompatible with the evidence from the trial data over equivalent timescales. The lack of flexibility to do scenario analysis meant that the model could not represent decision uncertainty. This specifically applied to the uncertainty generated because of the immature survival data available from CROWN. The company acknowledged the EAG's concerns and agreed at clarification stage to provide a revised model to address them. The committee agreed with the EAG that the original model was not appropriate for decision making because of how the current data had been applied within the partitioned survival model structure.

The company's revised economic model

3.13 The EAG explained that the company's revised model used a hybrid approach based on a partitioned survival model. But it also included a pseudo-state-transition approach to modelling post-progression survival (PPS). Importantly, this approach used survival data from second-line studies to estimate PPS in the model. In doing so, the company used 2 external studies to inform PPS in the revised model, specifically:

- PROFILE 1001/1005 for survival with chemotherapy used second line after progression on first-line lorlatinib: it included 2 single-arm trials of crizotinib with people with advanced ALK-positive NSCLC who had chemotherapy second line after crizotinib progression.
- Study 1001 for survival with lorlatinib used second line after progression on first-line alectinib or brigatinib: it was a single-arm trial of lorlatinib in adults with metastatic ALK-positive NSCLC who had had 1 or more ALK TKIs first line.

  The EAG considered this revised model to be better aligned with NHS practice, and to better reflect the range of treatments that people have post progression. The EAG further explained that using elements of a state-transition approach represents an important change to how health state occupancy is determined and how transition probabilities are generated. Rather than modelling state occupancy using trial-derived survival curves with an area under the curve approach, state occupancy is a function of the transition probabilities applied to each health state, with explicit state-transition probabilities modelled. This offers an advantage in the context of a limited evidence base, such as for overall survival data (from CROWN, ALEX

and ALTA-1L), which was heavily confounded by the range of treatments people had after progression. Also, it did not reflect NHS practice. The state-transition approach allows for more representative data sources to be used to model PPS, so can better reflect current NHS practice. The flexibility offered by a state-transition approach can also overcome inconsistencies in available survival evidence, which are more likely when that evidence is immature. By using a state-transition approach, a structural relationship could be imposed between progression-free and overall survival, such that the curves are not permitted to cross. But the EAG also noted several significant limitations in this revised model, which were either linked to the company's modelling approach or availability of evidence. Despite the clear theoretical improvements in the company's revised model, the EAG had further concerns over its implementation. At technical engagement, the EAG discovered an error in which people in the progression-free survival state could not progress to death. The company agreed that this was an error and it was rectified. The committee concluded that the company's revised model structure and the EAG's preferred approach of determining health state occupancy were appropriate for decision making. But the committee also noted the significant limitations in the company's model, and concluded that it would take these into account in its decision making.

Modelling the CNS PD health state

3.14 The EAG disagreed with implementing a CNS PD health state in the company's revised economic model. It noted that it is clinically plausible to assume that people whose condition progresses may later develop CNS metastases. But that while this transition from non-CNS PD to CNS PD was described in the company's evidence submission, it was not appropriately built into the company's model. The EAG noted that the scenario presented by the company at technical engagement aimed at establishing a structural link between non-CNS PD and CNS PD appeared to have been incorrectly implemented by the company. This was because exploratory scenarios did not pass simple validation tests. It was also concerned about the availability of data from CROWN to inform these transitions. In response to consultation on the draft guidance consultation document, the company explained that, in CROWN, people with non-CNS progression who started a new anticancer treatment were censored, but that people who continued

treatment were not censored. This data is available to inform the number of people who had CNS progression after non-CNS progression (see section 3.7). The EAG noted that, after consultation, the company's model continued to exclude a non-CNS PD to CNS PD transition. At the second committee meeting, the company acknowledged the limited number of events currently available to inform this transition in the model, but considered that more data would be available from future data cuts of CROWN. The EAG considered that:

- given the available data, the key transitions in a 4-state model cannot be appropriately represented
- there were limitations in the way that the company had modelled the rate of CNS progressions for alectinib and brigatinib (see section 3.15)
- with the 4-state structure, it is not possible to meaningfully present the prognosis of people with CNS metastases (see section 3.16), particularly the effect of CNS progression on PPS outcomes (see section 3.19).

The committee noted these flaws in the model. It recognised that similar 4-state models were previously accepted in NICE's technology appraisals guidance on alectinib for untreated ALK-positive advanced non-small-cell lung cancer and brigatinib for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor. At the first committee meeting, the committee considered that it may be reasonable to assume that having CNS progression would be associated with worse quality of life than having non-CNS progression. It agreed that a 4-state model was conceptually appropriate. But the committee agreed with the EAG that the company's 4-state model was flawed and that there was a lack of data from the trial to inform the transition to the CNS PD health state. To improve model transparency and to avoid introducing unnecessary uncertainty, the committee concluded that the EAG's preference for removing the CNS PD health state was appropriate. At the second committee meeting, the committee concluded that it had not been presented with evidence to change its view that there was insufficient data to model the CNS PD health state. It noted that there were further concerns with the way the CNS PD health state was modelled, including the:

- rate of CNS progressions for alectinib and brigatinib (see section 3.15)

- accounts for CNS metastases status at baseline (see section 3.16)
- difference in the effect of CNS progression on PPS outcomes (see section 3.19).

It concluded that removing the CNS PD health state would improve transparency and avoid introducing uncertainty. The committee acknowledged that removing the CNS PD health state also had its limitations, such as not capturing the potential benefit of lorlatinib in preventing CNS progression (see section 3.25). It confirmed that it would take this into account in its decision making but, on balance, concluded removing the CNS PD health state was the most appropriate approach.

Modelling transitions to the CNS PD state for alectinib and brigatinib

3.15 In the company's model, the rates of CNS progression for people having alectinib and brigatinib were calculated by applying progression-free survival hazard ratios for alectinib and brigatinib compared with crizotinib from ALEX and ALTA-1L to the intracranial time-to-progression curve for crizotinib in CROWN. In its critique of the company's response to consultation, the EAG explained that by doing this rather than using CNS progression-free survival hazard ratios, the company assumed that alectinib and brigatinib have the same size effect on CNS progression compared with crizotinib as on overall progression. It explained that this was not supported by data from CROWN and ALEX, which showed that lorlatinib and alectinib both had a larger effect in delaying CNS progression than in delaying overall progression. So, the company's model may have underestimated the relative effectiveness of alectinib and brigatinib in delaying CNS progression. The EAG presented a scenario analysis using a weighted CNS time-to-progression hazard ratio from ALEX that included people with and without CNS metastases at baseline. This scenario resulted in a decrease in the incremental quality-adjusted life years gained for lorlatinib compared with alectinib compared with the company's base case. The EAG noted that this data was not available for brigatinib. At the second meeting, the company noted that CROWN recorded intracranial time to progression (which does not class deaths as events). But ALEX and ALTA-1L recorded intracranial

progression-free survival (which does class deaths as events). So, the company said that it could not carry out a formal synthesis of CNS progression-free survival outcomes. The committee recalled that lorlatinib may offer improved blood-brain barrier penetration compared with other ALK TKIs (see section 3.1), but that any effect on CNS progression was uncertain. The committee considered that the company's approach likely underestimated the ability of alectinib and brigatinib to delay CNS progression. It considered that the EAG's scenario analysis using CNS time-to-progression data from ALEX may provide a more plausible representation of the effect of alectinib in delaying CNS progression. But it noted that this data was not available for brigatinib. It also noted that delaying CNS progression may be a key benefit of treatment with lorlatinib and that this benefit was not modelled in the EAG's preferred 3-state model structure. It noted that it would take this uncaptured benefit into account in its decision making. But it concluded that it had not been presented with evidence to change its view that there was insufficient data to model the CNS PD health state and that removing it would improve transparency and avoid introducing uncertainty.

Modelling of CNS metastases at baseline

3.16 The company's model includes people with and without CNS metastases at baseline, and does not consider these subgroups separately. In its critique of the company's response to the draft guidance consultation document, the EAG suggested that the subgroups with and without CNS metastases at baseline should be modelled separately. It noted that, in CROWN, ALEX and ALTA-1, most CNS progressions occurred in the subgroup with CNS metastases at baseline. Also, the risk of CNS progressions in the subgroup with CNS metastases at baseline may follow a different functional form to the subgroup without CNS metastases at baseline. The company's model used an exponential function to model CNS progression, based on the fit to the crizotinib data. The EAG noted that it was not appropriate to assume the same pattern of events for alectinib or that there was a constant event rate for CNS progression over the model time horizon. It noted that this assumption and using a single parametric function resulted in clinically implausible predictions for the number of people with CNS metastases at

baseline who had CNS PD when having alectinib. The committee recalled that CNS metastases may affect prognosis and modify treatment effect (see section 3.10). The committee concluded that this contributed to uncertainty in the results of the economic model, and that it would take this into account in its decision making.

Extrapolating progression-free survival and capping treatment effect

3.17 CROWN and the company's NMA were the primary sources of progression-free and CNS progression-free survival data for lorlatinib, alectinib and brigatinib. Because progression-free survival data from CROWN was not sufficiently mature, the company extrapolated the available progression-free survival data for lorlatinib and crizotinib using standard parametric models. Occupancy of the progression-free health state in the economic model was estimated directly from parametric curves fitted independently to each arm of CROWN. Progression-free survival on alectinib and brigatinib was calculated by adjusting the crizotinib curve using the hazard ratio between crizotinib and each treatment from the NMA. The company chose the exponential curve to model lorlatinib progression-free survival in the long term. The EAG noted that this curve represented the most conservative option, but it:

- had the worst statistical fit according to Akaike Information Criteria and Bayesian Information Criteria
- had a poor visual fit to the trial data
- overestimated progression-free survival compared with the Kaplan–Meier data from the trial, and likely also over the longer term.

  For example, progression-free survival was estimated to be about 8% higher than the corresponding data from CROWN for much of the first 2 years of the model. The EAG explained that, despite these limitations, the alternative parametric models provided even less clinically plausible results. At technical engagement, the EAG requested that the company provide further exploratory survival analysis techniques. The company presented a number of flexible parametric survival models, including a selection of 2-piece and cubic spline models. The company stated that the curves from the 2-piece models showed

a much improved visual and statistical fit to both treatment arms, although the EAG noted that fit statistics were not presented. The company also explored 1- and 2-knot cubic spline models, but noted that the survival estimates produced by the spline models would be too optimistic to be clinically plausible. The EAG agreed with the company that the better fit provided by these alternative models did not mean that they were more clinically plausible. They also did not resolve the issues associated with the immaturity of the data. The EAG was aware that the appraisals of alectinib and brigatinib considered scenario analyses in which the treatment-effect duration was capped at between 3 years and 20 years. Because of the immaturity of data from CROWN, and the lack of alternative plausible extrapolations for progression-free survival on lorlatinib, the EAG explored capping treatment effect at 7 years, 10 years, and 15 years. The committee understood that the exponential curve was the most conservative but highly uncertain given that the progression-free survival data from CROWN was immature. The committee was aware that NICE's manual on health technology evaluation describes the requirements for exploring treatment effect over the relevant time horizon, and considered that the company had not adequately investigated the uncertainty. It considered the EAG's exploratory analyses to be appropriate and that capping treatment effect at 10 years may be the most clinically plausible approach, but considered this uncertain. It concluded that it would take this into account in its decision making. In response to the draft guidance consultation document, the company revised its base case to include a treatment effect cap at 10 years. The company stated that the median progression-free survival predicted by the model (53.2 months) aligned with the expected median progression-free survival provided by its clinical experts (4 to 5 years). The EAG noted that, even with the treatment effect cap, the additional time people having lorlatinib in the model are expected to remain progression free produces an overall survival benefit for lorlatinib compared with alectinib and brigatinib. The committee acknowledged that the company had updated its base case to include a treatment effect cap at 10 years. But it considered that the progression-free survival extrapolations were still very uncertain. It concluded that it would take this into account in its decision making.

Modelling treatment beyond progression on lorlatinib

3.18 The clinical and patient experts explained that treatment beyond

progression is likely with lorlatinib. This is because it is currently positioned as the final targeted ALK TKI treatment available to people before they move to chemotherapy. The clinical experts explained that treatment beyond progression is common for all ALK TKIs in this disease area, usually for a period of around 3 months. They added that chemotherapy is a valid treatment option for people with ALK-positive NSCLC. But it may be associated with higher toxicity that affects quality of life. For this reason, people with the ALK-positive NSCLC and clinicians may be reluctant to suspend treatment with lorlatinib while it may be continuing to provide some clinical benefit. The company explained that clinical advice suggested that, at second line, around 50% of people will continue on lorlatinib beyond disease progression, and that treatment would continue for an average of 3 months. The expectation is that this would also apply equally to lorlatinib in a first-line position in the treatment pathway. This is because there are currently no further ALK TKIs that would be available after lorlatinib, so chemotherapy would be used second line. The committee was aware that there is no stopping rule for lorlatinib in its marketing authorisation, and that this decision is made by clinicians in consultation with people with ALK-positive NSCLC. The EAG noted that treatment beyond progression was not permitted in the company's model, in which it was assumed that treatment duration was the same as the period of progression-free survival. The EAG considered that treatment with lorlatinib beyond progression could be longer than the estimate of 3 months provided by the company. So, the EAG presented an exploratory scenario that was informed by a retrospective analysis of treatment beyond progression in Study 1001. In this study, 75.6% of people continued to have lorlatinib after progression on other ALK TKIs, for a median additional duration of 5.7 months. The clinical lead for the Cancer Drugs Fund also commented that it was likely that treatment for lorlatinib would continue beyond progression for more than 3 months. The clinical experts agreed with this. They stated that treatment beyond progression would be longer for the final ALK TKI than for an ALK TKI that could be followed by a subsequent ALK TKI. They further suggested that, in some cases, treatment with lorlatinib might continue for up to 6 months if it was thought that the person was continuing to benefit and quality of life was being maintained. The committee agreed that, because first-line lorlatinib would not be followed by an additional ALK TKI treatment, treatment beyond progression was

more likely to be closer to 6 months than 3 months. It considered that treatment beyond progression should have been included in the model. But the EAG noted that, because of the lack of evidence, these scenario analyses only explored the effect of treatment beyond progression on costs. It did not explore how it would affect treatment effect. The committee also noted the company's estimate that 95% of people having treatment with alectinib or brigatinib would progress to second-line lorlatinib. It also considered the EAG's preference of a lower estimate, equal to the proportion who had a subsequent anticancer treatment after progression on lorlatinib in CROWN (data deemed confidential and not reported here). The committee agreed that treatment beyond progression was highly likely and agreed that this would be beyond 3 months, and likely would extend up to 6 months. Given the uncertainty, it concluded that the EAG's exploratory analysis of 5.7 months beyond progression for both first line and second line was clinically plausible and was its preferred estimate. Because of the uncertainties, it also preferred the EAG's estimate for the proportion of people progressing to second-line lorlatinib after brigatinib and alectinib. In response to the draft guidance consultation document, the company updated its base case to include 5.7 months treatment beyond progression for both first-line and second-line lorlatinib. It also updated its base case to include the EAG's estimate for the proportion of people progressing to second-line lorlatinib after alectinib and brigatinib. The company recalled the clinical experts' comments at the first committee meeting that treatment beyond progression is common for all ALK TKIs in this disease area, usually for a period of around 3 months. So, it updated its base case to include 3 months of treatment beyond progression for alectinib and brigatinib. The EAG agreed that this aligned with the clinical experts' comments from the first committee meeting and updated its base case. The committee concluded that the company's revised approach to modelling treatment beyond progression on lorlatinib, alectinib and brigatinib was appropriate for decision making.

Modelling PPS

3.19 The committee considered how PPS was modelled and the data sources informing it. The EAG noted that overall survival data from CROWN was not used in the model because it was immature (see section 3.6).

Instead, the company used Study 1001 (first-line other ALK TKIs, second-line lorlatinib) and PROFILE 1001/1005 (first-line ALK TKIs, second-line chemotherapy) to inform PPS after first-line treatment with either alectinib or brigatinib, or lorlatinib (see section 3.13). This approach had the advantage of avoiding the confounding effect of using survival data from CROWN, in which subsequent treatments did not reflect NHS clinical practice (see section 3.5). The EAG explained that this allowed for alternative extrapolations to be explored for progression-free survival and PPS, and to capture the uncertainty associated with this data probabilistically. But the EAG identified several issues with the approach that the company had used to model PPS. Importantly, it noted that the risk of mortality was not adjusted according to whether people had non-CNS PD or CNS PD. Instead, the company used whole-population PPS data to reflect the survival of people who had intracranial progression. The committee recalled that CNS metastases may be associated with a poorer prognosis than for progression and metastases at other sites (see section 3.10). The EAG noted that Study 1001 and PROFILE 1001/1005 both included a mixed population with and without CNS metastases at study entry. But the company's model assumed that all people were at risk of having CNS progression as their first progression event. So, the EAG considered that using data from Study 1001 and PROFILE 1001/1005 in this way could have potentially overestimated the survival of people in the CNS PD health state. In the same way, using this data to estimate outcomes in a non-CNS PD population could have underestimated overall survival. It may be more appropriate to model the outcomes of this cohort as a whole rather than by progression type. This is because of differences in the type of progression seen in the cohort who progressed in CROWN and the cohorts entering Study 1001 and PROFILE 1001/1005. This is particularly important given the lack of appropriate evidence to inform the relevant health state transitions in the model (see section 3.14). For the data informing PPS in the model, the EAG agreed with the company that Study 1001 may have been the only mature study of second-line lorlatinib after 1 or more previous ALK TKIs. It also agreed that it may have represented the only appropriate data source to inform outcomes with lorlatinib after alectinib or brigatinib in an NHS setting. The EAG also noted that PROFILE 1001/1005 might have been a reasonable data source for PPS on chemotherapy after a first-line ALK TKI. The EAG

further noted that possible data sources for this were discussed in NICE's technology appraisal guidance on lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer. But the company did not explore this further in its analysis. The committee noted the high uncertainty associated with the company's modelling of PPS, but recognised the limitations of the evidence. The committee agreed that it would also prefer to see analyses exploring other data sources for the modelling of survival outcomes on chemotherapy after progression on first-line ALK TKIs. It concluded that it would prefer to see analyses in which the risk of PPS was adjusted by CNS-progression status. It would also prefer to see a range of alternative scenarios explored for survival outcomes on chemotherapy after progression on first-line TKIs. In response to the draft guidance consultation document, the company did not provide any analyses in which the risk of PPS was adjusted by CNS-progression status. It stated that lorlatinib shows efficacy at preventing CNS metastases. The company therefore considered that the model did not fully capture the PPS benefit of first-line lorlatinib. The company did a targeted literature search to identify alternative potential sources for PPS data. It stated that the studies identified were less relevant than the data sources used in the company's model and so did not do further analyses with these data sources. The EAG and committee agreed with the company that the studies the company identified were less relevant than the data sources used in the company's model. But the committee would have preferred to have also seen analyses in which the risk of PPS was adjusted by CNS-progression status. The committee considered that the company's approach to modelling PPS was associated with uncertainty. It concluded that it would take this into account during decision making.

Utility values in the economic model

3.20 Health-related quality-of-life data was collected in CROWN using the EQ-5D-5L questionnaire, and later mapped to EQ-5D-3L. The EQ-5D-5L questionnaire was done on day 1 of each 30-day treatment cycle. Less than 12% of responses were collected in people who had disease progression, and most of these were collected close to the date of clinical progression. The EAG noted that the utilities derived from CROWN and applied in the company's revised model were considerably

higher than those accepted in NICE's technology appraisal guidance on brigatinib for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor and other past appraisals in this treatment space. This was particularly true for the PD health state, in which there was only a minor reduction in utility compared with the progression-free health state. Because the health-related quality-of-life measures were taken close to the point of clinical progression, the EAG suggested that this utility value likely did not accurately represent the quality of life of people with progressed disease. Instead, the EAG explained that its preference was for the utility values used in NICE's technology appraisal guidance on brigatinib. It noted that similar issues were identified in that appraisal. But these utility values were not confounded by the subsequent treatments in CROWN, in which second-line ALK TKIs were used, contrary to NHS clinical practice. The committee was also aware of the uncertainties associated with the utility values used in NICE's technology appraisal guidance on brigatinib. It noted that the progressed disease utilities used in that appraisal were taken at 30 days into progression. But it also noted that they were from an open-label trial and measured by a cancer-specific quality-of-life measure (EORTC-QLQ-C30), and then mapped to EQ-5D-3L. The committee agreed that there was considerable uncertainty about the utility values from CROWN, and that the utility values from the brigatinib appraisal had stronger face validity. It concluded that on balance, the utility values from NICE's technology appraisal guidance on brigatinib were more appropriate for decision making. In response to the draft guidance consultation document, the company updated its base case to include the utility values from NICE's technology appraisal guidance on brigatinib. The committee concluded that this was appropriate for decision making.

Disutility values for adverse events

3.21 The company modelled the effect of adverse events on quality of life using the rates of adverse events from each technology's pivotal trials. The duration of each adverse event was assumed to be 5 days. The company also applied an annualised utility decrement of -0.037 for adverse events based on an analysis in NICE's technology appraisal guidance on brigatinib for ALK-positive advanced NSCLC that has not

been previously treated with an ALK inhibitor. The EAG noted that the 5-day duration was shorter than what was seen in CROWN or in the trials included in NICE's technology appraisal guidance on brigatinib. It was concerned it may underestimate the effect of adverse events on quality of life. So, it explored a scenario analysis applying utility decrement values more consistent with NICE's technology appraisal guidance on brigatinib. It also assumed a duration of 28 days for adverse events, which was aligned with estimates used in that appraisal, unless data collected in CROWN was available. In response to the draft guidance consultation document, the company updated its approach to assume a duration of 30 days for adverse events, or data from CROWN when this was available. The EAG considered the company's approach to be appropriate and implemented it in its base case. The committee concluded that the company's revised approach was appropriate for decision making.

Dosing calculations

3.22 Lorlatinib is available in 2 pack sizes: 90x25 mg tablets and 30x100 mg tablets. The company used detailed dosing data from CROWN to estimate the proportion of people having a reduced dose of lorlatinib after dose reductions, with 75 mg, 50 mg, 25 mg and 0 mg per day allowed in the model. For the comparator treatments, detailed dosing information was not available. So the company used mean relative dose intensity (RDI) from NICE's technology appraisal guidance on alectinib for untreated ALK-positive advanced NSCLC. The company also used NICE's technology appraisal guidance on brigatinib for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor to account for dose reductions. The EAG explained that it considered the treatment costs applied in the model to be mostly appropriate. But there remained uncertainties about wastage and differences in how dose reductions were accounted for. The EAG expressed concern that wastage could occur after dose reductions because the remainder of the old pack would be wasted after switching to lower dose tablets. The company explained that this was unlikely because most dose reductions occur at the end of a treatment cycle, so there is minimal wastage. The clinical experts explained that there would be minimal wastage with the 30x100 mg tablet pack size. The EAG noted the complexity of the

different available pack sizes and the differences in the price per mg between the packs. So, the EAG expressed its preference to use a unified approach across all technologies based on using RDI to model cost savings. This is a simpler approach that has been previously accepted by NICE technology appraisal committees. The committee was aware that the RDI approach aligned with methods used in previous technology appraisals. It concluded that this was the most appropriate method for calculating dosage in the model. In response to the draft guidance consultation document, the company stated that the RDI approach was less accurate than using detailed dosing data from CROWN. It further stated that using CROWN data could be incorporated into the model accurately, was aligned with clinical opinion and is more reflective of clinical practice. The EAG agreed that using the detailed dosing data from CROWN best captured the cost saving associated with dose reductions and missed doses in the trial. But the EAG noted that using the CROWN data resulted in a lower average total cost for lorlatinib. It noted that if similar data was available for alectinib and brigatinib, a reduction in total costs could also be seen for these treatments. The EAG explained that using the RDI approach for all treatments best reflected difference in total costs between lorlatinib, alectinib and brigatinib. The committee considered that the approach that provided the best measure of the relative difference in total costs should be used. So, it concluded that the RDI approach should be used consistently for lorlatinib, alectinib and brigatinib.

Arm-specific death as a proportion of progression-free survival

3.23 The EAG noted the differences in death events between the arms in the CROWN trial (data deemed confidential so not reported here). It disagreed with the company's approach of calculating deaths as a proportion of progression-free survival events across both arms. This was because the company's approach assumed that an additional proportion of people died in the trial while being progression free, alive and continuing to accrue benefits in the model. At clarification stage, the company made a correction by applying the mean proportion of deaths as progression-free survival events from the CROWN trial to both arms. But the EAG noted that mortality accounted for a much larger proportion of progression-free survival events in the lorlatinib arm than in the

comparator arm in CROWN. This meant that a substantial proportion of people in the progressed disease state on lorlatinib would have been modelled as dead if using arm-specific progression-free survival data. The EAG therefore preferred arm-specific death as a proportion of progression-free survival. The committee recognised the high level of uncertainty associated with the clinical evidence and modelling approach in the company's model. Because of this, it concluded that it would prefer to calculate arm-specific PFS death as a proportion of progression-free survival. In response to the draft guidance consultation document, the company updated its model base case to calculate arm-specific PFS death as a proportion of progression-free survival. The committee concluded that the company's revised approach was appropriate for decision making.

Cost effectiveness

Committee preferred assumptions

3.24 The committee acknowledged that, since the first committee meeting, the company had implemented a number of its preferred assumptions in the economic model base case. These included:

- using the hazard ratios from the global NMA, including data from the ALESIA trial (see section 3.8)
- applying a treatment-effect cap at 10 years (see section 3.17)
- including 5.7 months of treatment beyond progression for both first-line and second-line lorlatinib in the base-case analysis, and use the EAG's estimate for the proportion of people progressing to second-line lorlatinib (see section 3.18)
- using utilities from NICE's technology appraisal guidance on brigatinib for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor (see section 3.20)
- modelling arm-specific death as a proportion of progression-free survival (see section 3.23).

The committee noted that the company had chosen not to implement some of

its preferred assumptions from the first committee meeting. Instead, it had provided additional justification for maintaining its assumptions from the first committee meeting. The committee considered that the additional evidence provided by the company did not alter its preferred assumptions from the first committee meeting, and so retained its preferences for:

- removing the CNS health state (see section 3.14)
- using a consistent RDI costing method for all treatments (see section 3.22).

The committee also noted that the company had not done the following analyses that it had requested at the first committee meeting, and noted that this contributed to the uncertainty in the results of the economic model:

- an NMA assessing lorlatinib's treatment effect on grade 3 and 4 adverse events compared with other ALK TKIs (see section 3.11)
- an adjustment of the risk of PPS by CNS-progression status and exploration of the effect of alternative assumptions and data sources for the modelling of survival outcomes on second-line chemotherapy after progression on first-line ALK TKIs (see section 3.19).

Uncertainty in the cost-effectiveness estimates

3.25 The committee recalled the uncertainties in the evidence base and in the company's modelling assumptions, and how these had been implemented in the economic model. The committee considered that there remained substantial uncertainty in the cost-effectiveness estimates generated using its preferred assumptions because of:

- the subsequent treatments in CROWN not reflecting NHS clinical practice (see section 3.5)
- the highly immature progression-free survival and overall survival in CROWN (see section 3.6)
- the differences between the proportion of people with CNS metastases at baseline in the CROWN trial and other trials included in the NMA (see section 3.9)

- uncertainty in whether and how CNS metastases at baseline affects treatment effect (see section 3.10 and section 3.16)
- a higher incidence of grade 3 and above adverse events associated with lorlatinib compared with other ALK TKIs in trials but no NMA for adverse events (see section 3.11)
- a lack of appropriate data to inform the link between non-CNS and CNS PD health states in the model (see section 3.14)
- uncertainty in how to model the effect of lorlatinib, compared with alectinib or brigatinib, on CNS progression (see section 3.15)
- uncertainty in extrapolating progression-free survival using an exponential curve and capping treatment effect because of immature data (see section 3.17)
- uncertainty in modelling PPS, and the data sources that informed the outcomes after progression on first-line treatments in the lorlatinib and comparator arms in the model (see section 3.19)
- uncertainty associated with the utility values used in the model (see section 3.20).

The committee concluded that, because of the uncertainties in the clinical evidence and the modelling approach, the cost-effectiveness results for lorlatinib were consequently highly uncertain. It concluded that it would take this into account in its decision making.

Cost-effectiveness results

3.26 The committee considered the cost-effectiveness estimates generated by its preferred assumptions. There are confidential commercial arrangements in place for lorlatinib, the comparators and the subsequent treatments. So, the exact incremental cost-effectiveness ratios (ICERs) are considered commercial in confidence and cannot be reported here. Ahead of the second meeting, the company provided an updated commercial arrangement that would have increased the discount for lorlatinib. The higher discount would have applied at both first and second line if lorlatinib had been recommended for the whole population

considered in this appraisal. The committee noted that, even with the higher discount, the company's and EAG's revised base-case ICERs were substantially more than £30,000 per quality-adjusted life year (QALY) gained. The committee also noted the remaining uncertainty in the cost-effectiveness estimates (see section 3.25). It concluded that the most plausible ICER was substantially above the range considered to be a cost-effective use of NHS resources. So, it concluded that it could not recommend lorlatinib for routine use.

Managed access

3.27 Having concluded that lorlatinib is not recommended for routine commissioning in the NHS, the committee considered the possibility that it might be eligible for commissioning through managed access. The committee recalled that the company planned 2 further data cuts for CROWN, in 2025 and 2028. At the second committee meeting, the clinical lead for the Cancer Drugs Fund noted that more mature progression-free survival data from CROWN might reduce uncertainty about the most appropriate progression-free survival extrapolations for use in the model. The clinical lead for the Cancer Drugs Fund also noted that, although more mature overall survival data will become available from CROWN, it will not be generalisable to NHS practice. This is because the subsequent treatments used in CROWN do not align with those used in the NHS (see section 3.5). They also noted that the collection of data on CNS metastases in the Systemic Anti-Cancer Therapy dataset will be of limited value. This is because only data for known CNS metastases is collected and CNS metastases are not routinely assessed at diagnosis in NHS clinical practice (see section 3.9). The committee agreed that more mature progression-free and overall survival data from CROWN might reduce some of the resolvable uncertainty associated with treatment-effect duration and comparative effectiveness. But it recognised that the treatment sequences in the CROWN trial are not generalisable to the NHS. The committee acknowledged that, despite significant uncertainty, lorlatinib may offer improved clinical benefit for some people. It considered that a recommendation through a managed access agreement may resolve some of the uncertainties. But the company's and EAG's ICERs were substantially above the threshold that NICE considers to be a cost-

effective use of NHS resources. The committee considered its preferred assumptions and allowed for uncertainty in the clinical evidence. But it still thought that, at the price proposed by the company, lorlatinib did not have plausible potential to be cost-effective. It also noted the EAG's view that how data was applied in the original model structure did not represent a plausible alternative approach to modelling overall survival, even if further data was collected. So, it excluded any application of that model from its decision making. The committee concluded that it was unable to recommend lorlatinib for managed access.

Other factors

Innovation

3.28 The company considered lorlatinib to be innovative. It stated that lorlatinib has been granted ORBIS designation by the Medicines and Healthcare products Regulatory Agency. The company also highlighted that lorlatinib is a third-generation ALK TKI that is capable of crossing the blood-brain barrier and is retained in the intracranial space. So, it potentially addresses the unmet need for additional treatment options that can cross the blood-brain barrier more effectively than current treatments. The company added that it was specifically designed to inhibit resistant ALK mutations, including the ALKG1202R mutation that substantially increases after treatment with second-generation treatments. The clinical experts agreed that lorlatinib is an effective third-generation ALK TKI with good brain penetration, and that people would welcome additional treatment options. The committee concluded that its preferred model structure could mean that there were CNS benefits associated with lorlatinib that had not been fully captured (see section 3.15). It was aware that above a most plausible ICER of £30,000 per QALY gained, NICE's manual on health technology evaluation notes that an increasingly stronger case will need to be identified for supporting a technology as an effective use of NHS resources. The committee took into account that the company's preferred model structure likely underestimated the ability of alectinib and brigatinib to delay CNS progression (see section 3.15). It also noted the uncertainties in the evidence base and in the company's modelling assumptions (see

section 3.25). Overall, it concluded that allowing for lorlatinib's potential uncaptured benefits would not materially affect its decision.

Equality issues

3.29 The committee noted the stakeholders' comments that people with ALK-positive NSCLC having treatment at small district general hospitals are very likely to be disadvantaged. This is because, in these hospitals, the oncologists may not specialise in lung cancer or have any experience in ALK-positive NSCLC. The committee noted that access to treatment varies across the NHS. It noted that when a technology appraisal is published, it may improve the understanding of the condition and improve access to the treatment. But the committee noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. No other equality or social value issues were identified.

Conclusion

Lorlatinib is not recommended

3.30 The committee concluded that lorlatinib is not recommended for untreated ALK-positive advanced NSCLC in adults. It considered that there was a high degree of uncertainty in the clinical evidence and economic modelling for lorlatinib. When the committee's preferred assumptions were applied, the ICERs for lorlatinib were substantially above what NICE considers to be a cost-effective use of NHS resources.

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

Megan John
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 and a project manager.

Ross Wilkinson, Luke Cowie and Janet Boadu
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ISBN: 978-1-4731-5282-3