NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

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

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

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

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

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using lorlatinib in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 3 March 2023
- Second evaluation committee meeting: 16 March 2023
- Details of membership of the evaluation committee are given in section 4

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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. Ceritinib and crizotinib are also ALK inhibitors but are rarely used for untreated NSCLC. Lorlatinib is another ALK inhibitor and is used after alectinib or brigatinib. It is 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 this is uncertain. Also, 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 increases 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 unclear whether this difference will continue and if lorlatinib will improve how long they live.

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

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Collecting more data through managed access may resolve some of the uncertainty in the clinical evidence. But because of uncertainties in the clinical evidence and the economic model, it is unclear if lorlatinib has the potential to be cost effective. 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 recommended for previously treated ALK-positive advanced non-small-cell lung cancer (NICE technology appraisal guidance TA628)

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 January 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 brain metastases. They explained that brain 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 disease 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

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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 patient experts commented that some people find that lorlatinib has fewer side effects than other ALK TKIs. For example, they have had less fatigue and a better quality of life than they did when taking either alectinib or brigatinib. 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 3.15). For people who have lorlatinib first line, chemotherapy would be used at the 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.

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 it 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 (ALTA-1L) and brigatinib (ALEX) 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 was found. Considering the lack of evidence on an ECOG of 2, as noted by the EAG, 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. The subsequent treatments in CROWN include the other 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. This means 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). Evidence from the trial also showed that intracranial time-to-progression was longer in the lorlatinib arm compared with the crizotinib arm. The difference was also statistically significant (data deemed confidential so not reported here). But the EAG noted that the company only counted the first progression events in these analyses. This meant that if someone had non-central nervous system (CNS) progression and started a new anticancer therapy, they were censored in the trial. So, everyone who had a CNS progression event after progression by any other definition were excluded. 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 0.72, 95% confidence interval 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. So, there was no evidence that the increased progression-free survival would lead to increased overall survival benefit. It noted that no robust conclusions could be drawn about overall survival from CROWN. The company explained that this was because of a lack of death events at the later data cut-off point. 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. 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.

Network meta-analysis

3.7 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

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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 predominantly included sites in China, and so differences in healthcare systems and subsequent treatment options meant that ALESIA was not as applicable to the UK population as the ALTA-1L and ALEX trials were. 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 the results from the global NMA.

Identifying CNS metastases at diagnosis

3.8 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 major effect on the quality of life of people with ALK-positive NSCLC. 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 brain 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 brain metastases. This is because identification of 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

3.9 The EAG was concerned that CNS metastases at baseline could be associated with poor prognosis or a reduced treatment effect associated with ALK TKIs. It explained that the lower proportion of people with CNS metastases in CROWN 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

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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 brain 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 brain 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

3.10 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 in the literature, 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 potentially result in someone becoming disabled. The EAG summarised results from 3 published NMAs that compared the incidence of grade 3 and 4 adverse events for the different ALK TKIs. 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). The committee was aware that the safety profile for lorlatinib may be different from other ALK TKIs, but that there are also similarities. The committee concluded that a comparative analysis of grade 3 and 4 adverse events would help its decision-making.

Economic approach

The company's original economic model

3.11 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. The EAG did not consider this model to be methodologically robust. 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 accepted the EAG's concerns, and agreed at clarification stage to provide a revised model. The committee agreed with the EAG that the original model was not appropriate for decision making.

The company's revised economic model

3.12 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: Study 1001 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 weak 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 were not permitted to cross. But the EAG also noted several significant gaps 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 gaps in the company's model, and concluded that it would take these into account in its decision making.

Modelling the CNS PD health state

3.13 The EAG explained that one of the most problematic aspects of the company's revised economic model was the CNS PD health state. The EAG noted that it is clinically realistic to assume that people whose condition progresses may later develop intracranial metastases. While this transition was described in the company's evidence submission, it was not built into the company's revised model. On progression, people in CROWN had a range of anticancer therapies. This meant that data for people who had CNS progression after non-CNS progression would have been confounded by subsequent treatments. Also, it was not clear if appropriate data was captured in CROWN because people with non-CNS progression events appeared to have been censored from subsequent analysis (see section 3.6). This meant that only first progression events were counted in the trial and it is unknown what proportion of these people would have gone on to have CNS progression. The committee considered that it may be reasonable to assume that the CNS PD health state was more severe than the non-CNS PD health state, and that the health states affect quality of life differently. The company explained that there is no data from CROWN to inform transitions between non-CNS PD and CNS PD health states in either direction because of censoring. In addition to there being no link between non-CNS PD and CNS PD in the model, the EAG also noted that the data used to inform PPS for the CNS PD health state was not appropriate. The EAG explained that the company had used Study 1001 and PROFILE 1001/1005 to inform the PPS outcomes for both non-CNS PD and CNS PD health states in the model. But the EAG did not consider data from these studies appropriate to estimate PPS outcomes for the CNS PD health state. This was because these studies 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

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event. The prognosis of people with intracranial metastases may be worse than the general population with progressed disease, so using PPS outcomes from a population with a better prognosis may overestimate the benefit gain in people with CNS PD. The EAG further commented that the structural link between non-CNS PD and CNS PD appeared to have been incorrectly implemented by the company because exploratory scenarios did not pass simple validation tests. The committee noted these flaws in the model. It recognised that similar 4-state models were previously accepted in NICE's technology appraisal guidance on alectinib for untreated ALK-positive advanced NSCLC and on brigatinib for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor. It agreed that a 4-state model was conceptually appropriate but noted that the circumstances in those appraisals differed from the current appraisal, particularly the availability of relevant evidence to inform the model. The committee agreed with the EAG that the company's 4-state model was flawed and that there was an absence 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.

Extrapolating progression-free survival and capping treatment effect

3.14 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

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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 (AIC) and Bayesian Information Criteria (BIC)
- 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 do 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

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CROWN was immature. The committee was aware that NICE's methods manual 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.

Modelling treatment beyond progression on lorlatinib

3.15 The clinical and patient experts explained that treatment beyond progression was likely with lorlatinib. This is because it is currently positioned as the final targeted TKI therapy 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 condition 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 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 TKI treatments 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 the patient. 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, and stated that treatment beyond progression would be longer for the final TKI than for a TKI that could be followed by a subsequent TKI. They further suggested that, in some cases, treatment with lorlatinib might continue for up to 6 months if it was felt 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 targeted 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. They did not explore how it would affect treatment effect. The committee also noted the company's estimate that 95% of people being treated 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 therapy after progression on lorlatinib. The committee agreed that treatment beyond progression was highly likely and it 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. It considered that it was appropriate for decision making and should have been included in the base-case analysis. 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.

Modelling PPS

3.16 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. 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 3.12). 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 alterative 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. The EAG noted 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 (see section 3.13). 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 3.13). 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.

Utility values in the economic model

3.17 Health-related quality-of-life data were 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 are 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, although the progressed disease utilities used in that appraisal were taken at 30 days into progression, 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.

Dosing calculations

3.18 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 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

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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 relative dose intensity (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.

Other uncertainties in the model

3.19 The committee recognised the high level of uncertainty associated with the clinical evidence and modelling approach in the company's revised model. Because of this, it agreed that it would prefer to use the following assumptions that were included in the EAG's more conservative exploratory base case:

- Arm-specific death as a proportion of progression-free survival: 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 PFS events in the lorlatinib arm than in the comparator arm in CROWN. This means that a substantial proportion of people in the progressed disease state on lorlatinib would have been modelled as dead if using arm-specific PFS data. The EAG therefore preferred arm-specific death as a proportion of progression-free survival.

- Disutility correction and use of CROWN durations for adverse events: in its revised model, the company modelled the impact of adverse events on quality of life. The rates of adverse events were based on 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 observed in CROWN or in the trials included in NICE's technology appraisal guidance on brigatinib. It was concerned it may underestimate the impact of adverse events on quality of life, so 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 unless data collected in CROWN was available.

Cost effectiveness

Cost-effectiveness estimates

3.20 Because of confidential discounts for subsequent treatments, the cost-effectiveness results are commercial in confidence and cannot be reported here. But, the company's base-case incremental cost-effectiveness ratio (ICER), including all discounts was more than £30,000

per quality-adjusted life year (QALY) gained. The EAG made several changes to the company's base case and presented 2 alternative base cases, which also both produced ICERs above £30,000 per QALY gained.

The plausible ICERs for lorlatinib are also highly uncertain. 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's concerns included:

- the highly immature data from CROWN with regard to progression-free survival and overall survival, and that no conclusion on overall survival could be drawn (see section 3.6)
- subsequent treatments in CROWN did not reflect NHS clinical practice (see section 3.5)
- the company's NMA did not include the ALESIA study (see section 3.7)
- 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 3.8)
- uncertainty in whether and how CNS metastases at baseline affects treatment effect (see section 3.9)
- a higher incidence of grade 3 and above adverse events associated with lorlatinib compared with other ALK TKIs in trials but an NMA for adverse events was not done (see section 3.10)
- a lack of appropriate data to inform the link between non-CNS and CNS PD health states in the model (see section 3.13)
- uncertainty in extrapolating progression-free survival using an exponential curve and capping treatment effect because of immature data (see section 3.14)
- uncertainty in modelling treatment effect beyond progression on lorlatinib (see section 3.15)
- 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 3.16)

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- uncertainty associated with the utility values used in the model (see section 3.17)
- uncertainty about different methods of dosing calculations (see section 3.18).

The committee noted the uncertainty in the evidence base and the economic model. It agreed that its preferred assumptions should reflect the high degree of uncertainty. It concluded that its preferred ICERs were calculated using the assumptions outlined in the EAG's more conservative alternate base case. The committee would prefer to see further analyses or additional scenario analysis exploring some of the uncertainties. The committee's preferred analysis would:

- use the hazard ratios from the global NMA, including data from the ALESIA trial (see section 3.7)
- conduct an NMA assessing lorlatinib's treatment effect on grade 3 and 4 adverse events compared with other ALK TKIs (see section 3.10)
- remove the CNS PD health state unless there is new credible data to support the modelling, and there are analyses that explore the differences in quality of life between CNS PD and non-CNS PD (see section 3.13)
- apply a treatment effect cap at 10 years (see section 3.14)
- include 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 3.15)
- adjust the risk of PPS by CNS progression status and explore the impact 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 3.16)
- use utilities from NICE's technology appraisal guidance on brigatinib for ALK-positive advanced NSCLC that has not been previously treated

with an ALK inhibitor in the model where CNS PD is removed (see section 3.17)

- use a consistent RDI costing method for all treatments (section 3.18)
- model arm-specific death as a proportion of progression-free survival (see section 3.19)
- correct adverse event disutility and use CROWN durations for adverse events (see section 3.19).

Other factors

Innovation

3.21 The company considered lorlatinib to be innovative. It highlighted that it is a third-generation ALK TKI that penetrates the CNS and is retained in the intracranial space. So, it potentially addresses the unmet need for additional treatment options for people who develop brain metastases. It was specifically designed to inhibit resistant ALK mutations, including the ALKG1202R mutation that increases substantially 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. Given the uncertainties in the evidence and model, the committee concluded that it had not been presented with evidence or analysis to show that there were benefits associated with lorlatinib that had not been fully captured in the model.

Equality issues

3.22 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.

Conclusions

Lorlatinib is not recommended for routine use in the NHS

3.23 The committee agreed that further analysis was needed to address the high degree of uncertainty in the clinical evidence and economic modelling for lorlatinib. Using the preferred assumptions and modelling approach, the ICERs for lorlatinib were substantially above what NICE considers to be a cost-effective use of NHS resources. So, lorlatinib is not recommended for untreated ALK-positive advanced NSCLC in adults.

Managed access

3.24 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. It agreed that improved maturity of progression-free and overall survival data from CROWN might reduce some of the resolvable uncertainty associated with treatment effect duration and comparative effectiveness. The committee recalled that the company planned 2 further data cuts, in 2025 and 2028. It recognised that the treatment sequences in the CROWN trial were generalisable to the NHS, but agreed that additional data may be informative in resolving some of the clinical uncertainties. The committee was minded to consider a recommendation through a managed access agreement. But it was unable to do so because it could not be confident that lorlatinib has the potential to be plausibly cost effective given the uncertainties in the evidence and modelling. So the committee concluded that lorlatinib did not meet the criteria to be considered for managed access.

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.

Luke Cowie and Janet Boadu
Technical leads

Yelan Guo and Michelle Green
Technical advisers

Kate Moor
Project manager

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