Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

Contents:

The following documents are made available to stakeholders:

1. **Draft Guidance Document (DG)** as issued to consultees and commentators

2. **Comments on the Draft Guidance from** Pfizer
   a. Company Draft Guidance response
   b. Company appendix to Draft Guidance response

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. ALK Positive UK
   b. Roy Castle Lung Cancer Foundation
   c. British Thoracic Oncology Group – *written by clinical expert Dr Shobhit Baijal*
   d. Takeda UK
   e. Centre for Reviews and Dissemination and Centre for Health Economics – York

4. **External Assessment Group critique of company response to the DG**

5. **Feasibility Assessment**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

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

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

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

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

Issue date: April 2025

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

After consultation:

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

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

The key dates for this evaluation are:

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

1 Recommendations

1.1 Lorlatinib should not be used for untreated ALK-positive advanced non-small-cell lung cancer in adults who have not had an ALK inhibitor.

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

What this means in practice

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

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

Why the committee made these recommendations

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

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

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

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

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

2 Information about lorlatinib

Marketing authorisation indication

2.1 Lorlatinib (Lorviqua) is indicated for the 'treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) previously not treated with an ALK inhibitor or whose disease has progressed after prior treatment with an ALK inhibitor.'

Dosage in the marketing authorisation

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

Price

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

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

3 Committee discussion

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

The condition

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

Clinical management

Current treatment and comparators

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

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

Unmet need

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

uncertain how this would influence efficacy.

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

Subgroups

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

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

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

Clinical effectiveness

CROWN trial and its generalisability to the NHS

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

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

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

Progression-free survival

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

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

Time to intracranial progression

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

Overall survival

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

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

Network meta-analysis

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

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

Economic model

Model structure

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

Progression-free survival extrapolation

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

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

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

Additional sources used to model post-progression survival

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

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

Modelling approach for post-progression survival

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

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

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

Time on treatment and treatment after progression

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

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

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

Relative treatment effect waning

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

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

Utility values

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

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

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

Implementation of lorlatinib discount

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

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

Severity

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

Cost-effectiveness estimates

Acceptable ICER

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

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

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

Committee's preferred assumptions

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

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

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

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

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

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

Managed access

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

Other factors

Equality

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

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

Uncaptured benefits

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

Conclusion

Recommendation

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

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Amanda Adler

Interim vice chair, technology appraisal committee D

NICE project team

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

Tom Palmer

Technical lead

Alex Sampson

Technical adviser

Kate Moore

Project manager

Ian Watson

Associate director

ISBN: [to be added at publication]

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Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 2 May 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer UK Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Victoria Brodbin, Senior HTA Manager

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Committee referred base case assumptions are incorporated into the revised company base-case and updated analysis requested from NICE** The company is disappointed that the Draft Guidance (DG) does not recommend lorlatinib for the treatment of untreated ALK-positive advanced non-small-cell lung cancer (NSCLC) [ID6434][1]. Lorlatinib is available as a first line (1L) treatment option for these patients in most other EU countries and the majority of EU countries have had access since 2022. Nonetheless, the company remains committed to collaborating with NICE to achieve access to lorlatinib and is grateful for the opportunity to provide comments for the consultation of the DG. Patients with ALK-positive advanced NSCLC require new treatment options that delay progression, prolong survival, reduce symptom burden, prevent development of new brain metastases and control existing brain metastases, and offer long-lasting benefits by preventing the emergence of treatment resistant mutations in the ALK genes. The company strongly believe that the introduction of lorlatinib would fulfil this important unmet need for patients given it is undoubtedly the most effective ALK TKI available to date at delaying systemic and CNS progression. During the Appraisal Committee Meeting (ACM), patient and clinical experts clearly conveyed the anticipated benefits of lorlatinib as highlighted in the quotes on ACM slides [2]:

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- 'Increase in PFS with lorlatinib is seen as a game-changer'
- 'Lorlatinib PFS benefit is one of the most pronounced and impressive seen in solid tumours'

[redacted]

[redacted]

Summary of company response comments, additional analysis and the revised company base case

To remove uncertainty for the committee, the company has accepted all committee preferred modelling assumptions and include these in the new revised company base-case as summarised in Table 1 below and consider these issues resolved. However, the company do highlight the conservative nature of some of these assumptions, as explained below in the table and in the comments sections below.

In the DG, the committee requested a 4-health state (4HS) model structure that differentiates 1L progression from second line (2L) progression and the company has provided this model, as requested, with this consultation response (see comment 1 and Appendix 1). The 4HS model, with the committee's preferred assumptions, now forms the company's revised base case. The company agrees with the EAG and committee that a 4HS model better reflects the sequencing being modelled and allows better differentiation of the costs and benefits of subsequent treatment options and provides greater transparency for decision making.

Additionally, the company has provided an updated 3HS model incorporating the committee's preferred assumptions and the post progression survival output from the 4HS model for information and context (see comment 1 and Appendix 1).

The updated cost-effectiveness results are presented in Appendix 1 and summarised in comment 8. The results demonstrate lorlatinib is a cost-effective use of NHS resources.

Table 1: Summary of committee preferred assumptions and alignment with company revised base case

Committee preferred assumption	Revised company base case aligned with Committee preference?
Lorlatinib to be used as the reference arm to which hazard ratios are applied to model progression-free survival for the comparators	Yes
36-month piecewise Gompertz curve should be used to extrapolate lorlatinib progression-free survival	Yes
State transition approach for post-progression survival in both the lorlatinib and comparator arm	Yes.

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	However, the company comment on this being a conservative approach for lorlatinib (see comment 3).
Time on treatment, for all treatments, to be equal to progression-free survival with treatment after progression of 3.5 months for 75.6% people	Yes However, the company comment on this being a conservative approach for lorlatinib (see comment 4). An amendment to the 3HS model to allow this scenario to be accurately incorporated is explained in comment 2.
Progression-free survival hazard rates should be waned to the hazard rates of alectinib after 10 years	Yes
Health state utility values should align with the EAG's approach (section 3.16 of the DG)	Yes The new 4-HS model explicitly models duration and utility values for PFS2 health state (see comment 2).
New conditional PAS discount for lorlatinib should apply only to the intervention arm of the model	Yes

Scenario analyses:
Several scenarios have been conducted altering different model parameters and assumptions in the 4HS model. Results are shown in Appendix 1 and summarised in comment 8, in summary in all scenarios lorlatinib remains cost-effective versus alectinib.

Additional consultation comments
Additionally, in response to the DG the company has also provided detailed comments on the following topics:

- ***Overall survival data (see comment 5):*** The company believe OS uncertainty has been accounted for in the modelling approach and assumptions used. The company highlight the strength of the 5-year CROWN PFS data, and why this is expected to translate into OS advantage for lorlatinib compared to the existing treatment options. The final OS data analysis is expected in December 2028.
- **Sequencing (see comment 6):** The company believe sequencing uncertainty has been captured in the updated modelling approach and assumptions used. The company highlight that the treatment duration on 1L lorlatinib will be longer than the alternative treatment sequence
- **Acceptable ICER (see comment 7):** The company has aligned with all committee's preferred assumption addressing the committee's areas of uncertainty and applied a number of conservative assumptions for lorlatinib and therefore believe that the upper end of the ICER threshold is more appropriate for decision

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	making. Particularly, in light of the unprecedented PFS data and the innovative nature of 1L lorlatinib. The company also provide minor comments on subgroups, managed access and a factual inaccuracy.
2	**Model structure (section 3.10, page 13)** **The company has provided a new 4 health state (4HS) economic model and updated 3HS model and therefore any uncertainty associated with the original 3HS model has been accounted for by assuming the alternative structure and by assuming conservative assumptions for lorlatinib** ***Rationale why the company had not considered a 4HS model in the original submission*** The company did not consider a 4HS model in the original submission: 1. As the company wished to keep the model as simple as possible and align the model as far as possible with the previous lorlatinib 1L submission (TA909) where sequencing in the modelling approach was not raised as an issue in the appraisal [3] 2. The company felt that, based on clinical expert feedback on the 5-year CROWN data, lorlatinib is a highly efficacious alternative to the current sequence and many clinicians would favour using it upfront to maximise time on what they now regard as the most efficacious ALK TKI sequencing; therefore, the company felt sequencing may not be a relevant clinical issue However, the company agrees with the EAG and committee that a 4HS model is likely to better reflect the sequences being modelled and allows better differentiation of the costs and benefits of subsequent treatment options as well as providing greater transparency overall. Therefore, as requested by NICE committee, the company has provided a 4HS model to help the committee with decision making, which differentiates 1st progression from 2nd progression and uses more robust data sources and assumptions than the initial 3HS model discussed at the first committee meeting. This new 4HS model, which aligns with all committee preferred assumptions, now forms the revised company base case. A summary of the updated 4HS model is provided below. A detailed description of the updated models and revised base case results are provided in Appendix 1 and comment 8 respectively. ***4HS model with new data sources*** The 4HS model uses a state-transition approach for post-progression survival in both the lorlatinib and comparator arms as per the committee preferred assumption. A diagram of the 4HS model structure and the updated efficacy sources is provided in Figure 1.

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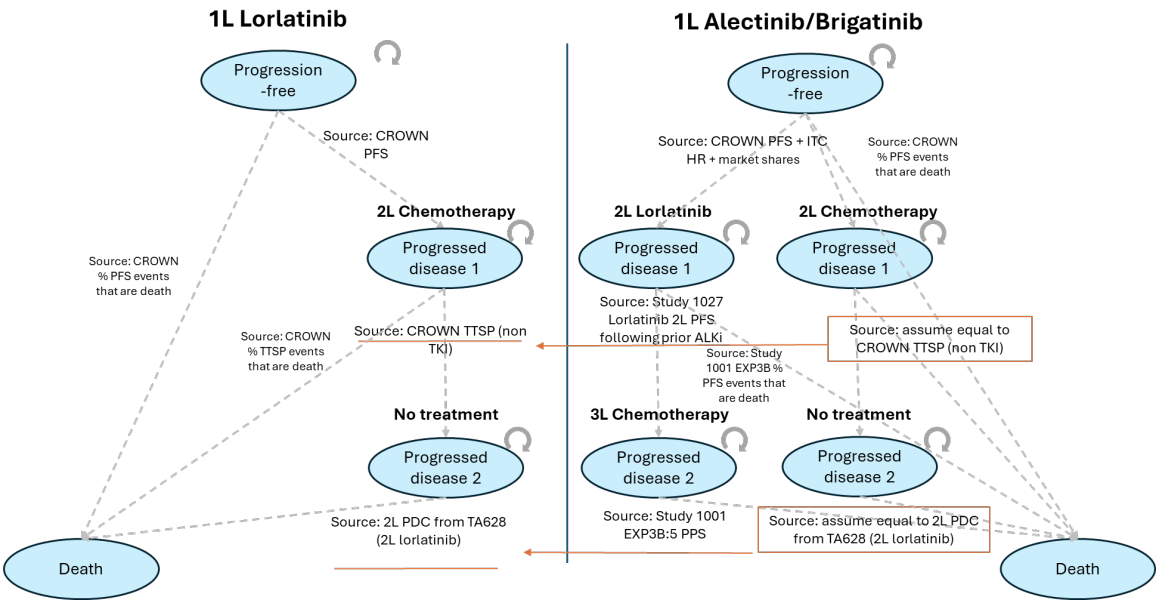
Figure 1: Lorlatinib, alectinib and brigatinib transitions in the four-health state model and efficacy data sources



Key: 1L, first line; 2L, second line; 3L, third line; ITC, indirect treatment comparison; PDC, platinum doublet chemotherapy, PFS, progression-free survival; TTSP, time-to-second progression

To populate the new progressed disease 1 and progressed disease 2 health states in the 4HS model the company has used updated data for the following compared to the 3HS model in the base case:

1. Time-to-second progression (TTSP; measured from the time of first progression), based on5-year CROWN data for 2L chemotherapy (applied following lorlatinib, alectinib or brigatinib). and PFS data from Study 1027 (Phase IV study) for 2L lorlatinib (applied following alectinib or brigatinib). A scenario is also provided using PFS data from study 1001, which was used in the original 3HS model for 2L lorlatinib and in TA628 (applied following alectinib or brigatinib).
2. Post-second progression survival, based on committee preferred approach to model post-progression of the chemotherapy arm in TA628.
3. Updated utility data in the progressed disease 1 and progressed disease 2 health states, based on TA628.

The approach and data sources used in the 4HS model are summarised in Figure 2 and Table 1 and in more detail in this comment below and in Appendix 1. The data sources best reflect the NICE decision problem and the UK treatment pathway. All other data and inputs remain unchanged in the 4HS model versus the initial 3HS model. The company highlight that the modelling of OS is still conservative with respect to lorlatinib, as it assumes post-second-

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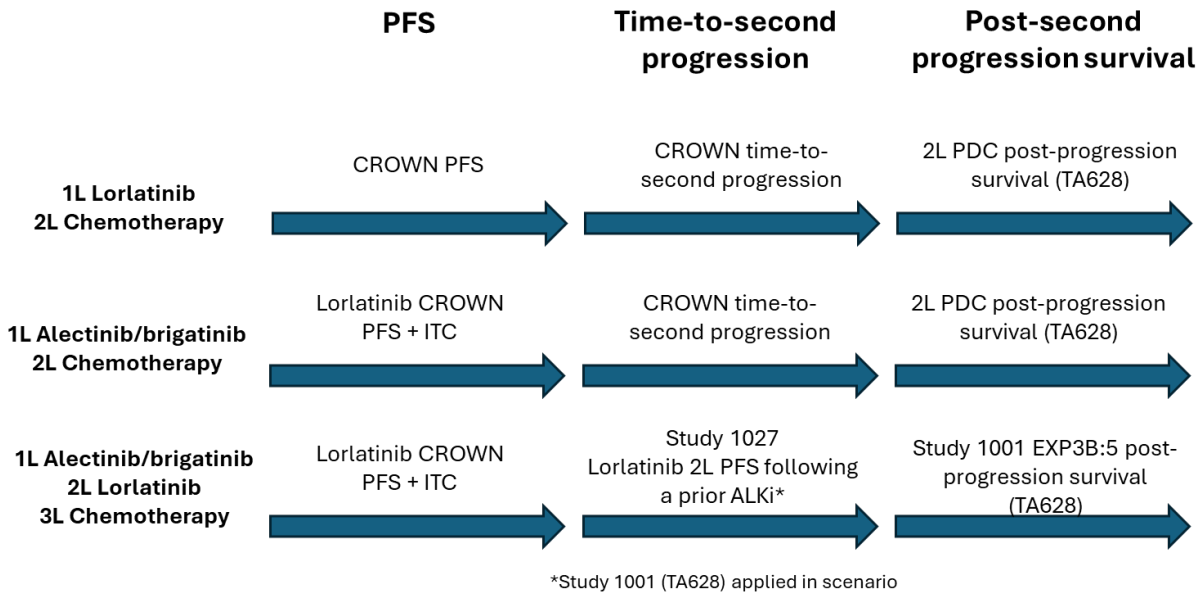
progression survival (after 1L lorlatinib followed by 2L chemotherapy) to be equal to post-progression survival in the chemotherapy arm of the lorlatinib 2L submission (TA628) (after ceritinib/crizotinib 1L, followed by chemotherapy 2L). Considering lorlatinib's ability to cross the blood brain barrier and therefore increased potency and effect on brain metastasis, it is expected that the post-second progression survival after 1L lorlatinib followed by chemotherapy is longer than after first-line crizotinib or ceritinib followed by chemotherapy.

Figure 2: Four-health state sources and assumptions



Key: 1L, first line; 2L, second line; 3L, third line; ITC, indirect treatment comparison; PDC, platinum doublet chemotherapy; PFS, progression-free survival.

Table 2: Summary of the approach and sources used to derive the 4HS model

	Original 3HS committee preferred assumption i.e. STM approach (taken from ACM1 slide 28)		**4HS STM model**	
	Lorlatinib	*Alectinib/ Brigatinib*	*Lorlatinib*	*Alectinib/brigatinib*
Progression-free survival	Fitted curves to lorlatinib PFS *Source*: CROWN	Fitted curves to *lorlatinib* PFS + hazard ratio *Source*: CROWN + NMA	Fitted curves to lorlatinib PFS *Source*: CROWN	Fitted curves to *lorlatinib* PFS + hazard ratio *Source*: CROWN + NMA

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	Post first progression to second progression survival	Transition probability estimated (STM) *Source*: PROFILE 1001/1005	Transition probability estimated (STM) *Source*: Study 1001 (EXP3B-5) and PROFILE 1001/1005	Transition probability estimated from exponential curve fitted to time-to-second progression, defined as time from first progression to second progression *Source:* CROWN	Alectinib/brigatinib followed by chemo: Assume same time-to-second progression as 1L lorlatinib *Source:* CROWN Alectinib/brigatinib followed by lorlatinib: Transition probability estimated from exponential curve, fitted to progression free survival Source: Study 1027, Phase 4 2L lorlatinib study	
	Post second progression			Transition probability estimated from exponential curve, based on the median post-progression survival observed in the chemotherapy arm of the lorlatinib 2L submission *Source*: TA628	*Alectinib/brigatinib followed by chemo:* Same assumptions as lorlatinib arm *Source*: TA628 *Alectinib/brigatinib followed by lorlatinib followed by chemo:* Based on the committee's preferred PFS on TA628, and the committee's preferred OS curve in three health-state model structure (exponential), a post-progression mortality rate was derived so that the combined PFS and PPS generates the same mean survival as the selected (exponential) OS curve *Source: Study 1001 EXP3B:5*	

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Overall survival	PFS plus PPS	PFS plus PPS	PFS plus time-to-second progression plus post-second progression survival	PFS plus time-to-second progression plus post-second progression survival

Key: 1L, first line; 2L, second line; 3L, third line; ITC, indirect treatment comparison; NMA, Network Meta-Analysis; PDC, platinum doublet chemotherapy; PFS, progression-free survival.

1. Time-to-second progression (from the time of first progression)

Different sources and assumptions are used for lorlatinib and alectinib/brigatinib time-to-second progression from first progression, a summary of the data is provided in Table 3 Table 1 below and a detailed description of the data is provided in Appendix 1.

The new 4HS model is using robust data sources that reflect time from first to second progression and accurately reflect the UK NHS treatment pathway.

2L chemotherapy following 1L Lorlatinib, 1L alectinib or 1L brigatinib: Uses randomised 5-year CROWN data for people who progressed on 1L lorlatinib and did not receive a ALK TKI as their subsequent 2L treatment after 1L lorlatinib. In contrast, the original 3HS model had to utilise second-line OS data from Ou et al. 2014 (PROFILE 1001/1005), in to capture PPS following first-line treatment with an ALK TKI. Ou et al. 2014 was not fully aligned with the decision problem as patients received chemotherapy after 1L crizotinib. Therefore, the 4HS model allowing direct application of TTSP data has data to be incorporated that better reflect UK clinical practice.

2L lorlatinib following 1L Alectinib or 1L brigatinib: Uses PFS data from a Phase IV study (n=71), investigating the efficacy and safety of 2L lorlatinib in ALK+ metastatic NSCLC patients specifically previously treated with only one prior ALK TKI. This data was recently presented at the European Lung Cancer Congress in March 2025 [4]. This is a robust source of data to model time from first to second progression for 2L lorlatinib following 1L alectinib or 1L brigatinib given 100% of people enrolled had received a second generation ALK TKI 1L, which is aligned with UK clinical practice and reflects the decision problem. A summary of the study is presented in Appendix 1. The data demonstrates that the median PFS for lorlatinib 2L following one prior second generation ALK TKI is 12.2 months [4]. The original 3HS model used cohort 3B:5 PFS data from study 1001 (2L lorlatinib study) to derive the time-to-progression with 2L lorlatinib following 1L alectinib or brigatinib. However, given the timing of Study 1001, some patient received 2nd generation TKIs, but some also received 1st generation TKIs. In the 4HS model, the company also provide a scenario where this data is used to derive time-to-second progression instead of study 1027. All data and assumptions used in this scenario align with the committee preferred assumptions from NICE TA628. Results are presented in Table 11.

Table 3: Summary of the approaches to extrapolate time-to-second progression from first progression in 4HS model

Treatment	PFS rate	PFS events that are death	Approach	Source

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	Lorlatinib followed by chemotherapy	[redacted]	[redacted]	**Updated data in the 4HS model:** Exponential curve based on based on time-to-second progression, defined as time from first progression to second progression	CROWN 5-year time from first to second progression data for progressed patients without subsequent ALK TKi (see Appendix 1)
	Alectinib/ brigatinib followed by chemotherapy	[redacted]	[redacted]	**Updated data in the 4HS model:** Assume same time-to-second progression as 1L lorlatinib	CROWN 5-year time from first to second progression data patients without subsequent ALK TKi (see Appendix 1)
	Alectinib/ brigatinib followed by lorlatinib	[redacted]	[redacted]	**NEW data in the 4HS model:** Exponential curve based on 2L lorlatinib PFS **Scenario – using data from 3HS model:** Generalised gamma fitted to the 2L lorlatinib PFS, as agreed in TA268	Study 1027: Phase IV 2L lorlatinib study [4] - Study investigating the efficacy and safety of 2L lorlatinib in patients with *ALK*+ metastatic non-small cell lung cancer previously treated with an ALK TKI. Study 1001 EXP3B:5 cohort

2. Post-second progression survival

Due to the 4HS model structure, different sources and assumptions are used for lorlatinib and alectinib/brigatinib post-second progression survival in the 4-HS model. Post-second progression survival after 1L lorlatinib and 2L chemotherapy is not available in CROWN and after 1L alectinib or brigatinib and 2L lorlatinib overall survival data is not available in Study 1027. Therefore, post-second progression survival is based on the committee's preferred approach to

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estimate post-progression survival of the 2L chemotherapy from TA628. Post progression second progression survival for 1L alectinib/brigatinib followed by 2L lorlatinib is based on the committee's preferred PFS in TA628, and the committee's preferred OS curve in three health-state model structure (exponential), a post-progression mortality rate was derived so that the combined PFS and PPS generates the same mean survival as the selected (exponential) OS curve.

A summary of the approach used for each treatment in the 4HS model is presented in Table 4 and further details are provided in Appendix 1.

The company highlight that the modelling of OS is still conservative with respect to lorlatinib, as it assumes post-second-progression survival (after 1L lorlatinib followed by 2L chemotherapy) to be equal to post-progression survival in the chemotherapy arm of the lorlatinib 2L submission (TA628) (after ceritinib/crizotinib 1L, followed by chemotherapy 2L). Considering lorlatinib's effect on brain metastasis, it is expected that the post-second progression survival is longer than with first-line crizotinib or ceritinib followed by chemotherapy.

Table 4. Summary of the approaches to extrapolate post-second progression survival

Treatment	Post-second progression survival (mortality rate)	Approach	Source
Lorlatinib followed by chemotherapy	[redacted]	Assume equal to the modelled post-progression survival of the chemotherapy arm in the second-line setting from TA628 (second-line lorlatinib submission)	TA628: 2L chemotherapy arm[5]
Alectinib/brigatinib followed by chemotherapy	[redacted]	Assume equal to the lorlatinib arm	TA628: 2L chemotherapy arm[5]
Alectinib/brigatinib followed by lorlatinib (1st subsequent treatment) followed by chemotherapy (2nd subsequent treatment)	[redacted]	Based on the committee's preferred PFS on TA628, and the committee's preferred OS curve in three health-state model structure (exponential), a post-progression mortality rate was derived so that the combined PFS and PPS generates the same mean survival as the selected (exponential) OS curve	Study 1001 EXP3B:5

Key: PFS, progression-free survival; PPS, post-progression survival; OS, overall survival

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3. Utilities

The 4HS model is aligned with the committee's preferred assumptions regarding utilities as summarised in Table 1 in comment 1. However, the new 4HS model requires additional utility values to differentiate progressed disease 1 and progressed disease 2 health states. The utility model values applied in the model are presented in Table 5 and new data is highlighted.

- *Progressed disease 1 on second-line chemotherapy* utility values are based on the progressed disease utility values from NICE TA670 [6](as per the 3HS model).
- *Progressed disease 1 on lorlatinib second-line after alectinib/brigatinib*, the progression-free values from NICE TA628 [5] are not used as they lacked face validity compared to progression-free values (progression-free on second-line lorlatinib is 0.785, while progression-free on first-line lorlatinib is 0.793). Therefore, in line with the committee preferred assumptions the mid-point recommended by the EAG was used (0.725).
- Utility values for the off-treatment state are considered not applicable as patients are on treatment until progression. Off-treatment is only available for patients that received second-line chemotherapy after lorlatinib/alectinib/brigatinib as no third-line treatments are considered after second-line chemotherapy. For patients that received alectinib/brigatinib followed by lorlatinib followed by chemotherapy, they will experience both on and off treatment during progressed disease 2.
- *Progressed disease 2*, the progressed disease value from NICE TA628 [5] was applied.

Table 5: Summary of the mean utility values in the 4HS model

State	On treatment	Off treatment	On treatment (treatment beyond progression of the previous line)
Progression-free			
Lorlatinib	0.793 (TA670)	N/A	N/A
Brigatinib	0.793 (TA670)	N/A	N/A
Alectinib	0.793 (TA670)	N/A	N/A
Progressed disease 1			
Lorlatinib followed by chemotherapy	0.624 (TA670)	N/A	0.793 (TA670)
Brigatinib followed by chemotherapy	0.624 (TA670)	N/A	0.793 (TA670)
Alectinib followed by chemotherapy	0.624 (TA670)	N/A	0.793 (TA670)
Brigatinib followed by lorlatinib	0.725 (EAG assumption)	N/A	0.793 (TA670)
Alectinib followed by lorlatinib	0.725 (EAG assumption)	N/A	0.793 (TA670)

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Progressed disease 2			
Lorlatinib followed by chemotherapy	N/A	0.460 (TA628) NEW data in 4HS model	N/A
Brigatinib followed by chemotherapy	N/A	0.460 (TA628) NEW data in 4HS model	N/A
Alectinib followed by chemotherapy	N/A	0.460 (TA628) NEW data in 4HS model	N/A
Brigatinib followed by lorlatinib followed by chemotherapy	0.460 (TA628) NEW data in 4HS model	0.460 (TA628) NEW data in 4HS model	N/A
Alectinib followed by lorlatinib followed by chemotherapy	0.460 (TA628) NEW data in 4HS model	0.460 (TA628) NEW data in 4HS model	N/A

Revised 3 HS model

The company has also provided an updated 3HS model incorporating all the committee's preferred assumptions and the revised post-progression survival estimated in the new 4HS model only. It was not possible to add in 3.5 months additional time on treatment for all treatments in the EAG model 3HS model and therefore the company has updated this in the revised 3HS model.

A detailed description of the implementation of the updated 3HS model is provided in Appendix 1. In summary, the 3HS model has been updated to reflect the new assumptions derived for CROWN time-to-second progression in the 4HS model. Alectinib/brigatinib followed by lorlatinib has not been updated to reflect the new phase IV study 1027 PFS as OS data is not available from study 1027 data. Therefore, in order to be aligned with the committee's preferred assumptions this data source has not been updated. However, the scenario with the application of Study 1001 PFS instead of Study 1027 PFS for time to second progression on lorlatinib after alectinib/brigatinib aligns with the 3HS data source. Lorlatinib/alectinib/brigatinib followed by chemotherapy post-progression survival in the 3HS model has been updated to match the modelled post-progression survival from the 4HS state model. The post-progression survival in the 4HS model is defined as time-to-second progression plus post-second progression survival. A post-progression survival rate for the 3HS model was estimated to generate the same mean survival as the post-progression survival modelled in the 4HSmodel. The estimate post-progression mortality rate is [redacted]

Summary

The updated 4HS model structure better differentiates the costs and benefits of subsequent treatment options and uses a more a robust and accurate source of data for post-progression survival by using randomised CROWN data; the initial post-progression survival estimate in the original 3HS model was considerably below the time from first to second progression from CROWN and therefore is not plausible (see Appendix 1 and comment 3 for further information). In the new 4HS model, treatment sequences are adequately modelled, PPS survival assumptions for the lorlatinib arm remain conservative and the company believes that uncertainty related to model structure has been addressed for the committee with the new 4HS.

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	The updated base case results in the 4HS and updated 3HS model are presented in comment 8.
3	**Modelling approach for post-progression survival (section 3.13, page 15)** The company has aligned with the Committee's preferred assumptions for a state-transition approach in both arms of the model in their revised base case. This approach removes the uncertainty of both relying on immature OS CROWN data and of applying different structural approaches in both arms and therefore this uncertainty no longer remains. However, the company wishes to highlight in using the committee preferred approach it provides conservative survival assumptions for lorlatinib. *New 4 HS model:* Detailed description of the different sources and assumptions are used for lorlatinib and alectinib/brigatinib post-second progression survival in the 4HS model is described in comment 2 and in Appendix 1. In the original 3HS model the STM model approach was too conservative for lorlatinib, as the lorlatinib arm applied second-line OS data from Ou et al. 2014 (PROFILE 1001/1005) to capture PPS following first-line treatment with an ALK TKI, which represents data from patients receiving chemotherapy after first-line crizotinib. The new analysis of the 5-year CROWN data used in the 4HS model for the time from first to second progression was for progressed patients who did not receive a ALK TKI as their subsequent 2L treatment after 1L lorlatinib to align with the UK treatment pathway, the decision problem and ensure that the data being used was not confounded by post-progression treatment. The data shows that this initial post-progression survival estimate in the 3HS model was considerably lower than the time–to-second progression in the 5-year CROWN data and therefore is not plausible; the median PPS based on PROFILE 1001/1005 is 6.90 months, while the median time to secondary progression from first progression in the 5-year CROWN data is [redacted] months. The 4HS model removes reliance on this overly conservative estimate of post-progression survival used in the initial 3HS model. The company had not used this data previously as the company wished to keep the model as simple as possible and align the model as far as possible with the previous lorlatinib 1L submission (TA909). Additionally, given the 5-year CROWN analysis shows that median PFS was not reached for lorlatinib, over half of the lorlatinib patients have not progressed yet therefore the patients who have been analysed for the time from first to secondary progression are those than can be defined as the early progressors given they have already progressed on lorlatinib. As the data continues to mature, the time from first to secondary progression is likely to extend as we start to collect data from those patients who have had a more favourable response from lorlatinib. This potential increase is attributed to lorlatinib's ability to delay and protect from brain metastases and prevent the development of ALK-resistant mutations, which could result in a longer duration before secondary progression occurs in patients who respond positively to lorlatinib treatment. Clinical feedback suggests that intracranial progression is a key factor in patient progression, but lorlatinib offers remarkable levels of neuroprotection. In the CROWN trial no new IC progression events were observed after 28 months. As mentioned above to align the data used in the 4HS model with the decision problem and NHS treatment pathway the time to secondary progression data used is for CROWN participants who had both PFS1 and PFS2 events and did not receive an ALK TKI as their subsequent 2L treatment after 1L lorlatinib. To confirm that second-line ALK TKI treatment after lorlatinib does

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	not affect time to secondary progression to first progression, an analysis was undertaken for all CROWN participants who had both PFS1 and PFS2 events, regardless of the subsequent 2L treatment type, after 1L lorlatinib. The Kaplan-Meier results are shown in Figures 3 and 4 in the Appendix 1 and show that the results of the overall population and the results of subgroup of CROWN patients who did not receive an ALK TKI as their subsequent 2L treatment after 1L lorlatinib is aligned, supporting the notion that 2L ALK TKIs have no efficacy when used after lorlatinib (median time-to-second progression for all progressed patients is [redacted] and [redacted] for all progressed patients with no ALK TKI as first subsequent treatment in the lorlatinib arm). The updated CROWN data used in the 4HS model is not confounded by post-progression treatment. The company highlight that the modelling of OS is still conservative with respect to lorlatinib, as it assumes post-second-progression survival to be equal to post-progression survival in the chemotherapy arm of the lorlatinib 2L submission (TA628) which pools first-line first-generation TKI crizotinib and second-generation TKI ceritinib. Considering lorlatinib's effect on brain metastasis, it is expected that the post-second progression survival is longer than with first-line crizotinib or ceritinib followed by chemotherapy. This conservative assumption also applies in the updated 3HS model. Scenario analyses were conducted in the 4HS model to explore uncertainty around the post-secondary progression survival parameter by varying post-secondary progression mortality rate and results are presented in Appendix 1 and comment 8; lorlatinib remains cost-effective versus alectinib.
4	**Time on treatment (TOT) and treatment after progression (section 3.14, page 17)** In the NICE DG, the NICE committee requested the company to update the model to assume that for all treatments, TOT was equal to PFS, with 3.5 months of treatment after progression for 75.6% of people. The company believes that using the CROWN trial observed relationship between TOT and PFS would be the most appropriate, based on the NICE view of the hierarchy of evidence. With even more mature ToT from the 5-year CROWN data, there continues to be a ToT < PFS observed relationship (explained in detail in company submission document B.3.3.5 and shown in Figure 30 of the company submission). This is likely due to the unusually long duration of treatment for lorlatinib compared with second generation ALK TKIs; the greater the duration of treatment with an ALK TKI, the greater the likelihood of stopping treatment before disease progression. Therefore, the company highlight that assuming TOT=PFS and treatment beyond progression for lorlatinib are both conservative assumptions for lorlatinib given both assumptions add additional cost for lorlatinib but not additional benefit. There is no alternative source of data to confirm what the benefit would be if TOT=PFS given CROWN, the relevant data source, demonstrates TOT<PFS. The company has also validated with UK HCPs that these are both conservative assumptions. It would be expected, in assuming TOT=PFS for lorlatinib this would results in additional benefit in PFS, time to second progression and post-secondary progressions survival and that any additional treatment beyond progression would also translate into additional benefit, which will not be captured under the current base-case assumptions. However, the company has included this committee preferred assumption in the new 4HS model and forms part of the revised company base case. Modelling treatment beyond progression in the 4HS model and updated 3HS model is applied as a one-off cost based on the mean time on

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	treatment beyond progression and the percentage of patients in the committee preferred base case (3.5 months for 75.6% people).
5	**Overall Survival (DG pg. 10, section 3.8)** **The company believe OS uncertainty has been accounted for in the modelling approach and assumptions used. The company highlight the strength of the 5-year CROWN PFS data, and why this is expected to translate into OS advantage for lorlatinib compared to the existing treatment options.** ***Explanation of why no further OS analysis can be provided*** The CROWN statistical analysis plan was pre-determined before the trial commenced. The first specified OS interim analysis was conducted at the time of the primary data cut-off at a median follow-up of 18 months and OS data were still maturing. According to the global trial protocol, the number of pre-specified events in the global trial protocol required to conduct the next OS analysis (second OS analysis) is when 139 deaths have occurred, representing a 70% information fraction. At the time of the 5-year CROWN analysis in 2023, and continuing to the present, this required number of 139 deaths have not occurred. Therefore, this OS analysis, and any other OS analysis, cannot be conducted to uphold protocol integrity and comply with regulatory guidelines. Updated OS results from CROWN will be reported once the 70% information fraction is achieved, [redacted]. The final OS analysis is estimated to be in December 2028. OS is an alpha protected endpoint, meaning that any analyses conducted before reaching this endpoint must be pre-specified in the protocol to prevent selective and biased reporting of trial result. Pfizer UK is unable to amend a global international trial protocol. The CROWN trial remains the sole ongoing phase 3 study for ALK+ NSCLC, offering a unique opportunity to demonstrate a clinically meaningful and significant OS advantage. It is crucial, therefore, to maintain the trial's statistical integrity and avoid expending alpha on premature data cuts. Given the number of deaths required to do the second OS analysis have not occurred, the company and the clinical community believe this should be viewed as a positive uncertainty for patients and clinicians and should not be a barrier to access to lorlatinib. Analysis on other endpoints related to PFS, including PFS1 and PFS2, were able to be provided by the company in the updated submission as these were “unplanned” descriptive analyses that have only occurred after protocol specified analyses in which the primary endpoint of PFS (BICR) was met, which does not break trial reporting conventions. ***OS uncertainty has been accounted for in the modelling approach*** The company has acknowledged throughout the submission and appraisal process that having 18 months of OS data for modelling purposes poses challenges in decision making and as a result, have taken this into account by using state transition approach for post-progression survival for lorlatinib, which does not use OS data from CROWN or the OS results from the NMA, and by using conservative modelling assumptions to model OS for lorlatinib, for example assuming that post-second-progression survival after lorlatinib equals post-progression survival

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	of the chemotherapy arm from TA628. As a result, company believe that OS uncertainty has been accounted for. ***Clinical opinion is that PFS will translate into an OS benefit*** During submission development and at the ACM, clinical advisers noted that the PFS data is the most important data from CROWN and that the latest available PFS results from CROWN were highly clinically significant and all agreed that the PFS advantage will translate into an OS advantage [3]. Clinical expert advice suggests that given the lack of progression events and the neuroprotective effect, the median OS for lorlatinib could be expected to be up to at least 10 years. A recent publication, from leading clinicians, supports the theory that lorlatinib's OS will surpass that of alectinib and other earlier-generation TKIs [7]. ***Lorlatinib OS HR is expected to improve over time compared with the 18-month data*** The company acknowledges that due to the immature OS data, the magnitude of the OS benefit is currently unclear. However, the CROWN data already supports that there is an OS advantage of lorlatinib over the other ALK TKIs as explained below: • The 5-year CROWN data provide the longest ever PFS reported for a targeted therapy in NSCLC and other solid tumours [8]. At the 5-year CROWN analysis median PFS was not reached for lorlatinib (95% CI: 64.3, NR) and was 9.1 months for crizotinib (95% CI: 7.4, 10.9) [8]. This data demonstrates that people in the lorlatinib arm were having fewer progression or death events than the crizotinib arm; the lower bound of the CI for lorlatinib (64.3) is considerably higher than the upper bound CI for crizotinib (10.9) and therefore it can be inferred that there is likely to be an OS benefit for lorlatinib versus crizotinib, the magnitude of which is currently uncertain. • There was an 81% reduction in the risk of progression or death in favour of lorlatinib versus crizotinib (HR: 0.19; [95% CI: 0.13, 0.27]) [8]. • Since lorlatinib has an unprecedented 5-year CROWN investigator assessed PFS rate of 60% [8] the 5-year OS rate is expected to be considerably above 60%. • A recent publication also highlights that very few progression events were reported after 3 years in CROWN (3 yr PFS was 65% compared with the 5-year PFS of 60% for lorlatinib) which is consistent with an impression of flattening of the tail of the PFS curve [9]. • As discussed above, OS data had not reached maturity at the 5-year data cut-off so currently only 18-month data is available and at this time point only 51 death events had occurred. A survival benefit for lorlatinib versus crizotinib (and versus alectinib, brigatinib) is expected to emerge over time as the PFS benefit feeds through into later OS data cuts and this is supported by clinical opinion. The HR for 18-month OS data showed a trend towards a reduction in the risk of death in the lorlatinib arm compared with the crizotinib arm (HR: 0.72 [95% CI: 0.41, 1.25])[10]. An improvement in OS HRs as OS data matures has been demonstrated by other ALK TKIs:

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- ALEX trial, where with a median follow-up of 18.6 months the OS HR between alectinib and crizotinib was 0.76 (95% CI: 0.48–1.20) compared to 0.67 (95% CI: 0.46–0.98) with a median follow-up of 48.2 months[11, 12].
- ALESIA trial, at the median follow-up of 61 months, OS HR between alectinib and crizotinib was 0.60 (95% CI: 0.37–0.99)[13].

CROWN PFS data is similar to the OS data for comparators at similar time points

As mentioned above in the 5-year CROWN analysis, median PFS was not reached for lorlatinib (95% CI: 64.3, NR) and was 9.1 months for crizotinib (95% CI: 7.4, 10.9) [8]. In contrast for the second generation ALK TKIs, alectinib and brigatinib, their mPFS was reached at 34.8 months and 24 months respectively [14, 15]. Importantly, the 5-year CROWN PFS data for lorlatinib is similar to the OS data for the comparator treatments at similar time points, as summarised in Table 6. Additionally, the PFS2 (randomisation to 2nd progression) from CROWN 5-year data was 67%, which is also higher than the OS data for the comparator treatments at similar time points. Therefore, the OS benefit from lorlatinib has the potential to be of higher magnitude than with 2nd generation TKIs. A recent publication also supports that lorlatinib OS is expected to surpass that of other TKIs [7].

Table 6: OS rates in comparator ALK TKIs compared to lorlatinib CROWN PFS rates

	Alectinib (ALEX) [12]	**Alectinib (ALESIA)[13, 16]**	**Brigatinib (ALTA-1L) [14]**		**Lorlatinib (CROWN) [8]**
4-year OS rate (95% CI)	65.3% (55.3-73.3%)	-	66% (56%-74%)	**4-year PFS rate (95% CI)**	63%
5-year OS rate (95% CI)	62.5% (54.3-70.8%	66.4% (57.9-74.9%)	-	**5-year PFS rate**	60% (51 to 68%)
7-year OS rate (95% CI)	-	56% (47.0-65.0)	-	**-**	-
Median OS	NR at 48 months	NR at 61 months	NR at 40 months	**Median PFS**	NR at 60.2 months

Key: CI, confidence interval, NR, not reported; OS, overall survival, PFS, progression free survival

Study 1001 study results

The potential for OS benefit with lorlatinib is further supported by data from a subgroup of 30 patients who did not receive prior ALK TKIs (EXP1 arm) in the lorlatinib 2L trial (Study 1001). This study demonstrated that at the median duration of follow-up for OS of 72.7 months [95% CI: 69.3, 76.3], the median OS was NR [95% CI: NR, NR] and 5-year OS probability was 76.3%[17], higher than the OS reported for comparators at similar time points as highlighted in Table 6 above. The current 4HS model predicts a lower % OS at 5 years (62.3%), further supporting the model is conservative. This data indicates a strong potential for improvement in OS with 1L lorlatinib, as noted above this is higher than the OS rate seen in comparator treatments.

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	Summary In summary, although no further OS data for lorlatinib is currently available the company believe this should be viewed as a positive uncertainty; not being able to conduct further OS analysis because the number of death events required to conduct protocol pre-specified analyses have not occurred is positive for clinicians and patients and should not be a barrier to access to this treatment. Given the 5-year follow-up of CROWN demonstrates lorlatinib provides the longest PFS ever observed for a single targeted agent in any solid tumour trial, it is expected that this PFS benefit will feed through into an OS benefit and this is supported by clinical experts. The 5-year CROWN PFS data for lorlatinib is similar to the OS data for the comparator treatments at similar time points, which shows that the OS benefit from lorlatinib is likely to be of a higher magnitude than with second generation TKIs. The systemic efficacy results from CROWN, coupled with prolonged intracranial efficacy and the absence of new safety signals, represent unprecedented outcomes for patients with ALK-positive advanced NSCLC and set a new benchmark for targeted therapies in cancer. Considering the considerable benefits of lorlatinib over second generation ALK TKIs, it should be available as a first-line treatment option for people with ALK-positive advanced NSCLC.
5	**Sequencing (section 3.5, page 8)** **The company believe any sequencing uncertainty has been captured in the updated modelling approach and data sources. The company highlight that the treatment duration on 1L lorlatinib will be longer than the alternative treatment sequence** ***Clinicians suggested lorlatinib is a highly efficacious alternative to the current sequence and that many would favour using it upfront to maximise time on what they now regard as the most efficacious ALK TKI*** Clinician feedback during the submission development, and at the ACM, suggested that HCP's main priority is to be able to use the most effective treatment option first to give patients the best outcome to delay progression and intracranial progression. HCPs and patients have highlighted treating patients upfront with the most effective progression-delaying treatment (and so longest duration treatment) is in line with current treatment paradigms and ALK-positive NSCLC should not be an exception to this. A recent publication also highlights that the greatest therapeutic benefit of lorlatinib is when used first line as part of a treatment strategy to prevent or delay progression events, such as brain metastases, and to suppress potential mechanisms leading to treatment resistance as opposed to it being used sequentially after earlier-generation TKIs. Preventing and controlling for devastating progression events should be the priority for patients, particularly as up to 50% of patients will develop a brain metastases at some point in their illness [9]. This highlights that lorlatinib 1L represents the most efficacious treatment sequence available for patients . Findings from CROWN and the company NMA demonstrate that lorlatinib provides impressive improvements in PFS for patients with ALK-positive advanced NSCLC compared with the current options for first-line treatment. Additionally, 10 further NMAs (including nine independent NMAs) support the use of lorlatinib as a clinically effective first-line treatment for patients with ALK-positive advanced NSCLC [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28]

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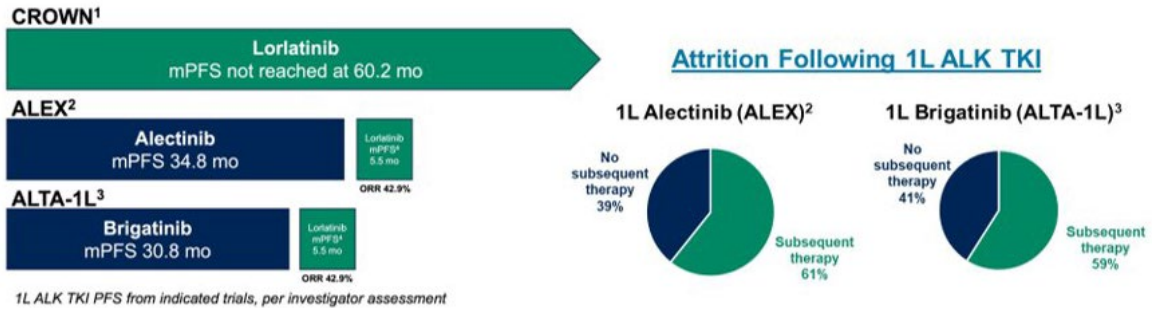
[11]. A review of all 10 NMAs found consistent results, demonstrating that the totality of evidence supports lorlatinib's benefit when compared with other ALK TKIs [18].

The treatment duration on 1L lorlatinib will be longer than the alternative treatment sequence

The uniquely long PFS for lorlatinib demonstrates that many patients who would receive lorlatinib 1L line would have a duration of treatment longer than the sequence of alectinib or brigatinib followed by lorlatinib in 2L, based on the RCT data, as illustrated in Figure 3 below which was presented at ASCO 2024 [29].

Figure 3: Length of mPFS for lorlatinib in CROWN compared to mPFS in key trials for alectinib and brigatinib including lorlatinib second-line treatment



Key: 1L, first-line; ALK, anaplastic lymphoma kinase; mo, month; mPFS, median progression-free survival; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Sources: 1. Solomon et al. 2024 [8] 2. Mok et al. 2020[15] 3. Camidge et al. 2021[14] 4. Felip et al. 2021; Taken from Lin J ASCO 2024 presentation [29]

The original model structure accounted for sequencing and the new 4HS model accounts for sequencing more explicitly

The original cost effectiveness model provided by the company accounted for sequencing using the same approach used during TA909[3]. The state transition modelling approach accounts for the confounding effect introduced by subsequent therapies. Additionally, the new 4HS model accounts for sequencing even more explicitly (see comment 2 for further details) and therefore the company believes any uncertainty related to this has been accounted for.

Treatment sequencing in CROWN is consistent with previous solid tumour NICE appraisals and progression data used in the 4HS model is not confounded by treatment sequencing

The company acknowledge that treatment sequences used in CROWN do not reflect current NHS practice, however, the level of discordance between subsequent therapies observed in international pivotal trials and local practice is consistent with previous solid tumour NICE appraisals. In addition, advice from three 1–1 clinical consultation with experts suggested that this would have a limited bias given that the second generation ALK TKIs were not designed to be used after lorlatinib, given its status as a third-generation inhibitor and greater coverage of

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	ALK resistance mutations. Subsequent ALK TKI use in CROWN was low with only 26.1% using alectinib and 6.5% using lorlatinib upon disease progression in the lorlatinib arm (8.1% and 2.0% of the overall population), and so this is not thought to greatly bias OS when compared to other solid tumour appraisals. The CROWN data used in the 4HS model for time from first to second progression is for patients who did not have a 2L ALK TKi following 1L lorlatinib and is therefore not confounded by treatment sequencing (see comment 2). ***Flatiron real world evidence (RWE) scenario*** At clarification question (CQ) stage, the company provided an alternative RWE alectinib arm using flatiron data to provide additional validation for the main comparator survival projections to help address uncertainty. This analysis reflects the efficacy impact of most patients receiving lorlatinib as a second-line treatment and provided a validation of the approach for modelling alectinib OS (the main comparator, as highlighted by clinical experts at ACM1 stating alectinib is the treatment currently used in the vast majority of patients 1L). It confirmed that this method had not significantly underestimated sequence efficacy. It showed the uncertainty deriving from the efficacy (OS and PFS) of the alectinib to lorlatinib sequence, is unlikely to have an upward effect on the (lorlatinib versus alectinib) ICER and may well reduce it (see clarification questions flatiron addendum). ***Summary*** In summary, the 4HS model structure explicitly accounts for sequencing, using data sources that are not confounded by subsequent treatment options in the comparator trials and therefore uncertainty associated with this is likely to be minimal. 1L lorlatinib treatment will be longer than the alternative treatment sequence and clinicians wish to treat patients upfront with the most effective, progression-delaying treatment (and so with the longest duration of treatment) to prevent or delay progression events to give patient the best possible outcomes. Additionally, sequencing has been accounted for appropriately in the modelling and therefore uncertainty associated with this is likely to be minimal.
7	**Acceptable ICER (Section 3.19, page 22)** **The company has aligned with all committee's preferred assumption addressing the committee's areas of uncertainty and applied a number of conservative assumptions for lorlatinib, and therefore do not believe that the lowest ICER threshold should be applied for decision making . The company believe that an acceptable ICER at the upper end of the threshold is more appropriate** A summary of the company comments regarding the areas of high uncertainty noted by the committee in the DG is provided in Table 7 below, with more details included in responses above. The company believes that 6 of the 7 areas of high uncertainty have been addressed and only one remains which has been partially addressed. **Table 7: Summary on company comments on committee views on uncertainty**

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Uncertainty flagged by the committee	Addressed in the updated 4HS model?	Justification
Treatment sequences used in CROWN did not represent current NHS practice	Yes	The new 4HS model overcomes the sequencing issue due to it explicit structure and by using transition probabilities informed by data sources that reflect unaffected by treatments sequences representative of NHS practice. Furthermore, data used from CROWN in the 4HS model (time from first-progression to second progression) is adjusted to directly reflect the NHS treatment sequence. Additionally, clinicians suggested lorlatinib is a highly efficacious alternative to the current sequence and the treatment duration on 1L lorlatinib will be longer than the alternative treatment sequence
Overall survival data from CROWN was immature and that new data, beyond that considered in TA909, was not available	Yes	The 4HS model overcomes the lack of longer-term OS data by incorporating time-to-second progression data from CROWN and PPS data from study 1001 EXP3B:5 conservatively assuming that post-second progression survival after chemotherapy after lorlatinib is the same as post-progression survival observed in the chemotherapy arm of the lorlatinib 2L submission (TA628). Additionally, please see comment 5 for further rationale on why OS data immaturity is not an area of high uncertainty: OS uncertainty has been accounted for in the modelling approach Clinical opinion is that PFS will translate into an OS benefit Lorlatinib OS HR is expected to improve over time compared with the 18-month data CROWN PFS data is similar to the OS data for comparators at similar time points
Trials of the comparators were biased by treatment sequences that would not be used in the NHS	Yes	Lorlatinib as a second-line treatment was not widely used during alectinib and brigatinib trials. Therefore, the comparator trials cannot inform the current survival estimates after the first progression. Instead, the current 4HS model structure accounts for these sequences and uses the best available source to inform post- first progression

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			Additionally, please see comment 6 for further rationale on why sequencing uncertainty is not an area of high uncertainty.
	Results of the NMA were uncertain because of the issues with treatment sequences in all trials, the immaturity of the overall survival data from CROWN, and the possible violations of the proportional hazards assumption	Yes	The new 4HS model follows STM approach for both treatment arms, which does not rely on the OS NMA or CROWN OS data.
	The 3-state model structure may have been too simplistic to differentiate the benefits of second-line treatment	Yes	The 4HS model explicitly models the costs and health benefits of both first and second-line treatments in both treatment arms. It links the survival on the progressed disease 1 and progressed disease 2 to acquisition costs and QALYs.
	Non-randomised external sources were used to model post-progression survival (Study 1001, and PROFILE 1001 and 1005)	Partially	The new 4HS model uses the time-to-second progression from CROWN for 2L chemotherapy following 1L lorlatinib and no longer requires PROFILE 1001/1005. This data is then conservatively assumed as the same time-to-second progression on chemotherapy in the alectinib and brigatinib arms. The 4HS model applies more recent a open label phase IV study for time-to-second progression on 2L lorlatinib following 1L alectinib or 1L brigatinib, however, this is the most robust source reflecting the decision problem (see comment 2). Although this data is non-randomised, all patient received a 2nd generation ALK prior to the study. Data from Study 1001 EXPB:5 is also provided as a scenario. The 4HS model still requires data from Study 1001 EXPB:5. Despite this being non-randomised, utilising this source conservatively assumes that post-second progression survival after chemotherapy after lorlatinib is the same as post-progression survival observed in the chemotherapy arm of the lorlatinib 2L submission (TA628). Furthermore, sensitivity analysis on this have been conducted

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		demonstrating the robustness of the model. If incorporating discounts for comparator treatments changes in the ICER are expected to be minimal in scenario analysis.
Treatment after progression assumptions added to the cost of each treatment but did not add to the efficacy	Yes	Treatment after progression is incorporated into the company base case in the 4HS model, as per the committee preferred assumptions. However, not accounting for the survival benefit is a conservative assumption for lorlatinib, as with the same treatment beyond progression, lorlatinib is expected to improve survival more than alectinib or brigatinib (see comment 4).

The NICE DG guidance states '*The committee concluded that an acceptable ICER would be towards the lower end of the range that NICE usually considers to be a cost-effective use of NHS resources'.*

The company consider this to be an extremely low ICER threshold for an innovative treatment in an area of high unmet need, where the new treatment option offers people a step change in treatment. The company has acknowledged throughout the submission and appraisal process that there is uncertainty in certain elements, including immature OS data and treatment sequences in the trial evidence not being reflective of the NHS. However, the company has taken relevant steps to address uncertainty as summarised below:

1. The model minimises the uncertainty by using alternative model structure (e.g. not relying on OS CROWN data or OS NMA data) and the best available data sources
2. Accepted the committee's preferred assumptions which, as highlighted in comments 3 and 4 above, are conservative with respect to lorlatinib. Other conservative modelling assumptions are listed in Table 8 below.

Table 8: Summary of conservative model assumptions

Assumption	Rationale on why this assumption is conservative for lorlatinib
STM approach for lorlatinib	Conservative post-second progression survival assumptions: post-second progression survival (after lorlatinib and chemotherapy) is the same as post-progression survival in the chemotherapy arm of the lorlatinib 2L submission, see comment 3.
TOT=PFS for lorlatinib	The assumption of TOT=PFS is conservative for lorlatinib, see comment 4. As highlighted in comment 5 the 5-year CROWN data showed a TOT<PFS relationship and therefore assuming TOT=PFS to align with committees preferred assumptions and additional treatment beyond progression for lorlatinib is a conservative assumption for lorlatinib given this adds additional cost for lorlatinib but not additional benefit

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AEs of special interest for alectinib and brigatinib are not included	All AEs of special interest, regardless of grading, are included in the model for lorlatinib but not for alectinib or brigatinib and therefore this is a conservative assumption for lorlatinib. Additionally, in the model the management of AEs is costed separately from regular visits which is a conservative approach as UK clinicians have advised that managing AEs will not require additional resources as they would be considered during the regular visits and tests [30].
No reduction in resource use for lorlatinib 1L with longer term use	Resource use has been kept consistent over time in the model. However, it is anticipated that after several years of 1L lorlatinib treatment the frequency of healthcare resource use is likely to reduce. The company have validated this with HCPs who have confirmed that with long term 1L lorlatinib use they expect patients to require less frequent healthcare visits and monitoring. Therefore, this represents a conservative assumption with respect to lorlatinib.

The company believes that they are potentially being requested to account for uncertainty twice; first by applying conservative assumptions to account for any uncertainties (which the company believes are low), and then secondly by having a low ICER threshold despite any uncertainty already being accounted for in the modelling approaches and acceptance of the committee preferred assumptions.

Totality of evidence

As discussed previously (see comment 5), 5-year outcomes from the CROWN trial suggest an unprecedented change in progression expectations with the longest PFS ever reported for a single-agent treatment in metastatic NSCLC and solid tumour oncology. These systemic efficacy results, coupled with prolonged intracranial efficacy and the absence of new safety signals, represent unprecedented outcomes for patients with ALK-positive advanced NSCLC and set a new benchmark for targeted therapies in cancer[8]. It is unusual for NICE committee to have 5-years of evidence, especially for an oncology treatment, upon which to make a recommendation. Given the number of deaths required to do the next OS analysis have not occurred (see comment 5) this should be viewed as a positive uncertainty for patients and clinicians and should not be a barrier to access to lorlatinib. Therefore, given the totality of the evidence, we believe this shows lorlatinib is clinically and cost-effective.

NMA derived-HRs for lorlatinib versus the comparators shows statistically significant risk reductions for PFS (51% and 56%) and IC-TTP (61% and 80%) versus alectinib and brigatinib, respectively. PFS by BICR endpoint gave comparable results (Document B.2.9.4). Ten further published NMAs (including nine independent NMAs) support the use of lorlatinib as a clinically effective first-line treatment for patients with ALK-positive advanced NSCLC [20-27, 31].

Precedent set in other ALK TKI technology appraisals (TAs)

The ICER threshold being applied is not consistent with that used in other TAs of the comparator treatments, alectinib and brigatinib, despite similar uncertainties e.g. immature OS data, as

highlighted below. In addressing the sequencing issue with the 4HS model the company do not believe that applying the lowest ICER threshold for decision making is acceptable.

The alectinib TA536 states [32]:

"The committee largely agreed with the ERG's preferred assumptions. Although it was aware of the uncertainties about overall survival benefit and subsequent treatment in the appraisal, the committee concluded that the most plausible ICER for alectinib compared with crizotinib in people with untreated ALK-positive advanced NSCLC was between £20,000 and £30,000 per QALY gained."

The brigatinib TA670 states [6]:

'It repeated the analyses and included the confidential discount for alectinib, which showed that the net monetary benefit remained positive with all overall survival analyses at the threshold of £20,000 per QALY gained and most overall survival analyses at the threshold of £30,000 per QALY gained. This showed that brigatinib is cost effective compared with alectinib at the range NICE considers an acceptable use of NHS resources.'

For consistency in decision making the company believes that at least the same ICER threshold should apply in this appraisal.

Other considerations

From a clinical perspective, ALK-positive NSCLC patients tend to be younger, generally do not have a smoking history, and most commonly present with an adenocarcinoma histology[33]. Patients are often working when diagnosed, having a treatment that could control disease progression, may allow people increased time to spend in good quality of life compared to standard treatment. For those who wish to continue working, this could bring benefits not necessarily captured. One patient explains if this treatment was approved, it could give them the chance of extra time before disease progression. Additionally, treatment which brings people the hope of being able to lead a normal life for longer than current standard of care, could also provide significant benefit to their loved ones which cannot be underestimated.

The consequence of decision error is low given the limited budget impact estimated within this appraisal and the existing indication for previously treated ALK-positive advanced NSCLC (TA628) [5].

Summary

In summary, the company believes that in providing the committee with the additional analyses requested and accepting all of the committee's preferred assumptions, the key uncertainties have been accounted for, leading to low remaining uncertainty. In addition, considering the precedent set-in prior appraisals and the totality and strength of the evidence available for lorlatinib, the company believes that an acceptable ICER at the upper end of the threshold is more appropriate. In summary, the company considers that the low acceptable ICER threshold

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	in this appraisal does not reflect the step change that lorlatinib could offer as 1) an innovative medicine that has the potential to address a significant unmet need and 2) the conservative nature of the current model.
8	**Updated cost-effectiveness results with committee preferred assumptions and scenarios** A detailed description of the updated cost-effectiveness results and scenario analyses, using the new 4HS model are provided in Appendix 1. For clarity, as mentioned in comment 1, the company revised base case includes the new 4HS model with all the committee's preferred assumptions. [redacted] ***New 4HS model base case results*** A summary of the incremental results in the 4HS model is provided below in Table 9. In the updated base case analysis, which addresses the majority of the uncertainties discussed by the committee (as highlighted in comment 7), the results demonstrate that lorlatinib is a cost-effective alternative versus comparator treatments; with a deterministic ICER of [redacted] versus alectinib per QALY gained. **Table 9: Incremental revised company base-case results in the new 4HS model versus comparators (deterministic, with PAS for lorlatinib)** [redacted] **Scenario analyses** Several parameter and assumptions have been investigated in scenario analyses in the 4HS model as summarised in Table 10 and results are presented in Table 11. In all scenarios, lorlatinib remains cost effective versus alectinib. **Table 10: Summary of scenario analyses and their respective settings**

Description	Base case setting	Scenario setting
Alternative 2L lorlatinib PFS data source	Phase IV study 1027 of 2L lorlatinib following 1 prior ALKi	Lorlatinib 2L PFS data from study 1001 EXP3B:5 cohort based on PFS extrapolation (generalised gamma) agreed in TA628

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Alternative curve for time from first to secondary progression following 1L lorlatinib	Exponential	Exponential (Gen Gamma) Exponential (Weibull) Exponential (Log-normal) Exponential (Log-logistic) Exponential (Gamma)
Alternative curve for 2L PFS lorlatinib based on the Phase IV study	Exponential	Exponential (Weibull) Exponential (Gamma)
Alternative post-second progression mortality in the lorlatinib arm	[redacted]	Post-second progression mortality rate in the lorlatinib arm is varied between -45% and +45%
Alternative post-second progression mortality in the alectinib arm	[redacted]	Post-second progression mortality rate in the alectinib arm is varied between -45% and +45%

Table 11: Results of scenario analyses versus alectinib

Scenario	Inc. Costs (£)	Inc. QALYs	Deterministic ICER £/QALY)	ICER difference vs base case (£/QALY)
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Gen Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Log-normal)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: Phase 4 trial. Exponential (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: Phase 4 trial. Exponential (Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: Phase 4 trial. Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: EXP3B:5. Exponential (gen gamma)	[redacted]	[redacted]	[redacted]	[redacted]

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Lorla post-second progression mortality: 45% lower	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 30% lower	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 15% lower	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 15% higher	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 30% higher	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 45% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 45% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 30% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 15% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 15% lower	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 30% lower	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 45% lower	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events that are death: CROWN all patients lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events that are death: CROWN all patients crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events that are death: CROWN all patients pooled lorlatinib and crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events that are death: EXP3B:5	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Updated 3HS model base results

A summary of the incremental results in the updated 3HS model (as described in comment 2) is provided below in Table 12. The results demonstrate that lorlatinib is a cost-effective alternative versus comparator treatments with an ICER versus alectinib of [redacted] per QALY gained.

Table 12: Incremental revised company base-case results in the updated 3HS model versus comparators (deterministic, with PAS for lorlatinib)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER

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Brigatinib	[redacted]	[redacted]	[redacted]				
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year							

The total life years are identical to those from the 4HS state model as lorlatinib post-progression survival in the 3HS model was derived to match that in the 4HS state model. Total QALYs are higher as the 3HS state model does not account for the lower utility values in the progressed-disease 2. Consequently, as lorlatinib post-second progression survival is low (i.e. few patients remain in the progressed disease health state) compared to the alectinib arm, the incremental QALYs are lower than in the 4HS state model. In addition, the 3HS state model does not accurately capture the second-line lorlatinib costs as it cannot link treatment costs to time-to-second progression. The overall effect is a higher ICER compared to the 4HS. However, the 3HS model is considered a less reliable source, as flagged previously by the EAG and summarised in comment 2 and 3.

Original 3HS model base case results (post EAG report

A summary of the incremental results in the original 3HS model (post EAG report), incorporating all the committee's preferred assumptions is provided below in Table 13 for reference only as highlighted in comment 3 this model includes implausibly low PPS for lorlatinib. The results demonstrate that lorlatinib is a cost-effective alternative versus comparator treatments.

Table 13: Incremental revised company base-case results in the original 3HS model with all committee preferred assumptions versus comparators (deterministic, with PAS for lorlatinib)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Brigatinib	[redacted]	[redacted]	[redacted]				
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year							

Overall conclusions

As previously presented in the company submission and acknowledged in the NICE DG, lorlatinib demonstrates a clinical benefit over comparators in terms of improved PFS and IC-TTP. This translates into substantial QALY and LY gains. As discussed, the base-case results in the 4HS model demonstrate that lorlatinib is less costly and more effective than both alectinib

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	and brigatinib and in the base case alectinib was dominated by lorlatinib. As discussed in comment 2, 4HS model is likely to better reflect the treatment sequences being modelled and allows better differentiation of the costs and benefits of subsequent treatment options as well as provider greater transparency overall. In conclusion, lorlatinib is undoubtedly the most effective ALK TKI available to date at delaying systemic and CNS progression in patients. Clinicians and patients strongly endorse it as an additional option for clinicians and patients in first-line. Lorlatinib will be transformational for patients as it represents the most effective ALK TKI currently available with a duration of treatment greater than the alternative sequence, lower risks of clinical and CNS progression, and a longer life.
Additional comments	
10	**Managed access** The company is unsure if a managed access route will address the committee's clinical concerns regarding overall survival. Nonetheless, the company is committed to gaining access to this treatment for patients and therefore the company would consider a managed access arrangement if the committee determine routine commissioning is not possible due to clinical uncertainty. The company have therefore provided a managed access application proposal which is being communicated with NICE separately.
9	**Subgroup (DG pg 7, section 3.4)** The Company do not believe that it would be appropriate to optimise a NICE recommendation for lorlatinib to a subgroup of people with CNS metastases; a recommendation should be made ALK+ NSCLC patients, irrespective of presence or absence of brain metastases. Clinicians and patients have expressed a wish for lorlatinib to be available for patients regardless of brain metastases status. The data from CROWN demonstrates that lorlatinib is effective in controlling pre-existing brain metastases as well as in protecting against development of new brain metastases in patients with ALK-positive NSCLC (see section B 2.6.4 of the company submission) and is summarised below: • At prespecified 18-month follow-up, lorlatinib demonstrated statistically significant reductions in the risk of overall and intracranial disease progression (BICR-assessed) across patients with and without pre-existing brain metastases • At the 5-year CROWN data analysis, lorlatinib showed a 94% reduction in the risk of intracranial progression by INV (HR of 0.06; 95% CI: 0.03, 0.12), compared with crizotinib. Median IC-TTP was NR (95% CI: NR, NR) with lorlatinib and 16.4 months (95% CI: 12.7, 21.9) with crizotinib. The probability of being free of intracranial progression at 5 years was 92% (95% CI: 85, 96) with lorlatinib and 21% (95% CI: 10, 33) with crizotinib [8]. • Lorlatinib's ability to prevent the development of brain metastases is shown by the fact that only 4 of 114 patients without baseline brain metastases developed intracranial lesion(s), which occurred during the first 16 months of treatment

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	(tumour assessments including brain magnetic resonance imaging [MRI] were performed every 8 weeks throughout CROWN). • Among patients with brain metastases at baseline, median IC-TTP was NR (95% CI: NR, NR) in the lorlatinib arm and 7.2 months (95% CI: 3.7, 11.0) in the crizotinib arm (HR, 0.03; 95% CI: 0.01, 0.13). At 5 years, the probability of being free of intracranial progression was 83% (95% CI: 64, 93) with lorlatinib and not evaluable with crizotinib as all the patients progressed in the brain or were censored within 2 years [8]. Additionally, this is not a restriction for existing ALK treatments, and the company do not believe it should be applied for lorlatinib
11	**Factual inaccuracy** The following statement on page 11 is factually incorrect, 'The company could not estimate when the analysis at 70% of overall survival was likely to occur'. An alternative statement is: 'The company could not estimate when 70% of the 198 OS events needed for the next OS analysis to occur will happen'.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 2 May 2025. Please submit via NICE Docs.

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Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID6434]

Draft Guidance Response Appendix 1

09 May 2025

File name	Version	Contains confidential information	Date
ID6434 Lorlatinib Draft Guidance Response Appendix 1.docx	Final	Yes	09 May 2025

Contents

B.1. Cost-effectiveness

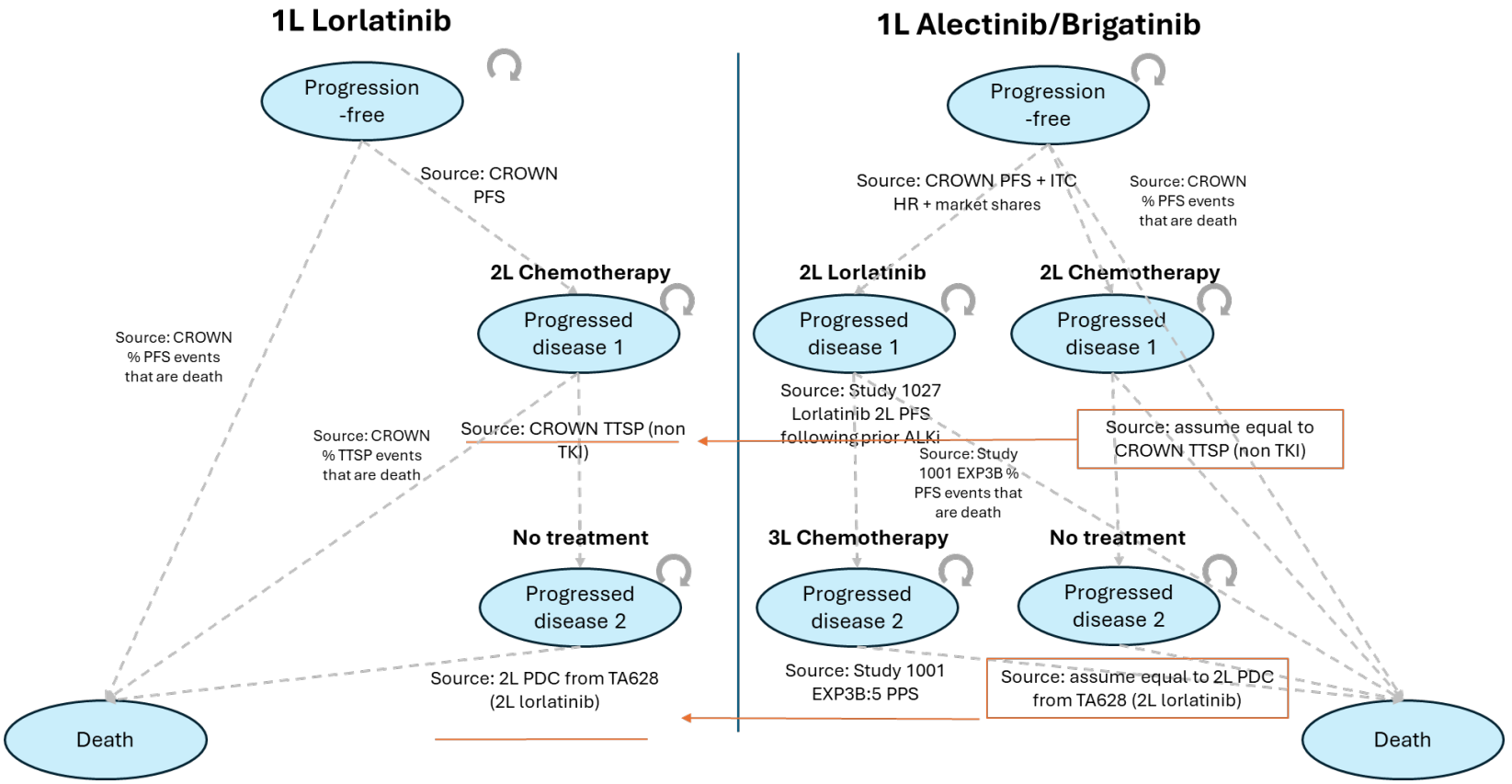
B.1.1. Economic analysis

B.1.1.1. Model structure and features

In the NICE draft guidance (DG), the committee noted that “The EAG noted that the company’s 3-state structure may have been unable to account fully for the impact of second-line treatments. To address this, the EAG suggested a 4-state structure, in which the progressed disease health state would be split into progression after first-line treatment and progression after second-line treatment. The EAG proposed that this 4-state structure would better differentiate the costs and benefits of second-line lorlatinib compared with other second-line treatments. It would also impose a structural relationship between a person’s health state and how long they had treatment, which was a key influencer of cost” [1].

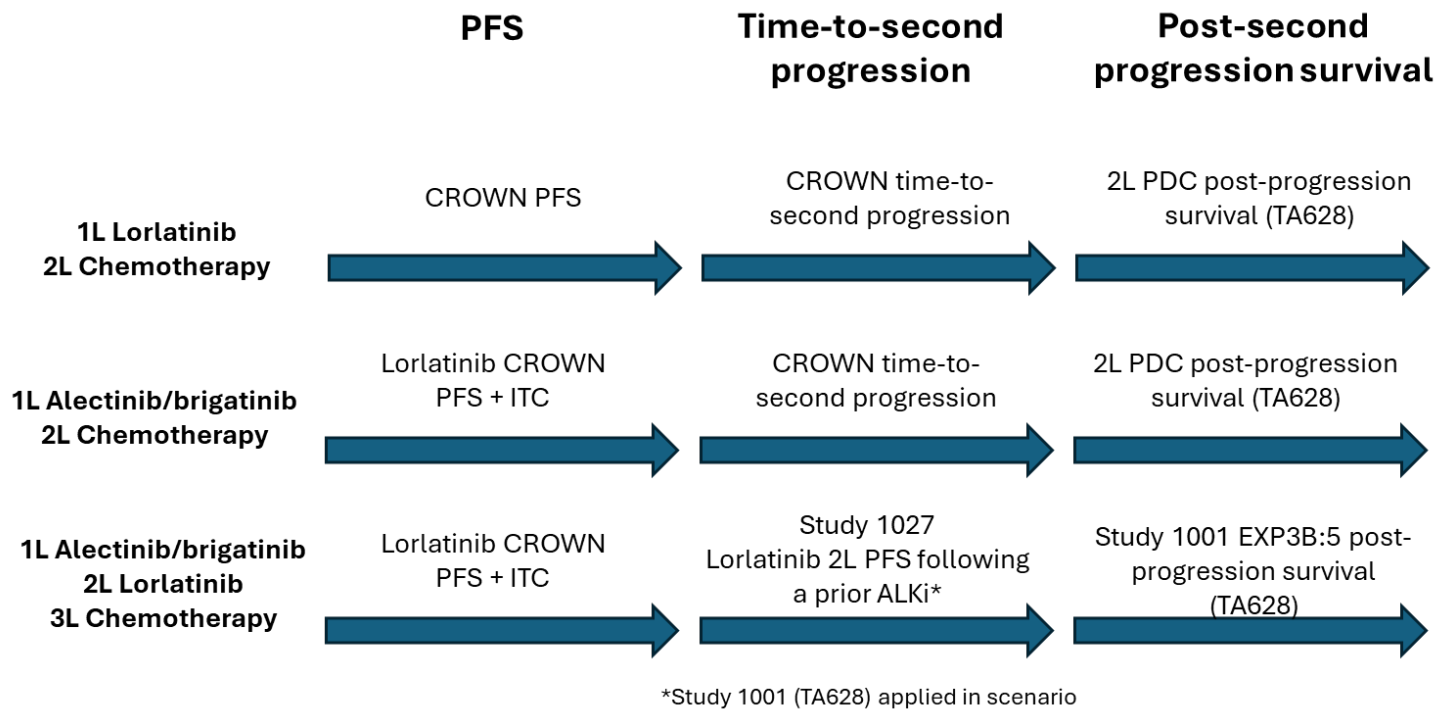
Therefore, as requested, the company has developed a 4-health state (4HS) model that allows to accurately capture the time on subsequent treatment , as well as the impact of second progression on survival and QALYs. Figure 1 and Figure 2 show the new model structure and data sources.

Figure 1: Lorlatinib, alectinib and brigatinib transitions in the 4HS model



Key: 1L, first line; 2L, second line; 3L, third line; ITC, indirect treatment comparison; PDC, platinum doublet chemotherapy; PFS, progression-free survival; TTSP, time-to-second progression

Figure 2: 4HS model sources and assumptions



Key: ALKi, ALK inhibitor; 1L, first line; 2L, second line; 3L, third line; ITC, indirect treatment comparison; PDC, platinum doublet chemotherapy; PFS, progression-free survival.

Table 1 provides a summary of the approach and sources used to derive the 4HS model. The company has also revised the base case to align with all the committee's preferred assumptions (DG section 3.20) [1]. These are highlighted in all the relevant section in this document.

Table 1: Summary of the approach and sources used to derive the 4HS model

	Original 3HS model committee preferred assumptions i.e. STM approach		4HS STM model	
	Lorlatinib	Alectinib/Brigatinib	Lorlatinib	Alectinib/brigatinib
Progression-free survival	Fitted curves to lorlatinib PFS *Source*: CROWN	Fitted curves to *lorlatinib* PFS + hazard ratio *Source*: CROWN + NMA	Fitted curves to lorlatinib PFS *Source*: CROWN	Fitted curves to *lorlatinib* PFS + hazard ratio *Source*: CROWN + NMA

First to second progression survival	Transition probability estimated (STM) *Source*: PROFILE 1001/1005	Transition probability estimated (STM) *Source*: Study 1001 (EXP3B-5) and PROFILE 1001/1005	Transition probability estimated from exponential curve fitted to time-to-second progression, defined as time from first progression to second progression *Source:* CROWN	*Alectinib/brigatinib followed by chemo:* Assume same time-to-second progression as 1L lorlatinib *Source:* CROWN *Alectinib/brigatinib followed by lorlatinib:* Transition probability estimated from exponential curve, fitted to progression free survival *Source:* Study 1027, Phase 4 2L lorlatinib study
Post secondary progression			Transition probability estimated from exponential curve based on the median post-progression survival observed in the chemotherapy arm of the lorlatinib 2L submission *Source*: TA628	Based on the committee's preferred PFS on TA628, and the committee's preferred OS curve in three health-state model structure (exponential), a post-progression mortality rate was derived so that the combined PFS and PPS

				generates the same mean survival as the selected (exponential) OS curve
Overall survival	PFS plus PPS	PFS plus PPS	PFS plus time-to-second progression plus post-second progression survival	PFS plus time-to-second progression plus post-second progression survival

B.1.2. Clinical parameters and variables

B.1.2.1. Progression-free survival

The Company has revised the base case to align with the committee's preferred assumptions:

- Lorlatinib should be used as the reference arm to which hazard ratios are applied to model progression-free survival for the comparators (Scenario 5a in EAG model assumptions)
- The 36-month piecewise Gompertz curve should be used to extrapolate lorlatinib progression-free survival (Scenario 5b in EAG model assumptions)
- Progression-free survival hazard rates should be waned to the hazard rates of alectinib after 10 years (Scenario 6c in EAG model assumptions).

B.1.2.2. Time-to-second progression (TTSP)

The Company has revised the base case to align with the committee's preferred assumption:

- The model should use a state-transition approach for post-progression survival in both the lorlatinib and comparator arms (Scenario 1a in the EAG model assumptions)

Different sources and assumptions are used for lorlatinib and alectinib/brigatinib time to second progression (after first progression). A summary of the approach and data sources used for each treatment base case in the 4HS model is presented in Table 2, where new data is used in this response, this is highlighted.

Table 2. Summary of the approaches to extrapolate time-to-second progression

Treatment	PFS rate	PFS events that are death	Approach	Source
Lorlatinib followed by chemotherapy	[redacted]	[redacted]	**NEW data in 4HS model:** exponential curve, fitted to time-to-second progression, defined as time from first progression to second progression	CROWN 5-year time from first to second progression data from progressed patients without subsequent TKi
Alectinib/brigatinib followed by chemotherapy	[redacted]	[redacted]	**NEW data in 4HS model:** Assume same time-to-second progression as 1L lorlatinib	CROWN 5-year time from first to second progression data from progressed patients without subsequent TKi
Alectinib/brigatinib followed by lorlatinib	[redacted]	[redacted]	**NEW data in 4HS model:** Exponential curve fitted to progression-free survival	Phase 4 Study 1027: Phase 4 Lorlatinib 2L study [3] - study investigating the efficacy and safety of lorlatinib in patients with *ALK*+ metastatic non-small cell lung cancer previously treated with an ALK inhibitor.
	[redacted]	[redacted]	**Scenario – using data source as 3HS model:** Generalised gamma fitted to	Study 1001 EXP3B:5 cohort

			the 2L lorlatinib PFS, as agreed in TA628.	

Key: HS, Health state; PFS, progression-free survival; PPS, post-progression survival; OS, overall survival; 1L, first line; 2L, second line, TTSP, Time to secondary progression

Lorlatinib

Two options are available for the time-to-second progression (TTSP) analysis: use of the CROWN data for all progressed patients that did not experience death as a PFS1 event (N=45), or the CROWN data for all progressed patients that did not experience death as a PFS1 event and that did not receive an ALK TKI as subsequent treatment (N=32).

Figure 3 and Figure 4 present the TTSP KM curves for both options. Figure 5 shows the overlayed KM curves. Both KM have very similar characteristics, with the only relevant difference being after month 40 that could be caused by the low numbers at risk. Table 3 presents the descriptive statistics of the two options, showing that the median lorlatinib TTSP for all progressed patients is [redacted] and [redacted] for all progressed patients with no ALK TKI as first subsequent treatment; the results in the two groups are aligned, supporting the notion that 2L ALK TKIs have no efficacy when used after lorlatinib.

Figure 3: Time-to-second progression from first progression Kaplan-Meier. Lorlatinib CROWN – All progressed patients

Figure 4: Time-to-second progression from first progression Kaplan-Meier. Lorlatinib CROWN – Progressed patients with no ALK TKI as first subsequent treatment

Figure 5: Time-to-second progression from first progression Kaplan-Meier. Lorlatinib CROWN – All progressed patients vs Progressed patients with no ALK TKI as first subsequent treatment

Table 3. Descriptive statistics: Lorlatinib CROWN

Treatment	Subjects	Events	Censors	Median (months; 95% CI)
Lorlatinib (All progressed patients)	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib (No subsequent ALK TKi)	[redacted]	[redacted]	[redacted]	[redacted]

Figure 6 and Table 4 present the TTSP extrapolations for lorlatinib using CROWN data for all progressed patients and the AIC/BIC table, while

Figure 7 and Table 5 present the analogous analysis for all progressed patients who did not receive an ALK TKI as subsequent treatment.

Figure 6: Time to second progression from first progression extrapolations for lorlatinib – CROWN All progressed patients

Table 4: Fit statistics of time to second progression extrapolation – lorlatinib using CROWN All progressed patients

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised-gamma	259.22	1	264.71	1
Exponential	268.75	6	270.58	5
Weibull	268.25	5	271.91	6
Log-normal	261.63	2	265.29	2
Log-logistic	263.70	3	267.36	3
Gompertz	264.85	4	268.51	4
Gamma	269.35	7	273.01	6

Key: in green, the curves that are within 5 points of the best fitting curve

Figure 7: Time to second progression from first progression extrapolations for lorlatinib – CROWN Progressed patients with no ALK TKI as first subsequent treatment

Table 6: Fit statistics of time to second progression extrapolation – lorlatinib CROWN Progressed patients with no ALK TKI as first subsequent treatment

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised-gamma	185.41	189.81	185.41	189.81
Exponential	186.07	187.54	186.07	187.54
Weibull	187.70	190.64	187.70	190.64
Log-normal	184.18	187.12	184.18	187.12
Log-logistic	185.55	188.48	185.55	188.48
Gompertz	187.01	189.94	187.01	189.94
Gamma	187.96	190.89	187.96	190.89

Key: In green, the curves that are within 5 points of the best fitting curve

The base case analysis has been conducted in all progressed patients with no subsequent ALK TKi as first subsequent treatment following 1L lorlatinib, as this data best reflects the NICE decision problem and the UK NHS clinical pathway and removes any uncertainty associated with confounding by subsequent treatments.

The curve is mature (Figure 7), therefore, all the parametric choices are within 5 points of each other (Table 5). This suggests there is not a large difference in the goodness-of-fit to the observed data. Due to the nature of the state transition model structure, only exponential curves can be used as they provide non-time varying transition rates. However, to test alternative values, and exponential rate was calculated to produce the same mean life years as the alternative curves in a 20 years' time horizon (time at which progression-free survival should have reached zero percent). Table 9 presents the rates using exponential curves equivalent to the alternative curves. The exponential curve presents the most conservative progression rate. Due to the uncertainty generated by the low numbers at risk (N=32), the most conservative survival has been selected. However, it should be noted that the low numbers at risk in the TTSP is caused by the low number of patients that have experienced first progression in the lorlatinib arm of CROWN in the 5-year data cut due to the due to unprecedented PFS benefit of first-line lorlatinib in ALK+ advanced NSCLC .

Table 7: Time-to-second progression alternative exponential curves. CROWN Progressed patients with no ALK TKI as first subsequent treatment

Curve	Rate
Exponential	[redacted]
Exponential based on generalised gamma	[redacted]
Exponential based on Weibull	[redacted]
Exponential based on Log-normal	[redacted]
Exponential based on Log-logistic	[redacted]
Exponential based on gamma	[redacted]
Exponential based on Gompertz	[redacted]

Using the exponential curve, the progression rate (including death) is [redacted]To account for those patients that die before the second progression, the rate is adjusted for the proportion of PFS2 events that were deaths [redacted]

TTSP from CROWN shows that the previous assumption for lorlatinib post-progression survival, based on data from PROFILE 1001/1005 (1L crizotinib followed by 2L chemotherapy) is too conservative and implausible, as the median PPS based on PROFILE 1001/1005 is 6.90 months, while the median TTSP from CROWN is [redacted]months.

Alectinib/brigatinib

To derive the TTSP for alectinib and brigatinib with second-line lorlatinib, the PFS curve from Study 1027 has been used. This is a Phase IV open label study, recently presented at the European Lung Cancer Congress (ELCC) in March 2025, specifically investigating the efficacy and safety of lorlatinib in patients with *ALK*+ metastatic NSCLC previously treated with only one prior ALK inhibitor [3]. This is the most robust source of data to model TTSP for 2L lorlatinib following 1L alectinib or 1L brigatinib, as it best reflects the UK treatment pathway. This is because 100% of people enrolled in this study had had received a second generation ALK TKI as their first-line, which is aligned with UK clinical practice and reflects the decision problem.

This data source also removes risk of confounding due to treatment sequencing. A summary of the study is provided below.

Study 1027: Study Design

Study 1027 was an open-label, multicentre, non-randomised prospective single-arm post-approval study conducted to confirm the efficacy of lorlatinib in patients whose disease had progressed after a single second-generation ALK TKi. Adult patients with ALK+ metastatic NSCLC that progressed on first line alectinib or ceritinib were treated with lorlatinib 100mg once daily.

Study 1027: Population

The study eligibility criteria:

- Adult patients with *ALK*+ metastatic NSCLC whose disease had progressed after 1 prior second generation ALK TKI (alectinib or ceritinib)
- ECOG PS 0 or 1
- At least one measurable target extracranial lesion per RECIST v1.1
- Patients with asymptomatic CNS metastases were allowed

Study 1027: Study Endpoints

The primary endpoint was confirmed objective response rate (ORR) per independent central review (ICR). Secondary endpoints included:

- Confirmed intracranial ORR per ICR
- Duration of response per ICR
- PFS per ICR
- Intracranial ORR and duration of response per ICR
- Safety

Study 1027: Baseline characteristics

85 patients were screened, and 71 patients were treated with lorlatinib. Baseline demographics and clinical characteristics are summarised in Table 8.

Table 8: Baseline demographics and clinical characteristics

	Lorlatinib (n=71)
Age, median (range), years	59 (26-87)
Male, n (%)	41 (58)
Race n (%)	
White	54 (76)
Asian	15 (21)
Not reported	2 (3)
ECOG performance status n (%)	
0	37 (52)
1	24 (48)
Prior anti-cancer drug regimen n (%)	
1	59 (83)
2	11 (15)
3	0
≥4	1 (1)
Prior ALK TKI therapy	
Alectinib*	60 (85)
Ceritinib	11 (15)
*One patient received ceritinib and then switched to alectinib	

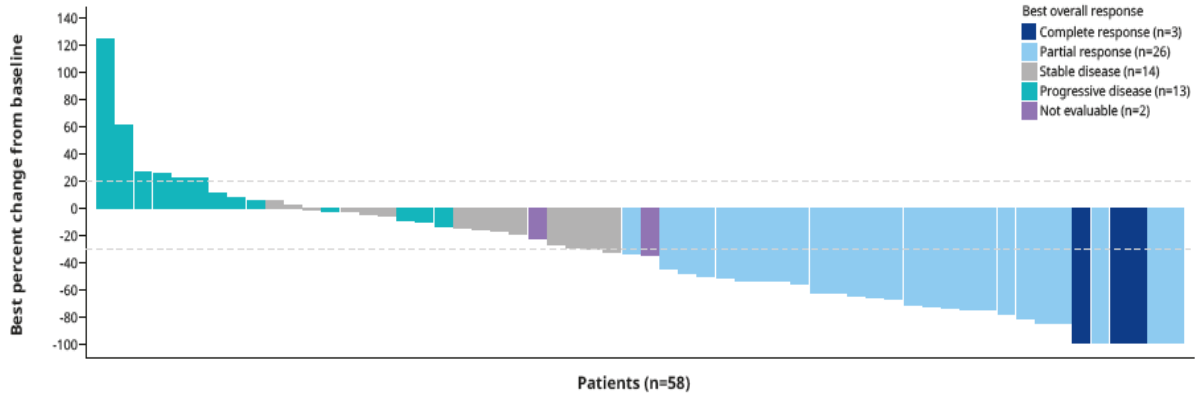
Study 1027: Primary endpoint - ORR

The study met its primary endpoint, with a confirmed ORR of 42% (95% CI 31-55%). Best overall response per ICR results are presented in Table 9 and best percent change from baseline in sum of diameters of target lesion is presented in Figure 8.

Table 9: Best overall response per ICR

	Lorlatinib (n=71)
Objective response rate (95% CI) %	42 (31-55)
Best overall response	41 (58)
Complete response	
Partial response	54 (76)
Stable disease	15 (21)
Non-CR/non-PD	2 (3)
Progressive disease	
Not evaluable	37 (52)
Reason for not evaluable	24 (48)
Non post baseline assessment due to early death	
Non post baseline assessment due to other reasons	59 (83)
Stable disease <6 weeks after treatment start	11 (15)
Duration of response, median (95% CI), months	0

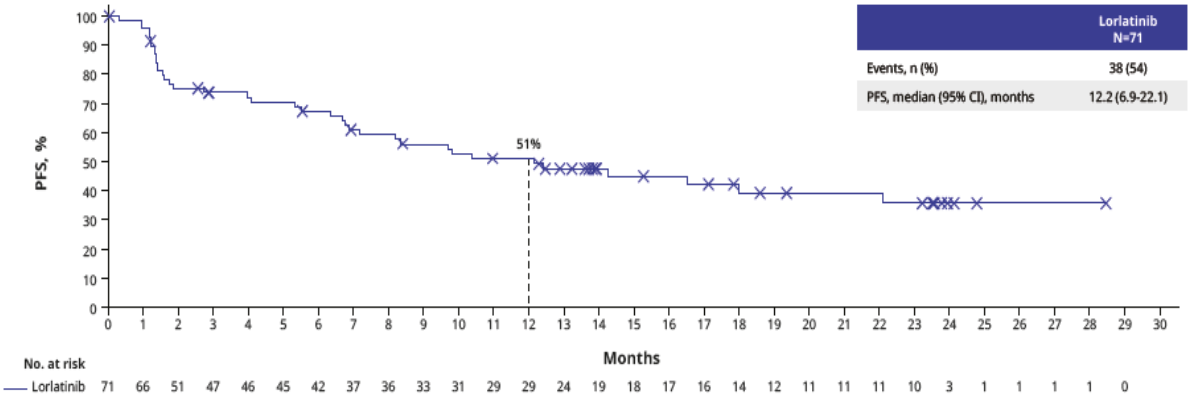
Figure 8: Best percent change from baseline in sum of diameters of target lesion



Study 1027: PFS

Median PFS was 12.2 months (95% CI, 6.9-22.1 months), with a 51% probability of patients being progression free at 12 months as presented in Figure 9.

Figure 9: PFS per ICR assessment



Study 1027: Safety

Any-grade treatment-emergent AEs (TEAEs) occurred in 97% of patients; grade 3/4 TEAEs occurred in 39% patients, a summary of the adverse events is presented in Table 10 and

Table 11. The most frequently reported (≥ 20% of patients) all-cause TEAEs were hypercholesterolemia (59%), hypertriglyceridemia (56%), oedema (46%), fatigue (27%), and peripheral neuropathy. A summary of TEAEs of any grade ≥10% are presented in Table 10. TEAEs led to dose interruption in 22 patients (31%), dose reduction in 11 (15%), and permanent treatment discontinuation in 9 (13%); no patients discontinued due to treatment-related TEAEs.

Table 10: Safety summary

	Lorlatinib (n=71)
TEAEs, n (%)	
Any grade	69 (97)
Grade 3 /4	28 (39)
Grade 5	10 (14)
Serious TEAEs	23 (32)
Dose interruption	22 (31)
Dose reduction	11 (15)
Permanent treatment discontinuation	9 (13)
Treatment related TEAEs	
Any grade	64 (90)
Grade 3 /4	19 (27)
Grade 5	0
Serious TEAEs	1 (1)
Dose interruption	10 (14)
Dose reduction	7 (10)
Permanent treatment discontinuation	0

Table 11: Treatment-emergent adverse events (any grade ≥10%)

	Lorlatinib (n=71)	
	Any grade	**Grade 3/ 4**
Any, n (%)		
Hypercholesterolemia	69 (97)	28 (39)
Hypertriglyceridemia	42 (59)	6 (8)
Oedema	40 (56)	9 (13)
Fatigue	33 (46)	3 (4)
Peripheral neuropathy	19 (27)	0
Dyspnoea	15 (21)	1 (1)
Diarrhoea	14 (20)	4 (6)
Anaemia	13 (18)	1 (1)
Hyperlipidaemia	12 (17)	1 (1)
Pyrexia	12 (17)	0
Arthralgia	12 (17)	0
COVID-19	9 (13)	0
Mood effects	9 (13)	1 (1)
Pain in extremity	9 (13)	0
Cough	8 (11)	1 (1)
Weight increased	7 (10)	0
Arthralgia		1 (1)

Study 1027: Summary

Lorlatinib provided clinically meaningful benefits in patients with *ALK*–positive metastatic NSCLC whose disease had progressed on alectinib or ceritinib as the first ALK TKi therapy. Efficacy and safety results from this study of lorlatinib were consistent with the pivotal phase 1/2 study and the known safety profile.

Figure 10 presents the TTSP extrapolations for alectinib/brigatinib 1L followed by 2L lorlatinib using Study 1027 and Table 12 show the AIC/BIC across parametric models.

Figure 10: Time to second progression extrapolations for alectinib/brigatinib – Study 1027

Table 12: Fit statistics of time to second progression extrapolation – alectinib/brigatinib using Study 1027

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised-gamma	281.42	1	288.21	1
Exponential	291.19	6	293.45	5
Weibull	289.84	5	294.37	6
Log-normal	283.80	2	288.32	2
Log-logistic	286.64	4	291.16	4
Gompertz	285.51	3	290.04	3

Key: in green, the curves that are within 5 points of the best fitting curve

Using the exponential curve, the progression rate (including death) is [redacted] To account for those patients that die before progression in Study 1027, the rate is adjusted for the proportion of PFS events that were deaths. As this value is not

available in the publication, the percentage observed in Study 1001 EXP3B:5 was used [redacted]

The exponential curve provides the worst statistical fit, however, the gompertz, log-logistic, log-normal and generalised gamma all predict high rates of patients' being progression free at 20 years which cannot be considered clinically plausible. Therefore, the extrapolation has been selected in the base case, with the Weibull and gamma applied in scenario analyses. Alternative progression rates have been calculated following the same approach as for CROWN TTSP (Table 13).

Table 13: Time-to-second progression alternative exponential curves. Study 1027

Curve	Rate
Exponential	[redacted]
Exponential based on generalised gamma	[redacted]
Exponential based on Weibull	[redacted]
Exponential based on Log-normal	[redacted]
Exponential based on Log-logistic	[redacted]
Exponential based on gamma	[redacted]
Exponential based on Gompertz	[redacted]

The original 3HS model used cohort 3B:5 PFS data from study 1001 (2L lorlatinib study) to derive the time-to-progression with 2L lorlatinib following 1L alectinib or brigatinib. In the 4HS model, the company also provide a scenario where this data is used to derive TTSP instead of study 1027. The generalised gamma curve is used, in line with committee preferred assumption from NICE TA628 (lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer). The result is presented in Table 25.

For patients with second-line chemotherapy, the same TTSP was assumed as in the lorlatinib arm. This assumption is conservative as lorlatinib TTSP with chemotherapy as the first subsequent treatment is expected to be higher than that of patients with

alectinib/brigatinib followed by chemotherapy, as explained in the company response Comment 2.

B.1.2.3. Post-second progression survival

Due to the 4HS model structure, different sources and assumptions are used for lorlatinib and alectinib/brigatinib post-second progression survival in the 4HS state model. A summary of the approach used for each treatment base case in the 4HS model is presented in Table 14.

Table 14. Summary of the approaches to extrapolate post-second progression survival

Treatment	Post-second progression survival (mortality rate)	Approach	Source
Lorlatinib followed by chemotherapy	[redacted]	Assume equal to the modelled post-progression survival of the chemotherapy arm (permetrexed) in the second-line setting from TA628 (second-line lorlatinib submission)	TA628: 2L chemotherapy arm [5]
Alectinib/brigatinib followed by chemotherapy	[redacted]	Assume equal to the lorlatinib arm	TA628: 2L chemotherapy arm [5]
Alectinib/brigatinib followed by lorlatinib (1st subsequent treatment) followed by chemotherapy (2nd subsequent treatment)	[redacted]	Based on the committee's preferred PFS on TA628, and the committee's preferred OS curve in 3HS model structure (exponential), a post-progression mortality rate was derived so that the combined PFS and PPS generates the same mean survival as the selected (exponential) OS curve	Study 1001 EXP3B:5

Key: PFS, progression-free survival; PPS, post-progression survival; OS, overall survival

Lorlatinib

Post-second progression with second-line chemotherapy after first-line lorlatinib is not available in CROWN. Therefore, post-second progression is based on the post-progression survival of the platinum doublet chemotherapy (PDC) arm from TA628 (second-line lorlatinib submission). Table 15 presents the committee's preferred approach to derive survival on the platinum doublet chemotherapy arm from TA628.

Table 15: Committee's preferred approach to derive survival on the platinum doublet chemotherapy arm from TA628

Source	ALUR and ASCEND-5 trials for progression-free survival and the PROFILE 1001 and PROFILE 1005 trials for overall survival ALUR compared alectinib with chemotherapy after previous treatment with PDC and crizotinib. ASCEND-5 compared ceritinib with chemotherapy after previous treatment with PDC and crizotinib. PROFILE 1001 was a single-arm phase 1 trial of crizotinib. PROFILE 1005 was a single-arm phase 2 trial of crizotinib after failure of 1 or more lines of systemic treatment for locally advanced or metastatic disease.
Approach	The committee's preferred approach is the direct estimation of progression-free and overall survival by fitting parametric curves to chemotherapy data from the clinical studies (method 5). The base case fits PSMs to the pooled Novello et al and Shaw et al data to estimate Pemetrexed PFS and fits PSMs to the Ou et al study to estimate Pemetrexed OS.
Adjustments	The patients in the chemotherapy arms of these trials had singlet chemotherapy (pemetrexed or docetaxel) rather than PDC. The committee agreed with the ERG and clinical experts that the company's assumption of equivalent clinical efficacy between doublet and singlet chemotherapy was not supported by clinical evidence, and that doublet chemotherapy was expected to be somewhat more effective than singlet chemotherapy. The committee noted that adjusting the hazard ratio by 20% to 0.8 to account for the difference in clinical efficacy between PDC and singlet chemotherapy was agreed to be appropriate at the technical engagement stage.

Median post-progression survival is derived as median OS ([redacted] months) minus median PFS ([redacted] months). Median values are based on the traces after incorporating the committee's preferred assumptions on TA628, which have been considered a superior source than the unadjusted median values from trials.

Based on the previous approach, the median post-progression survival (in the second-line setting) is [redacted] months, which represents a post-progression mortality rate of [redacted] The uncertainty in this parameter, alternative scenarios are tested assuming ± 45% variation. Scenarios in Table 25 show that results are not sensitive to variations in the post-second progression mortality rate.

Alectinib/brigatinib

Post-second progression survival for patients with second-line lorlatinib after first-line alectinib is derived based on the selected PFS and OS curves using the goal seek Excel function. Based on the selected PFS, and post-progression mortality rate is derived to generate the same mean life years as in the selected OS curve.

The generalised gamma is used for the PFS extrapolations based on the committee's preferred curve in TA628. Figure 11 presents the progression-free survival extrapolations using Study 1001 EXP3B:5.

Table 16 show the AIC/BIC across parametric models.

Figure 11: Progression-free survival extrapolations – Study 1001 EXP3B:5

Table 16: Fit statistics of progression free survival – Study 1001 EXP3B:5

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised-gamma	1315.43	1	1324.23	2
Exponential	1332.07	5	1335.01	5
Weibull	1333.85	6	1339.72	6
Log-normal	1316.37	2	1322.24	1
Log-logistic	1319.02	3	1324.89	3
Gompertz	1326.77	4	1332.64	4

Key: in green, the curves that are within 5 points of the best fitting curve

Figure 12 presents the overall survival extrapolations using Study 1001 EXP3B:5.

Figure 12: Overall survival extrapolations – Study 1001 EXP3B:5

Based on selected TTSP (see previous section), a post-second progression survival rate is estimated that generates the equivalent overall survival as the committee's

preferred base case for overall survival from Study 1001 EXP3B:5 (exponential curve) in the 3HS model structure. The estimated post-second progression mortality rate is [redacted] This simplifying assumption was made due to time constraints in the 4HS model construction. Figure 13 shows the comparison of the OS extrapolation from Study 1001 EXP3B:5 using an exponential (used as the base case in the 3HS model for the post-progression survival) versus the predicted OS using the PFS (TTSP in the first-line setting) from Study 1001 EXP3B:5 and the estimated post-progression survival (post-second progression in the first-line setting).

Figure 13: Overall survival. OS exponential curve vs OS derived based on PFS and PPS

For patients with second-line chemotherapy after first-line alectinib/brigatinib, it was assumed the same post-progression survival as patients with second-line chemotherapy after first-line lorlatinib.

B.1.2.4. Time on treatment

The model is aligned with the committee's preferred assumption:

- Time on treatment should, for all treatments in the model, be equal to progression-free survival with treatment after progression of 3.5 months for 75.6% people (Scenario 2 and Scenario 3)

However, the implementation of treatment beyond progression in the Engines has changed to accommodate the 4HS model. Modelling treatment beyond progression in the 4HS model is applied as a one-off cost based on the mean time on treatment beyond progression and the percentage of patients. However, it should be noted that NICE DG stated, “The committee also acknowledged that any treatment after progression may lead to better clinical outcomes. But, it highlighted that this would not be captured in the model’s estimates of clinical effectiveness, and so further contributed to uncertainty.”

B.1.3. Measurement and valuation of health effects

B.1.3.1.1. Utility values

The model is aligned with the committee's preferred assumptions regarding utilities:

- Applied the progression-free utility value from TA670 to the progression-free health state, irrespective of type of treatment, or whether on- or off-treatment (EAG preferred scenario 8a).
- In the progressed disease health state, the EAG agreed with using the values from TA670, given the issues with the CROWN data. But the EAG thought that separate on- or off-treatment utility values in the progressed disease state would be appropriate. This was because using second-line lorlatinib may confer a utility benefit. So, the EAG base case included separate on- or off-treatment utility values in the progressed-disease health state, with the progressed on-treatment value approximately midway between the progression-free and progressed off-treatment values (EAG preferred scenario 8b).

However, the 4HS model requires additional utility values to differentiate progressed disease 1 and progressed disease 2. Patient with progressed disease 1 on second-line chemotherapy utility values are based on the progressed disease utility values from NICE TA670. The remaining utility values have been sourced from the preferred assumptions from NICE TA628 (lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer). Utility values for the off-treatment state are considered not applicable as patients are on treatment until progression. Off-treatment is only available for patients that received second-line chemotherapy after lorlatinib/alectinib/brigatinib, as no third-line treatments are considered after second-line chemotherapy. For patients that received alectinib/brigatinib followed by lorlatinib followed by chemotherapy, they will experience both on and off treatment during progressed disease 2.

For patients with lorlatinib second-line after alectinib/brigatinib, the progression-free values from NICE TA628 are not used as they lacked face validity compared to progression-free values (progression-free on second-line lorlatinib is 0.785, while progression-free on first-line lorlatinib is 0.793). Therefore, the mid-point recommended by the EAG was used (0.725). The utility model values applied in the model are presented in Table 17 and new data is highlighted.

Table 17: Summary of the mean utility values

State	On treatment	Off treatment	On treatment (treatment beyond progression of the previous line)
Progression-free			
Lorlatinib	0.793 (TA670)	N/A	N/A
Brigatinib	0.793 (TA670)	N/A	N/A
Alectinib	0.793 (TA670)	N/A	N/A
Progressed disease 1			
Lorlatinib followed by chemotherapy	0.624 (TA670)	N/A	0.793 (TA670)
Brigatinib followed by chemotherapy	0.624 (TA670)	N/A	0.793 (TA670)
Alectinib followed by chemotherapy	0.624 (TA670)	N/A	0.793 (TA670)
Brigatinib followed by lorlatinib	0.725 (EAG assumption)	N/A	0.793 (TA670)
Alectinib followed by lorlatinib	0.725 (EAG assumption)	N/A	0.793 (TA670)
Progressed disease 2			
Lorlatinib followed by chemotherapy	N/A	0.460 (TA628) NEW data in 4HS model	N/A
Brigatinib followed by chemotherapy	N/A	0.460 (TA628) NEW data in 4HS model	N/A
Alectinib followed by chemotherapy	N/A	0.460 (TA628) NEW data in 4HS model	N/A
Brigatinib followed by lorlatinib followed by chemotherapy	0.460 (TA628) NEW data in 4HS model	0.460 (TA628) NEW data in 4HS model	N/A
Alectinib followed by lorlatinib followed by chemotherapy	0.460 (TA628) NEW data in 4HS model	0.460 (TA628) NEW data in 4HS model	N/A

B.1.4. Cost and healthcare resource use identification, measurement and valuation

B.1.4.1. Health state unit costs and resource use

Based on TA628 (lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer), the progression-free HCRU cost per cycle were £196.84, while progressed disease HCRU cost per cycle were £197.62. Given the minimal difference, the progressed disease HCRU costs from the 3HS model were used for progressed disease 1 and progressed disease 2 in the 4HS model.

B.1.4.2. Miscellaneous unit costs and resource use

B.1.4.2.1. Subsequent treatment

As opposed to the 3HS model, the 4HS model does not rely on assumptions of subsequent treatment durations. The distribution of subsequent treatment is used to define the transitions in the progressed disease 1 and progressed disease 2 health state as patients with second-line lorlatinib after alectinib/brigatinib will have different transitions as those with second-line chemotherapy after lorlatinib/alectinib/brigatinib. The distribution of patients by treatment after the first progression are applied to those patients that have progressed (i.e. as death is included as an event in the PFS curve, the progression rate is adjusted by the percentage of PFS events that are death – See Table 2). All other assumptions are as per the 3HS model.

B.1.5. Uncertainty

A DG (Section 3.19) summaries the committee's reasons for high uncertainty associated with decision making. The company believe that 6 of the 7 areas of high uncertainty have been addressed and only one remains which has been partially addressed as summarised in comment 7 in the company response document.

B.1.6. Base case results (deterministic)

Base case results assume a [redacted] PAS for lorlatinib. Alectinib and brigatinib have confidential discounts; therefore, NHS list prices have been used for alectinib and brigatinib. In the updated base case analysis, which aligns with all committee preferred assumptions and addresses the majority of the uncertainty discussed by the committee, show lorlatinib to be a cost-effective alternative versus comparator treatments; lorlatinib was associated with a deterministic ICER of [redacted] per quality-adjusted life year (QALY) gained vs alectinib. Results are presented in Table 18, Table 19, Table 20, Table 21, Table 22 and Table 23.

Table 18: 4HS model cost breakdown by treatment

Cost category	Lorlatinib	Alectinib	Brigatinib
Treatment costs (1L) - Until progression	[redacted]	[redacted]	[redacted]
Treatment costs (1L) - After progression	[redacted]	[redacted]	[redacted]
Treatment costs (2L Lorla) - Until second progression	[redacted]	[redacted]	[redacted]
Treatment costs (2L Lorla) - After second progression	[redacted]	[redacted]	[redacted]
Treatment costs (2L Chemo)	[redacted]	[redacted]	[redacted]
Treatment costs (3L Chemo)	[redacted]	[redacted]	[redacted]
Admin costs (1L) - Until progression	[redacted]	[redacted]	[redacted]
Admin costs (1L) - After progression	[redacted]	[redacted]	[redacted]
Admin costs (2L Lorla) - Until second progression	[redacted]	[redacted]	[redacted]
Admin costs (2L Lorla) - After second progression	[redacted]	[redacted]	[redacted]
Admin costs (2L Chemo)	[redacted]	[redacted]	[redacted]
Admin costs (3L Chemo)	[redacted]	[redacted]	[redacted]
HCRU progression-free	[redacted]	[redacted]	[redacted]
HCRU progressed1&2	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]
CNS progression	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Table 19: 4HS model life years breakdown by treatment

Health state	Lorlatinib	Alectinib	Brigatinib
Progression-free			

Progressed	[redacted]	[redacted]	[redacted]
Progressed1 - 2L Lorla	[redacted]	[redacted]	[redacted]
Progressed1 - 2L Chemo	[redacted]	[redacted]	[redacted]
Progressed2 - 2L Lorla	[redacted]	[redacted]	[redacted]
Progressed2 - 2L Chemo	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 20: 4HS model QALYs breakdown by treatment

Health state	Lorlatinib	Alectinib	Brigatinib
Progression-free	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]
Progressed1 - 2L Lorla	[redacted]	[redacted]	[redacted]
Progressed1 - 2L Chemo	[redacted]	[redacted]	[redacted]
Progressed2 - 2L Lorla	[redacted]	[redacted]	[redacted]
Progressed2 - 2L Chemo	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
CNS progression	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 21: 4HS model deterministic pairwise results versus alectinib - cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 22: 4HS model deterministic pairwise results versus brigatinib - cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 23: 4HS model deterministic incremental results – cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Brigatinib	[redacted]	[redacted]	[redacted]				
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

B.1.7. Exploring uncertainty

B.1.7.1. Scenario analyses

Several parameters and assumptions have been investigated in scenario analyses in the 4HS model as summarised in Table 24 and results are presented in Table 25. In all scenarios, lorlatinib remains cost effective versus alectinib.

Table 24: Summary of scenario analyses and their respective settings

Description	Base case setting	Scenario setting
Alternative curve for time from first to secondary progression following 1L lorlatinib	Exponential	Exponential (Gen Gamma) Exponential (Weibull) Exponential (Log-normal) Exponential (Log-logistic) Exponential (Gamma)
Alternative curve for 2L PFS lorlatinib based on the Phase IV study	Exponential	Exponential (Weibull) Exponential (Gamma)
Alternative 2L lorlatinib PFS data source	Phase IV study 1027 of 2L lorlatinib following 1 prior ALKi	Lorlatinib 2L PFS data from study 1001 EXP3B:5 cohort based on PFS extrapolation (generalised gamma) agreed in TA278
Alternative post-second progression mortality in the lorlatinib arm	[redacted]	Post-second progression mortality rate in the lorlatinib arm is varied between -45% and +45%
Alternative post-second progression mortality in the alectinib arm	[redacted]	Post-second progression mortality rate in the alectinib arm is varied between -45% and +45%
Lorlatinib percentage of PFS2 events that are death	CROWN progressed patients without subsequent TKis - Lorlatinib and crizotinib pooled	CROWN all lorlatinib patients CROWN all crizotinib patients CROWN all patients (lorlatinib and crizotinib pooled) Study 1001 EXP3B:5

Table 25: Results of scenario analyses versus alectinib

Scenario	Inc. Costs (£)	Inc. QALYs	Deterministic ICER £/QALY)	ICER difference vs base case (£/QALY)
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Gen Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Log-normal)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential (Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Lorla TTSP Source: Progressed patients no TKIs. Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: Phase 4 trial. Exponential (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: Phase 4 trial. Exponential (Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: Phase 4 trial. Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Alec PFS Source: EXP3B:5. Exponential (gen gamma)	[redacted]	[redacted]	[redacted]	[redacted]

Lorla post-second progression mortality: 45% lower	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 30% lower	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 15% lower	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 15% higher	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 30% higher	[redacted]	[redacted]	[redacted]	[redacted]
Lorla post-second progression mortality: 45% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 45% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 30% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 15% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 15% lower	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 30% lower	[redacted]	[redacted]	[redacted]	[redacted]
Alec followed by lorla post-second progression mortality: 45% lower	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events that are death: CROWN all patients lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]

PFS2 events that are death: CROWN all patients crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events that are death: CROWN all patients pooled lorlatinib and crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events that are death: EXP3B:5	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Updated three health state model

For reference, the 3HS model has been updated to reflect the new assumptions derived for CROWN time-to-second progression. Alectinib/brigatinib followed by lorlatinib post-progression survival remains constant and has not been updated to reflect the new time-to-second progression derived from phase IV study 1027. If study 1027 data were used, another OS would need to be derived for alectinib and brigatinib which would not be aligned with the committee's preferred assumptions. Lorlatinib/alectinib/brigatinib followed by chemotherapy post-progression survival in the 3HS model has been updated to match the modelled post-progression survival from the 4HS state model. The post-progression survival in the 4HS model is defined as time-to-second progression plus post-second progression survival. A post-progression survival rate for the 3HS model was estimated to generate the same mean survival as the post-progression survival modelled in the 4HS model using the goal seek excel function. The estimated post-progression mortality rate is [redacted]The switch to implement the new post-progression survival from the 4HS model (instead of using PROFILE 1001/1005) is located in the sheet PPS!F18.

Additionally, it was not possible to add in 3.5 months additional time on treatment for all treatments as per the DG committee's preferred assumptions in the EAG 3 HS model (from the EAG report stage) and therefore the company has updated this in the revised 3HS model (the switch is located in the sheet EAG_Additional_Analyses! N37). Table 26, Table 27 and Table 28 show the ICER's with all the committee's preferred assumptions and the [redacted]PAS for lorlatinib.

Table 26: 3HS model deterministic pairwise results versus alectinib - cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 27: 3HS model deterministic pairwise results versus brigatinib - cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 28: 3HS model deterministic incremental results – cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Brigatinib	[redacted]	[redacted]	[redacted]				
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]				

Original 3HS model with committee preferred assumptions

As mentioned above, it was not possible to add in 3.5 months additional time on treatment for all treatments as per the DG committee's preferred assumptions in the EAG model 3HS model (from EAG report stage) and therefore the company has updated the model to enable this. As mentioned previously, the switch to use the original PROFILE 1001/1005 is located in the sheet PPS!F18. Table 29,Table 30 and Table 31 show the ICER's with all the committee's preferred assumptions and the [redacted] PAS for lorlatinib.

Table 29: 3HS model deterministic pairwise results versus alectinib - cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 30: 3HS model deterministic pairwise results versus brigatinib - cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.

Table 31: 3HS model deterministic incremental results – cost per QALY

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Brigatinib	[redacted]	[redacted]	[redacted]				
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]				

Overall Conclusions

As previously presented in the company submission and acknowledged in the NICE DG, lorlatinib demonstrates a clinical benefit over comparators in terms of improved PFS and IC-TTP. This translates into substantial QALY and LY gains. As discussed, the base-case deterministic ICER in the 4HS model is [redacted] per QALY gained versus alectinib.

In conclusion, lorlatinib is undoubtedly the most effective ALK inhibitor available to date at delaying systemic and CNS progression in patients. Clinicians strongly endorse it as an additional option for clinicians and patients in first-line. The clinical and economic evidence suggests that even while displacing lorlatinib in the second-line, lorlatinib will be transformational for this patient group, with a duration of treatment on the most effective ALK inhibitor greater than on the alternative treatment sequence, lower risks of clinical and CNS progression, and a longer life.

References

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Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID6434]

Name	[redacted]
Organisation	ALK Positive UK
Comments on the DG:	

I am disappointed and surprised at the proposal not to approve Lorlatinib for first line use.

The results from the Crown Study have been described world-wide as being the best ever for a TKI.
Lorlatinib is now being used extensively for first line use in other countries, including Scotland.

Crown Study results may not be achieved in the real-world. But, this is also true of Alectinib.

Are you aware of - Real-world treatment sequencing and effectiveness of second-and third-generation tyrosine kinase inhibitors for ALK-positive advanced non-small cell lung cancer. Lung Cancer, Volume 195, 2024.

The mean time to discontinuation of treatment (TTD) with Alectinib was 21.9 months, substantially less that the 34.8 months mean PFS reported in the ALEX study. Furthermore, PFS is likely to be less than TTD.
In the Crown Study, mean PFS was not reached after 5 years. Even if this not achieved in the real world, PFS for Lorlatinib will exceed that for Alectinib by a wide margin.

Whilst I recognise that value for money is important and there may be some shortcomings in Pfizer data, I have to question your methodology for calculating vfm when faced with such overwhelming evidence.

My members are going to find it very difficult to understand why Lorlatinib is available for first line use throughtout the world, including Scotland, but not in England and Wales."

Response to the National Institute for Health and Care Excellence's Draft Guidance Consultation Document - Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909)

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are disappointed that the Committee's preliminary decision is not to recommend Lorlatinib in this indication.

- We note the Committee's acknowledgement, in the draft guidance, that despite no direct comparison being available, indirect comparison suggest that Lorlatinib increases how long people have before cancer gets worse, as compared with current standard of care – Alectinib and Brigatinib.

- We understand that the CROWN Study, with Crizotinib, is no longer a clinically relevant comparator for NHS practice. However, as in the British Thoracic Oncology Group submission to this appraisal, the progression free survival benefit observed for Lorlatinib is 'one of the most pronounced and impressive seen in solid tumours'. From a patient perspective, access to such a therapy is of obvious importance.

- As indicated, brain metastasis is of particular relevance to this patient group. Lorlatinib has been shown to have benefit both for those patients who have brain metastasis at diagnosis and those who do not.

- We note that with uncertainty in the clinical data, the Committee has concluded that there is not enough evidence that Lorlatinib, in this indication, is value for money.

- We note that there has been dialogue with the manufacturer on a Patient Access Scheme. In paragraph 3.20, we note that the Committee has asked the manufacturer to present additional information, to inform decision making. We hope that this dialogue will continue and that clarity will lead to this therapy being available for patients in this indication.

Roy Castle Lung Cancer Foundation
May 2025

NICE National Institute for Health and Care Excellence

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 2 May 2025. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Thoracic Oncology Group

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NICE National Institute for Health and Care Excellence

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Dr Shobhit Baijal

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the committee's recommendation has been based on the premise that the CROWN study has not read out overall survival data. The fact that this landmark has not been reached at the 5 year outcome should be looked upon as a significant positive in terms of how

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NICE National Institute for Health and Care Excellence

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	active and clinically effective the drug is. It is not feasible for a global study to break protocol to provide an interim OS analysis for this appraisal.
2	At the time of the trial Crizotinib on a global level was still the standard of care, hence the trial design (and comparator) was appropriate for when the trial was recruiting
3	We are concerned about the comment 'it is uncertain whether lorlatinib makes people live longer compared with alectinib and brigatinib'. With the cautions of cross-trial comparison the fact that the median PFS at 5 years has not been reached gives a very strong signal that in the first line setting Lorlatinib is more effective than alectinib or brigatinib
4	We are concerned that the CNS data has not been taken into account. The time to intracranial progression confirms the CNS protection that Lorlatinib provides, which has a huge positive impact on the quality of life of ALK patients as well as on health resources
5	We are concerned that the current negative recommendation is denying current ALK positive patients in England access to the most clinically active ALK inhibitor, which has become the first line standard of care on a global level
6	

Insert extra rows as needed

Checklist for submitting comments

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Takeda UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	In Section 3.5 of the Draft Guidance under the heading of "CROWN trial and its generalisability to the NHS" (page 8) there is a statement that *"In the NHS, people whose cancer progresses on a*

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	first-line ALK TKI do not have alectinib or brigatinib as a second-line treatment. Their options would be lorlatinib or chemotherapy." This statement is correct in relation to the absence of alectinib as an NHS funded option at 2L+. However, it is incorrect in relation to brigatinib which is NICE recommended and NHS funded in adults who have already had crizotinib (as per TA571). We do however acknowledge that, as per the statement in Section 3.2 of the Draft Guidance, crizotinib is now rarely used in the NHS and therefore the use of brigatinib after crizotinib is now very limited.
2	Has all of the relevant evidence been taken into account? Yes, we believe it has.
3	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes, we believe they are.
4	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? No comment.
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	York EAG

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted] on behalf of York EAG

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Draft guidance, Section 3.5, pp.7-8, does not quite reflect the EAG's position: "As the treatment sequences in CROWN did not align with NHS practice, the EAG considered that overall survival in CROWN could be confounded. For example, overall survival in the lorlatinib arm may have been increased by second-line use of alectinib or brigatinib, which would not typically happen in the NHS. The EAG was concerned that this would substantially limit the applicability of the evidence from CROWN to NHS clinical practice."

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	The EAG report does raise concerns about the applicability of the CROWN trial sequences to clinical practice, however, this is primarily because of the treatment sequences used in the comparator arm. Clinical advisers to the EAG also questioned the limited relevance of alectinib or brigatinib at second-line, given the narrower mutation coverage of these therapies compared with lorlatinib. See Lorlatinib EAR post FAC pp.31-32 for further details. Therefore, we request that the following sentence is changed from "As the treatment sequences in CROWN did not align with NHS practice, the EAG considered that overall survival in CROWN could be confounded." To "As the treatment sequences in CROWN did not align with NHS practice, the EAG considered that **relative** overall survival **estimates** in CROWN **may not reflect outcomes in NHS practice**." And that the following sentences are removed: "For example, overall survival in the lorlatinib arm may have been increased by second-line use of alectinib or brigatinib, which would not typically happen in the NHS. The EAG was concerned that this would substantially limit the applicability of the evidence from CROWN to NHS clinical practice."
2	Section 3.5, p.10 does not quite reflect the EAG's position. We request that: "But, the EAG also cautioned that, because CROWN is an open-label trial in which the investigators know which treatment participants are assigned to, there is a risk of bias in investigator-assessed outcomes." is replaced with: "But, the EAG also cautioned that, because CROWN is an open-label trial in which the investigators know which treatment participants are assigned to, **relative estimates of PFS assessed by the** investigator **are at higher risk of bias than PFS assessed by BICR."**
3	Section 3.2, p.6 states: "clinical experts and the CDF lead agreed that only a minority of people have second-line treatment with lorlatinib in the NHS". The EAG considers this wording inaccurate and overly strong, as it implies that very few patients receive lorlatinib as a second-line treatment, which is not the case. Figures suggested by the CDF lead indicated that approximately 40% of patients receive lorlatinib as a second treatment, and this percentage is much higher in many centres. The EAG's clinical advisers estimate that about 80% of patients in their centres receive it. The EAG requests that the wording in this section be modified to more accurately reflect the use of lorlatinib in the NHS.
4	Section 3.14, p.18 states that: "The committee considered that neither the company's nor the EAG's modelling approaches were appropriate. Instead, because of the uncertainties around treatment after progression, the committee thought that it was likely to be most appropriate to assume equal treatment after progression for each treatment." The EAG considers the committee's preferred approach to be clinically implausible. Clinical advice received by the EAG suggests that post-progression treatment with alectinib and brigatinib is likely to be much lower than with lorlatinib due to the availability of lorlatinib as a second-line treatment option. They further explained that for the same reason, the duration of post-progression treatment is likely to be shorter with alectinib/brigatinib than with lorlatinib. The EAG also notes that alectinib's marketing authorisation does not allow use post-progression and that in TA 536, the committee agreed not to model treatment beyond progression. No change to the guidance is required at this time, but we would suggest the committee reconsider this issue at any further meeting.

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NICE National Institute for Health and Care Excellence

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

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5	Section 3.14, p.18, the committee expresses a preference for assuming 3.5 months of treatment after progression, based on TA628. However, TA909 (which is arguably more relevant as this considers lorlatinib first-line) indicated a committee preference for 5.7 months. Given this inconsistency, we believe the committee should provide a more detailed justification for the choice of 3.5 months in the guidance document.

Insert extra rows as needed

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Single Technology Appraisal (STA)

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (review of TA909) [ID6434]

EAG Addendum: Review of the company's response to consultation on the draft guidance document

Produced by	York Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Date completed	22/05/2025

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR169038.

Declared competing interests of the authors

None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CON) data have been redacted.

Acknowledgements

Dr Robin Young, Consultant Medical Oncologist, Sheffield Teaching Hospitals NHS Foundation Trust provided expert clinical advice and commented on a draft of the report.

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1 OVERVIEW

The External Assessment Group (EAG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the consultation on the draft guidance document (DGD) and to identify any areas of remaining uncertainty. Due to the limited time available and breadth of the company's response, the additional work undertaken by the EAG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. Specifically, the EAG has not fully validated the updated model outlined in the company's response to the DGD. Instead, the EAG has conducted high-level checks of these proposed changes and ensured replication of the results presented by the company.

The company's response to the DGD comprises nine comments summarised in Table 1 and presents a revised base case that accepts all the committee's preferred assumptions. The company, however, contests the committee's preferences regarding the acceptable ICER threshold and the potential for an optimised decision in patients with central nervous system (CNS) metastasis. The company's responses to each of the issues are discussed in Section 2, while Section 3 presents the company's revised base case and the updated EAG base case.

Table 1: Summary of the key issues

Issue	
1	Updated cost-effectiveness model aligning with all the committee's preferred assumptions
2	Updated four health state model structure (DGD Section 3.10)
3	Modelling approach for post-progression survival (DG Section 3.13)
4	Time on treatment (TOT) and treatment after progression (DG Section 3.14)
5	Availability of overall survival from CROWN (DG Section 3.8)
6	Optimal treatment sequence (DG Section 3.5)
7	Acceptable ICER threshold (DG Section 3.19)
Additional comments*	
9	Subgroup analysis (DG Section 3.4)
10	Managed access

* Comment 8 reported the company's updated base case results

2 DESCRIPTION AND CRITIQUE OF RESPONSE

2.1 Comment 1: Updated cost-effectiveness model aligning with all the committee's preferred assumptions

The company provide a table in which the assumptions adopted in their updated base-case analysis are compared to the committee's preferred assumptions following ACM1. The company's updated base-case analysis now reflects the following committee's preferences in full:

- Lorlatinib used as the reference arm to which hazard ratios are applied.
- 36-month piecewise Gompertz curve used to extrapolate lorlatinib progression-free survival.
- State transition approach used to model post-progression survival in both the lorlatinib and comparator arms.
- Time on treatment, for all treatments, set equal to progression-free survival plus 3.5 months post-progression treatment for 75.6% of people.
- Progression-free survival hazard rates waned to the hazard rates of alectinib after 10 years
- Health state utility values aligned with the EAG's approach.
- New conditional PAS discount for lorlatinib applied only to the intervention arm of the model.

In addition to the above, the company has also revised the economic model to adopt a four-health-state (4HS) structure, which more explicitly differentiates the costs and benefits associated with subsequent treatment options. The company's revised base case also revises some of the data used to populate the economic model, which is outlined and discussed further in Section 2.2 (Comment 2).

The EAG's response

The EAG is satisfied that the company has fully implemented the committee's preferences. As noted in the company's response, it has adapted the EAG's approach to implementing health state utilities in the revised model structure. The EAG considers this adaptation broadly appropriate and in line with the rationale of its approach, namely, to account for the quality-of-life benefits associated with receiving an ALK inhibitor in the second line (2L) setting, but notes some issues with the values applied in the PD2 health state.

Health state values applied in the PD2 health state

The company's revised base case applies a utility value of 0.46 to the PD2 health state, referencing the values used in TA628, which were informed by Chouaid et al. (2013).[1]

The EAG is concerned that this utility value may underestimate the quality of life for patients who have experienced a second disease progression, particularly those still receiving active treatment in

this setting. The applied value also appears inconsistent with the model's predictions. In the revised base case, patients receiving the alectinib/brigatinib followed by lorlatinib treatment sequence are projected to live for an average of 1.30 life years (LY) after second progression. The EAG considers it implausible that patients expected to live this long would experience such a low quality of life.

Furthermore, the 0.46 utility value does not fully align with the committee's stated preferences in TA628. In that appraisal, the committee indicated a preference for a utility value of 0.65 for patients with previously treated disease who were still receiving lorlatinib after progression, and 0.46 for those who had progressed and were off treatment, in both arms.

As the economic model does not allow for separate utility values for patients on and off treatment, the ERG suggests a compromise. In its updated analysis, the EAG assigns a utility value of 0.62 for patients receiving lorlatinib as second-line treatment. This figure is based on the value currently applied to patients receiving chemotherapy at 2L.

Implementation of PAS

The EAG notes the committee's position on the differential pricing of lorlatinib, reflecting the conditional PAS offered by the company. The EAG reiterates its stance that implementing a differential PAS in this manner is inappropriate. As outlined in the evidence assessment report (EAR), this approach misrepresents the committee's decision as a comparison between a pre- and post-decision world, rather than as a point-in-time evaluation.

The EAG emphasises the importance of decisions being based on a consistent and clearly defined moment in time to ensure fairness and coherence in NICE's decision-making process. Moreover, given the proximity of the company's base-case ICER to decision-making thresholds, the EAG considers there to be a meaningful risk that a positive recommendation could result in NICE guidance that becomes self-invalidating. This is because the enhanced PAS discount applies to both first-line (1L) and 2L use and therefore alters the relative cost-effectiveness of the current standard of care.

In addition, clinical advice provided to the committee at appraisal committee meeting one (ACM1) indicated that recommending lorlatinib in the 1L setting would not displace the current standard of care. As such, future appraisals in this indication will be required to compare new interventions not only with lorlatinib 1L but also with existing treatment sequences (i.e. alectinib or brigatinib followed by lorlatinib). In this context, the appraisal of a new intervention may be significantly complicated, as the cost-effectiveness of comparators will differ substantially depending on the treatment pathway, thereby undermining the consistency and comparability of subsequent evaluations.

In Section 3, the EAG explores the implications of applying the updated PAS consistently across both 1L and 2L.

2.2 Comment 2 and 3: Updated four health state model structure (DGD Section 3.10) and Modelling approach for post-progression survival (DGD Section 3.13)

The company's revised base case updates the economic model to adopt a 4HS structure that aligns with the preferences of both the EAG and the Committee. In this revised structure, the previously singular "progressed disease" (PD) health state is split into two distinct states, PD1 and PD2. As a result, the model now includes the following health states: progression-free (PF), PD1, PD2, and death. This updated structure is illustrated in Figure 1 of the company's response.

Consistent with the preferences of the EAG and the Committee, the revised base case also changes how transition probabilities are estimated. A state-transition (Markov) approach is now applied across all treatment arms of the model. Previously, the lorlatinib arm was modelled using a partitioned survival approach. A detailed discussion of the implications of using state-transition approach can be found in Section 4.2.2 of the EAR.

As with the original three-health-state (3HS) model, the updated model compares a treatment sequence consisting of 1L lorlatinib followed by 2L chemotherapy and third-line (3L) best supportive care (BSC; no treatment) with comparator sequences comprising either:

- Alectinib or brigatinib 1L → lorlatinib 2L → chemotherapy 3L, or
- Alectinib or brigatinib 1L → chemotherapy 2L → BSC (no treatment) 3L.

Data used to populate the PF health state remains the CROWN trial and NMA. Several new data sources have, however, been used to populate the post-progression period compared to both the company's previous case and the EAG's base case reported in the EAR. These updates represent important changes with significant implications for modelled survival, total costs and overall cost-effectiveness. The EAG has attempted to summarise the data used across the different versions of the model in Table 2.

Other model inputs are in line with the previous 3 HS model and have been updated where appropriate to align with committee preferences.

Table 2 Summary of clinical data used in economic model

	Lorlatinib followed by chemotherapy	**Alectinib/brigatinib 1L followed by chemotherapy**	**Alectinib/brigatinib 1L followed by lorlatinib**
Company base case (3 health state model)			
Progression-free Survival	CROWN PFS	CROWN PFS + NMA	CROWN PFS + NMA
Progressed Disease	OS minus PFS	PROFILE 1001/1005	Study 1001 (cohorts 3B-5)

Overall survival	Pooled data from CROWN Trial - lorlatinib arm and Study 1001 (cohort 1)	Sum of PFS and PD	Sum of PFS and PD
EAG base case (3 health state model)			
Progression-free Survival	CROWN PFS	CROWN PFS + NMA	CROWN PFS + NMA
Progressed Disease	PROFILE 1001/1005	PROFILE 1001/1005	Study 1001 (cohorts 3B-5)
Overall survival	Sum of PFS and PD	Sum of PFS and PD	Sum of PFS and PD
Company revised base case (4 health state model)			
Progression-free Survival	CROWN PFS	CROWN PFS + NMA	CROWN PFS + NMA
Progressed Disease 1	Time to 2nd progression CROWN subgroup of patients who had progressed on 1L lorlatinib and did not receive a subsequent ALK TKI	Assumed the same as the lorlatinib arm	Time to progression study 1027[2]
Progressed Disease 2	Post progression survival as predicted in the committee's preferred model from TA628.[3a]	Assumed the same as the lorlatinib arm	Study 1001 (cohorts 3B-5) OS minus TTP study 1001(cohorts 3B-5).[b]
Overall survival	Sum of PFS, PD1 and PD2	Sum of PFS, PD1 and PD2	Sum of PFS, PD1 and PD2

Abbreviations: ALK TKI, Anaplastic Lymphoma Kinase Tyrosine Kinase Inhibitor; NMA, Network meta-analysis; PFS, progression free survival; PD, progressed disease; OS, overall survival; TTP, time to progression. [a] The model in TA 628[3] used pooled data from the ALUR and ASCEND-5 trials to estimate PFS and data from PROFILE 1001/1005 to estimate OS. These data were further adjusted using a hazard ratio of 0.8 (committee agreed assumption) to account for the potential benefits of doublet chemotherapy over single-agent chemotherapy. Post-progression survival, as used in the company's revised base case, was calculated as mean OS minus mean PFS. [b] Time spent in the PD2 state is estimated using the goal seek function to estimate a transition probability consistent with the Study 1001 (cohorts 3B-5) PFS and OS data.

The EAG's response

The EAG is satisfied that the company's revision to the model structure is appropriate and aligns with committee and EAG preferences in terms of how transitions are modelled. The new data, used to populate the PD1 and PD2 health states, raised several new issues outlined below.

Appropriateness of incorporating CROWN time to second progression data

As outlined in Table 2, the company's revised base case draws on data from the CROWN trial to estimate occupancy of the PD1 health state among patients receiving chemotherapy in the second-line (2L) setting (either following lorlatinib, alectinib or brigatinib). Specifically, the company used data on time to second progression (TTSP) from a subset of patients in the lorlatinib arm who experienced a progression-free survival (PFS) event that was not death and who did not receive a subsequent ALK TKI (Anaplastic Lymphoma Kinase Tyrosine Kinase Inhibitor; n=32). A scenario analysis was also conducted using data from all progressed patients, including those who received a 2L ALK TKI (n=45).

According to the company's response (Appendix Table 3), the median PFS in the subgroup that did not receive a subsequent ALK inhibitor was [redacted], while in the broader group of all progressed patients, the median PFS was [redacted] The company extrapolated these data using standard parametric survival models and selected the exponential function as the preferred approach, as it produced the most conservative estimate of TTSP. The EAG considers this approach reasonable.

The EAG finds the inclusion of additional data from CROWN to be beneficial and concurs with the company that this data better reflects outcomes for patients receiving chemotherapy after either lorlatinib, alectinib or brigatinib. However, the EAG observes that incorporating this information significantly increases the mean post-progression survival (PPS) time. In the EAG's original base case, the mean PPS for the lorlatinib arm was 0.82 life-years (LY); in the revised company base case, this figure nearly doubles to 1.64 LY.

The original three-health-state (3HS) model used data from PROFILE 1001/1005, which included patients treated with chemotherapy following 1L crizotinib. These data likely provided conservative estimates of PPS, as crizotinib is substantially less effective than later-generation ALK inhibitors, including lorlatinib. The increase in modelled PPS is therefore likely justified, and the EAR recognised PROFILE 1001/1005 as a suboptimal data source. One disadvantage of the CROWN data is that the sample size is much smaller than the sample available from PROFILE 1001/1005 (n=32 vs n=194), however, the EAG considers the greater relevance of CROWN data and the maturity of the data to outweigh this limitation.

Appropriateness of incorporating Study 1027

Another important change in the data used within the economic model is the incorporation of evidence from Study 1027.[2] Study 1027 is a Phase 4, non-randomised, single-arm trial that evaluated the efficacy of lorlatinib in patients who had received a single second-generation ALK inhibitor, i.e., in the 2L setting. Data from this study were used to inform the time spent in the PD1 health state. These data effectively replace those used in the original 3HS model from Study 1001 (cohorts 3B to 5), which included patients who had progressed on between one and three prior ALK inhibitors. A critique of Study 1027 is provided in the Appendix.

The key advantage of using Study 1027 data is that it excludes patients who have received multiple ALK TKIs, thereby better reflecting the current NHS treatment pathway. Furthermore, the majority of patients in Study 1027 received alectinib (85%) as their 1L therapy, with the remainder receiving ceritinib. This again, more closely aligns with the current NHS pathway and comparators considered in the model. The EAG, therefore, considers the inclusion of evidence from Study 1027 to be

appropriate and more likely to accurately reflect time to second progression for patients receiving lorlatinib in the 2L setting compared with data from Study 1001.

Extrapolating Study 1027

The EAG takes issue with the company's approach to extrapolating Study 1027. To extrapolate the evidence from Study 1027, the company considered alternative standard parametric extrapolations and identified the exponential function as the most appropriate. The EAG disagrees that this appropriate extrapolation and considers it to produce predictions that break the internal logic of the model. Specifically, it implies that TTSP is longer if a patient receives 2L chemotherapy than 2L lorlatinib (following 1L alectinib or brigatinib), see Table 2 of the company's response appendix for transition probabilities applied. This lacks clinical plausibility. Moreover, the exponential function has the worst statistical fit to the data. Of the remaining statistical functions, the EAG agrees that the Gompertz, log-logistic, log-normal and generalised gamma equally appear to lack clinical plausibility, as they predict high rates of patients being progression-free at 10 years and 20 years. Of the two remaining functions, gamma and Weibull, the EAG considers both to be plausible; however, the Gamma function appears more reasonable given the predictions for 10 and 20 years (note that the EAG was unable to consult clinical opinion on this point). Both the gamma and Weibull functions are consistent with other data used in the model.

2.3 Comment 4: Time on treatment and treatment after progression

The company implemented the committee's preference to assume that for all treatments, time on treatment (ToT) was equal to PFS, with 3.5 months of treatment after progression for 75.6% of people. The clinicians present at ACM1 explained that treatment beyond progression is common for all ALK TKIs in this indication. The company implemented this in the model in their interpretation of this scenario.

The EAG's response

Implementation error

The EAG has identified an error in the implementation of treatment progression. In the executable model provided by the company, 100% of patients are assumed to receive treatment beyond progression across all treatment arms. The EAG corrects this error and illustrates the impact on the ICER in Section 3.

Plausibility of the committee's preferred time on treatment and treatment after progression assumptions

The EAG agrees that a 3.5-month extension to ToT for alectinib and brigatinib is consistent with the clinical advice presented at ACM1. However, the EAG notes that treatment beyond progression is not permitted under alectinib's Summary of Product Characteristics and was not included in the

modelling assumptions for TA536.[4] As such, the appropriateness of modelling treatment beyond progression in the alectinib arm is unclear.

The EAG has consulted its clinical advisor regarding the committee's preferred assumption of treatment beyond progression. The advisor considered it unlikely that 75.6% of patients would receive treatment beyond progression with alectinib or brigatinib, estimating a more plausible figure to be below 25%. The 75.6% assumption adopted by the committee and implemented in the company's revised base case is s not deemed realistic by EAG clinical advisers, as it would imply a substantial delay in initiating lorlatinib as a 2L therapy. In the context of the model, this assumption also implies that patients in the PD1 health state who receive lorlatinib as a 2L therapy are assumed to be on an ALK TKI for more than 100% of their time in that state. As a result, drug acquisition costs in the PD1 health state are overestimated, leading to inflated total costs in the alectinib and brigatinib arms of the model.

In addition to the above, the EAG's clinical adviser indicated that treatment beyond progression would likely be longer with lorlatinib than with alectinib or brigatinib, given the availability of lorlatinib as a 2L treatment option. This aligns with the clinical opinion heard in TA909,[5] where it was stated that treatment beyond progression would be longer for the final ALK TKI than for an ALK TKI that could be followed by another ALK TKI. Clinical experts consulted as part of TA909[5] further elaborated an expectation that treatment with lorlatinib might continue for up to six months if a patient continued to benefit. The EAG also notes that the 5.7 months treatment beyond progression modelled in the EAG base case was informed by committee-preferred assumptions in TA909[5] and is data-driven, as it draws on evidence from Study 1001. In contrast, the 3.5-month figure preferred by the committee was based on clinical opinion elicited as part of TA628.[3]

Given these uncertainties and the clinical advice received, the EAG updates its base case to assume 5.7 months of treatment beyond progression in 75.6% of patients in the lorlatinib arm, and 3.5 months of treatment beyond progression in 25% of patients in the alectinib and brigatinib arms.

2.4 Comment 5: OS uncertainty has been accounted for in the modelling and assumptions used. CROWN PFS data is expected to translate into OS advantage compared to existing treatment options.

The company reiterated the reasons why no further OS data cuts can be provided at this time. Updated OS results from CROWN are projected [redacted], and the final OS analysis is anticipated to be accessible in December 2028. The company noted that naïve comparisons between OS rates in alectinib and brigatinib trials and PFS rates in lorlatinib (presented in Table 6 of the company response) suggest that lorlatinib demonstrates highly promising PFS results relative to

existing 1L options. They restated that, given the 5-year follow-up of CROWN shows lorlatinib offers the longest PFS ever observed for a single targeted agent in any solid tumour trial, this PFS benefit is expected to translate into an OS benefit. The company argued that OS uncertainty has been accounted for by employing a state transition approach for post-progression survival for lorlatinib (and no OS data from CROWN or from the company NMA), along with using conservative assumptions to model OS for lorlatinib.

The EAG's response

EAG clinical advisers agree that, given the highly promising PFS results from the CROWN trial and the OS outcomes from Study 1001, it is plausible that lorlatinib will ultimately demonstrate an OS benefit relative to other existing treatment options. They consider a median OS of at least 10 years to be clinically plausible for lorlatinib. However, in the absence of mature OS data from CROWN, the EAG notes that there is still no direct evidence showing that lorlatinib provides superior OS compared to either crizotinib, alectinib or brigatinib.

While Study 1001 reported an encouraging 5-year OS probability of 76.3% in patients who had not previously received an ALK TKI, these findings are based on limited evidence from a small, non-randomised subset of patients and are subject to the inherent limitations of the study (see EAR Section 3.2.2). The EAG agrees with the company that the current 4HS model adopts a conservative approach, predicting a substantially lower 5-year OS rate of 62.3%, which is comparable to the 62.5% observed in the alectinib arm of the ALEX trial.

The EAG agrees with the company that existing NMA evidence suggests that lorlatinib has significantly improved PFS outcomes in the 1L setting compared with alectinib and brigatinib. However, all existing NMAs are limited by the immaturity of OS data from CROWN. Therefore, the EAG accepts that OS evidence from CROWN and the NMA is limited to inform the economic model.

Although EAG clinical advisers noted that it was clinically plausible that PFS results would translate into OS benefits for lorlatinib compared with current 1L treatment options, the EAG notes that the magnitude of any possible relative OS benefit is unknown.

In the absence of mature OS evidence from a randomised trial comparing treatment sequences that are reflective of practice, OS uncertainty cannot be fully resolved. The extent to which OS uncertainty is addressed in the company's updated model is further discussed below (Comment 7).

2.5 Comment 6: Treatment sequencing and lorlatinib treatment duration

The company argues that the 4HS model structure accounts for treatment sequencing appropriately, using data sources that are not confounded by subsequent treatment options in the comparator trials,

therefore, the uncertainty associated with this issue is likely to be minimal. They also noted that 1L lorlatinib treatment will be longer than the alternative treatment sequence, and clinicians wish to treat patients upfront with the most effective, progression-delaying treatment.

The EAG's response

Treatment sequencing and risk of confounding due to subsequent therapies

The EAG agrees with the company that the 4HS model structure and the use of relevant PFS evidence sources (including Study 1027, which is critiqued in the Appendix) largely address the risk of confounding for OS estimates due to treatment sequences in trials of lorlatinib, alectinib, and brigatinib. The 4HS model structure allows for the evaluation of treatment sequences that are significantly more reflective of current practice than those observed in CROWN, ALEX, or ALESIA. However, it also requires the use of multiple sources of evidence and relative estimates of OS benefit are no longer directly derived from randomised evidence; therefore, it does not fully eliminate the risk of confounding for OS.

The company presents CROWN PFS2 data in this response (see Comment 3 and Appendix 1, Figures 3–5). Kaplan–Meier curves are provided for time to second progression, measured from the point of first progression, for all patients who progressed on lorlatinib (n=45), as well as for a subgroup of patients who did not receive an ALK TKI as their first subsequent treatment (n=32). These curves suggest that subsequent ALK TKI treatment following first-line lorlatinib offers limited benefits. This finding is consistent with clinical advice provided to both the EAG and the company, suggesting that older-generation ALK TKIs are likely to have limited efficacy due to their narrower activity against ALK resistance mutations.

However, these results are limited by their post hoc, non-randomised, and unadjusted nature, and are based on a small subset of patients. As such, the evidence presented by the company is insufficient to conclude that subsequent ALK TKI therapy has no effect on overall survival.

Preference for upfront treatment with lorlatinib

Clinical advisers to the EAG agreed that, in light of the trial evidence for ALK TKIs in the 1L and 2L settings, treating patients upfront with lorlatinib as the most effective progression-delaying treatment, including in patients with CNS metastases, would likely be the preferred option in practice. However, NMA evidence suggests that alectinib has a more favourable safety profile compared with lorlatinib overall (as discussed in EAR Section 3.5). Clinical advice, including to the EAG and to the company[6{Lam, 2025 #338] indicated that, in view of the balance of benefit and harms of 1L treatment options, lorlatinib would not fully displace currently available 1L options if it were approved in this setting. This is in line with NICE Draft Guidance Section 3.3.

2.6 Comment 7: Acceptable ICER threshold

In its response, the company argues that the upper end of the NICE threshold should be considered, as the company aligns with the committee's preferred assumptions regarding areas of uncertainty, applying several conservative assumptions for lorlatinib. Furthermore, the company cites that lorlatinib is an innovative treatment for a high unmet need, where this new treatment option offers people a step change in treatment. They also mention precedents set in other ALK TKI appraisal with quotes from TA536[4] (alectinib) and TA670[7] (brigatinib). Additional considerations include the younger working-age profile of patients and the argument that the consequences of decision error are low.

The EAG's response

The EAG acknowledges that the company has faithfully applied the committee's preferred assumptions, resulting in a decision model that is both structurally consistent and representative of the NHS treatment pathway. The EAG also notes that revisions to certain clinical data improve alignment between the economic analysis and the decision problem, thereby reducing uncertainty.

However, significant and fundamental uncertainties persist. The company's response does not provide any new evidence on OS. As outlined in Section 2.4 and within the EAR, there is no direct clinical evidence demonstrating that lorlatinib improves OS compared to either comparator treatment. While the economic model (under both the company's and the EAG's revised assumptions) predicts an OS benefit, this should not be interpreted as evidence per se. Economic models synthesise existing data; they do not generate new data. Furthermore, the model draws on evidence from multiple sources and implicitly assumes that OS is the summation of outcomes from each of these studies, all of which draw from different patient samples, some of which do not fully reflect the target population. Importantly, OS estimates in the economic model are not derived from randomised comparisons. As such, the usual limitations associated with non-randomised evidence apply.

These issues are important factors in evaluating decision uncertainty and differ significantly from the appraisals cited by the company, as the economic models in those cases were informed by clinical evidence from randomised trials.

2.7 Comment 8: Updated results

The updated results from the company base case are presented in Section 3.

2.8 Additional issues raised by the company

2.8.1 Comment 9: Subgroup analysis

In the draft guidance document, the committee indicates that it may be appropriate to consider the clinical and cost effectiveness of lorlatinib specifically in a subgroup of people with central nervous system (CNS) metastases.

In its response, the company argues that an optimised recommendation limited to patients with CNS metastases would not be appropriate. It emphasises that the benefits of lorlatinib are not confined to patients with baseline CNS metastases, but also extend to those without pre-existing CNS metastases. The company further notes that improvements in intracranial outcomes have been observed in both patients with and without pre-existing CNS metastases; data from CROWN reports 94% reduction in the risk of intracranial progression on lorlatinib (HR of 0.06; 95% CI: 0.03, 0.12), compared with crizotinib.

The company did not present subgroup analysis in patients with CNS metastasis at baseline as part of its response.

The EAG's response

Patients with pre-existing CNS metastases may represent an important subgroup that could particularly benefit from treatment with lorlatinib. The EAG, however, agrees with the company that the PFS benefits of lorlatinib are not limited to this subgroup. This is supported by subgroup analyses presented in the company submission and several published NMA, which compared lorlatinib with alectinib and brigatinib in patients with baseline CNS metastases.

While focusing on patients with pre-existing CNS metastases could potentially improve the cost-effectiveness of lorlatinib, the evidence required to support such a subgroup-specific analysis is incomplete. Although the CROWN, ALTA-1, ALEX, and ALESIA trials report subgroup analyses for PFS in patients with CNS metastases (allowing the progression-free health state to be informed), it is less clear whether comparable data are available for the post-progression period. Any attempt to model outcomes in this setting would therefore likely require strong assumptions about the equivalence of post-progression outcomes between patients with and without CNS metastases.

In the EAG's view, such a subgroup analysis would introduce substantial additional uncertainty beyond that already present in the existing base-case analysis, and it is unclear whether any such analysis would be suitable for decision making.

2.8.2 Comment 10: Managed access

The company is unsure if a managed access route will address the committee's clinical concerns regarding overall survival. Nonetheless, the company would consider a managed access arrangement if the committee determine routine commissioning is not possible due to clinical uncertainty.

The EAG's response

The EAG believes that OS data cuts from the CROWN study would be helpful. The EAG has serious reservations about whether the SACT database analysis would be able to resolve clinical uncertainties, due to the limited follow-up and lack of randomisation, but it may be useful in determining the duration of treatment beyond progression and the type of patients for whom lorlatinib is most appropriate.

2.9 Additional issues raised by the EAG

2.9.1 Proportion of patients receiving second-line lorlatinib

The company's revised base case and the EAG's base case following the EAR assume that 86.8% of patients will receive 2L lorlatinib following either alectinib or brigatinib. According to the company's submission, this assumption was based on UK market share data and further validated by clinical expert opinion. The EAG's clinical advisers also supported this assumption, noting that in their experience, the vast majority of patients would proceed to receive 2L lorlatinib.

However, evidence presented by the clinical lead of the Cancer Drugs Fund (CDF) at ACM1 appears to contradict this. Citing NHS England data, the CDF lead stated that fewer than 40% of patients who receive 1L alectinib or brigatinib go on to receive lorlatinib in the 2L setting. Furthermore, clinical expert opinion heard at ACM1 confirmed that lorlatinib is used in a minority of patients in real-world clinical practice.

The proportion of patients receiving 2L lorlatinib is a key driver of cost-effectiveness. Alectinib or brigatinib followed by chemotherapy is significantly more cost-effective than sequences involving 2L lorlatinib. Therefore, reducing the proportion of patients receiving 2L lorlatinib substantially increases the ICER.

In light of the evidence presented at ACM1, the EAG has updated its base case to assume that 40% of patients will receive lorlatinib in the 2L setting.

3 COMPANY REVISED BASE CASE AND EAG BASE CASE

3.1 Results

The results of the company's updated base case are summarised below. These results are inclusive of the approved PAS discounts for lorlatinib (both 1L and 2L) but are exclusive of confidential PAS discounts for other comparators and subsequent treatments. Results with PAS discounts for all comparators and subsequent treatments are provided in a confidential appendix separate to this document. All results presented are deterministic as a probabilistic version of the 4HS model was not presented by the company in its response.

Table 3 presents the results of the company's revised base case using the 4HS specification of the economic model. As noted in Section 2.3, the EAG identified an error in the implementation of the scenario modelling treatment beyond progression. Table 4 presents the results of the company's revised base case, correcting for this error.

Table 3: Company's revised base-case (deterministic)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year							

[a] Was reported in the company's response as £-153,175.

Table 4 EAG-corrected Company's revised base-case (deterministic)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year							

Table 5 reports selected scenario analysis vs. alectinib presented in the company response using the EAG corrected company base case as a reference.

Table 5 Results of scenario analyses versus alectinib

Scenario	Inc. Costs (£)	Inc. QALYs	Deterministic ICER £/QALY)	ICER difference vs base case (£/QALY)
Alternative extrapolations for time from first to secondary progression following 1L lorlatinib				
Exponential (Gen Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Exponential (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]
Exponential (Log-normal)	[redacted]	[redacted]	[redacted]	[redacted]
Exponential (Log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]
Exponential (Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Alternative extrapolations of 2L PFS lorlatinib based on the Phase IV study				
Exponential (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]
Exponential (Gamma)	[redacted]	[redacted]	[redacted]	[redacted]
Alternative 2L lorlatinib PFS data source				
Study 1001 cohorts: 3B to 5	[redacted]	[redacted]	[redacted]	[redacted]
Alternative post-second progression mortality in the lorlatinib arm				
45% lower	[redacted]	[redacted]	[redacted]	[redacted]
30% lower	[redacted]	[redacted]	[redacted]	[redacted]
15 lower	[redacted]	[redacted]	[redacted]	[redacted]
15% higher	[redacted]	[redacted]	[redacted]	[redacted]
30% higher	[redacted]	[redacted]	[redacted]	[redacted]
45% higher	[redacted]	[redacted]	[redacted]	[redacted]
Alternative post-second progression mortality in the alectinib arm				
45% lower	[redacted]	[redacted]	[redacted]	[redacted]
30% lower	[redacted]	[redacted]	[redacted]	[redacted]
15 lower	[redacted]	[redacted]	[redacted]	[redacted]
15% higher	[redacted]	[redacted]	[redacted]	[redacted]
30% higher	[redacted]	[redacted]	[redacted]	[redacted]
45% higher	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib percentage of PFS2 events that are death				
CROWN all patients lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
CROWN all patients crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
CROWN all patients pooled lorlatinib and crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Study 1001 cohorts: 3B to 5	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life year.				

Table 6 presents results of an additional scenario analysis in which the company updates the 3HS model to align with the new assumptions and data used in the 4HS model.

Table 6 Company's revised base case using the 3HS model

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year							

[a] Was reported in the company's response as 6.31. [b] Was reported in the company's response as 0.00. [c] Was reported in the company's response as 1.53. [d] Was reported in the company's response as £-156,339.

3.2 EAG scenario analysis

The following deterministic exploratory analyses were conducted by the EAG following corrections to the company's revised base case.

1. Utility values in the PD2 health state

The EAG is concerned that the utility values applied in the PD2 health state may be too low and may not adequately reflect quality of life in patients receiving third-line treatment. Scenario 1, therefore, updates the utility values applied in the PD2 health state to 0.62 to patients receiving 3^{L} pemetrexed, aligning with those applied in the PD1 health state.

2. Treatment beyond progression

The EAG is concerned that treatment beyond progression assumptions preferred by the committee and adopted by the company may not adequately reflect clinical practice. Scenario 2a, updates the proportion of patients who receive treatment beyond progression in the alectinib and brigatinib arms to 25%. Scenario 2b updates the duration of treatment beyond progression in the lorlatinib arm to 5.7 months.

3. Proportion of patients who proceed to 2L lorlatinib

Evidence heard at ACM1 indicated that only a minority of patients will receive lorlatinib in 2L setting. Scenario 3 therefore, assumes that only 40% of patients will receive lorlatinib 2L broadly aligning with figures provided by the CDF lead.

4. Extrapolation of Study 1027

The EAG considers the company's preferred extrapolation of Study 1027 to lack clinical plausibility. The EAG therefore conducts scenario analysis considering gamma extrapolation (scenario 4a) and Weibull extrapolation (scenario 4b).

5. Differential PAS for Lorlatinib

The EAG considers it inappropriate to apply a different PAS discount for lorlatinib in the 1L to that applied in the 2L. Scenario 5, therefore, explores the implications of applying the updated PAS consistently across both 1L and 2L.

The results of the EAG scenario analyses described above are presented in Table 7. All results are inclusive of the correction to the company's revised base case.

Table 7 EAG Exploratory fully incremental scenario analyses (deterministic)

Scenario		Technology	Total		Incremental		Fully incremental ICER
			Costs	QALYs	Costs	QALYs	
Company revised base case (corrected)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	**Utility in PD2**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2a	**25% alectinib & brigatinib treatment beyond progression**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2b	**5.7 months lorlatinib treatment beyond progression**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	**40% 2L lorlatinib**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4a	**Gamma extrapolation of TTSP**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4b	**Weibull extrapolation of TTSP**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	**Lorlatinib PAS same for 1L & 2L**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line; 2L, second line, ICER, incremental cost effectiveness ratio; PAS, patient access scheme; PD2, progressed disease 2 (health state); PSM, partitioned survival model; QALY, quality-adjusted life-year; .TTSP, time to second progression

3.3 EAG base-case analysis

The cumulative impact of the EAG's preferred assumptions is presented in Table 8 below.

The EAG base case adopts the following scenarios described in Section 3.2

- Scenario 1: Revised utility values
- Scenario 2a: 25% of patients receive alectinib or brigatinib beyond progression
- Scenario 2b: Patients receive lorlatinib for 5.7 months beyond progression
- Scenario 3: 40% of patients receive lorlatinib 2L
- Scenario 4a: Gamma distribution used to extrapolate Study 1027
- Scenario 5: Same PAS for lorlatinib 1L and 2L

Table 8 EAG's preferred model assumptions (Deterministic)

Technology	Total		Incremental		Fully incremental ICER
	Costs	QALYs	Costs	QALYs	
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, evidence assessment group, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years

3.3.1 Additional scenario analysis on the EAG base case

Table 9 presents the EAG preferred base case without scenario 5 applied i.e. with a differential PAS discount for Lorlatinib.

Table 9 EAG's preferred model assumptions without Scenario 10 PAS (Deterministic)

Technology	Total		Incremental		ICER (£ per QALY)
	Costs	QALYs	Costs	QALYs	
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, evidence assessment group, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years

4 REFERENCES

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5 APPENDIX: CRITIQUE OF STUDY 1027

To inform the 4HS model base-case, the company provided new evidence for PFS outcomes in patients on 2L lorlatinib following 1L alectinib/brigatinib. This replaces PFS evidence from Study 1001 (cohorts 3B-5), which was included in the company's 3HS and in TA628, although this evidence source is still included in a scenario analysis of the company's 4HS model.

Study 1027 (NCT04362072) is a phase IV, multi-centre, international open-label trial. The NCT record indicates that trial sites were located in countries including USA, India, Spain, Switzerland, Poland and the UK.[2] The study was completed in October 2024. A total of 71 participants with ALK mutated metastatic NSCLC whose disease had progressed following 1L therapy with either alectinib (85%) or ceritinib (15%) were treated with lorlatinib 100mg once daily. Patients with ECOG 0-1, with or without asymptomatic CNS metastases, were eligible for inclusion.[8] The primary outcome was ORR (Objective Response Rate; independent central review [ICR]). Secondary outcomes included PFS by ICR, and safety.

The median duration of lorlatinib treatment was 9.7 months (range, 0.3 to 42.8). The median duration of follow-up for response was 18.0 mo (95% CI, 9.6 to 22.1), and ORR was 42% (95% CI, 31% to 55%). Median PFS was 12.2 mo (95% CI, 6.9 to 22.1) with 51% probability of being progression-free at 12 months. Serious TEAEs occurred in 32%, and grade ≥3 in 39% of patients. Treatment-emergent adverse events (TEAEs) led to dose reduction in 14% and treatment discontinuation in 13% of patients.

Results were only available in a conference abstract and as a conference poster, which limits the EAG's ability to appraise the study. Although none of the participants included had prior brigatinib therapy and a minority had received ceritinib, most participants had received 1L alectinib therapy, which is reflective of clinical practice in England and Wales. Reported patient baseline characteristics were broadly aligned with characteristics of patients with ALK-positive NSCLC in 2L, However, although a higher proportion of patients with Asian heritage and no patients of other non-white heritage were included, this is a common feature of NSCLC trials and according to clinical advice to the EAG is not a significant treatment effect modifier.

OS was not pre-specified nor reported. PFS was measured by ICR and median PFS was reached. Median PFS was higher in Study 1027 (12.2 months; 95% CI, 6.9 to 22.1) compared with Study 1001 cohort EXP3B (cohort with previous non-crizitonib ALK TKI ALK TKI with or without chemotherapy, 5.5 months; 95% CI, 2.7 to 9.0).

Study 1027 has a number of limitations, notably due to its lack of a control arm, lack of OS data and limited reporting as a conference abstract. However, unlike Study 1001 Cohorts 3B-5, which included

a combination of patients with one or more prior therapies, Study 1027 included only patients with one prior ALK TKI (alectinib in most cases, which is more reflective of current practice). Study 1001 Cohort 3B included patients with one prior non-crizotinib ALK TKI with or without chemotherapy and was smaller (n=28). Overall, the EAG found that, compared with Study 1001, Study 1027 is likely to be a more relevant source of PFS outcome evidence for lorlatinib in the 2L setting.

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name: **Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer**
Topic ID: **6434**
Managed Access Lead: **Milena Wobbe**
Date of assessment(s): **17/06/2025**

Feasibility of successful managed access	Comments / Rationale	
Yes	Rationale for rating	A period of data collecting within the CDF would allow for useful data collection.
	Previous ratings and rationale for change	No managed access proposal. The managed access team has re-evaluated the suitability for managed access once the proposal was received.

Managed Access Proposal	Yes (on request)	
Managed Access Team input at Committee meeting	Medium	It is possible that the managed access may have to engage with committee during the meeting.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF.
Are there outstanding uncertainties that could be resolved with further data collection?	High	A period of managed access would allow for further data collection on some key uncertainties, most notably further data cuts on OS.

Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Yes	Further data collection would be possible through the CROWN clinical trial as well as real world evidence generation through SACT.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	The SACT dataset could collect some useful information, in particular time on treatment and subsequent treatment as well as some information on the patient population (in combination with Blueteq criteria)
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	It is expected that there are no substantive issues

Key questions for committee if Managed Access is considered	
1	Would CDF allow a clear recommendation at the end of managed access?
2	Are the main uncertainties sufficiently resolvable through further data collection?
3	Only OS data is likely to be fully resolved at managed access exit. How much of an impact do the other uncertainties have? If they are still apparent at managed access exit, will it allow the committee to make a routine recommendation?
4	CMT1 uncertainty - Are the people who would be scanned in clinical practice representative of the brain metastases subgroups? Would leaving out people who have asymptomatic brain metastases mean the data from SACT would not represent the subgroup?
5	
6	

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	
2	
3	
4	
5	
6	

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for managed access.

Date agreed with NHSE	17/06/2025

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF.

System implementation	Supporting Evidence
Has the technology has been flagged as a potential IMF candidate to NICE by NHSE horizon scanning?	No

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify its decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
High	A period of managed access would allow for further data collection on some key uncertainties, most notably further data cuts on OS.

Key Uncertainties

Number	Title	Summary of issue	Impact on ICER	Data available to resolve uncertainty	Data collection in company proposal	Resolvable with managed access	Managed Access Team view on feasibility
CMT1	Subgroups	Lorlatinib may be particularly effective for intracranial outcomes. However, the committee was not given any relevant subgroup analyses. Furthermore, there is variation within the NHS in identifying CNS metastases.	Unclear	Blueteq/SACT and CROWN clinical trial	Whilst this is not directly mentioned in the managed access proposal provided by the company, the managed access team have met with the company and data collection on this was discussed.	Low	At the start of treatment, Blueteq criteria have to be filled out by the clinician. If the Blueteq criteria have a section on CNS metastases, the outcome for relevant patients could be analysed. However, the trial data included mandatory scans for all patients. This is unlikely to happen within the NHS and will include some regional variation. Many patients (and clinicians) do not wish to undergo scanning for brain metastases if there are no symptoms or suspicions of CNS metastases, as even very small and asymptomatic metastases (which are likely to be cleared with lorlatinib) would have a significant impact on patient's lives, such as the loss of their driver's license. This means that identifying the correct subgroups within the NHS is challenging. The company have reiterated that further data from subgroups will be collected in CROWN.

CMT2	Generalisability to the NHS	There are several concerns about the generalisability of the CROWN trial data. Namely, crizotinib was used as a comparator, the treatment sequencing in the trial does not reflect NHS practice, and the 2L treatment does not correlate with NHS practice. This results in high levels of uncertainty in the clinical evidence after cancer progression.	Unclear	SACT and CROWN clinical trial	Whilst this is not directly mentioned in the managed access proposal provided by the company, the managed access team have met with the company and data collection on this was discussed.	Medium	Through SACT, OS and time on treatment can be collected. However, it cannot collect PFS data and therefore the relationship between PFS and time on treatment cannot be explored within SACT. Furthermore, data collection would be time limited to the duration of managed access, which may not be sufficient. The company have suggested entry into the CDF for up to three years. SACT could be used to collect survival data for brigatinib and alectinib. More detail on this is discussed for uncertainty CMT8. The company have stated that further data from CROWN could be collected that is used in the 4HS model for time to second progression after progression on 1L lorlatinib to help address this uncertainty. The 4HS model uses CROWN data for patients who had progressed on 1L lorlatinib who then received 2L chemotherapy as per the NHS treatment pathway (i.e. did not receive an ALK TKI as their subsequent 2L treatment), to removing uncertainty associated with treatment sequencing.
CMT3	Progression-free survival	Lorlatinib PFS benefit is significant. However, there is a risk of bias in the data as it was investigator-assessed.	Unclear	Committee judgement required	No	Low	No data collection would help address the potential of bias in the data. However, the company have stated that the PFS benefit of lorlatinib over crizotinib is consistent between BICR and investigator assessed assessments (See A4c of CQ response), which may alleviate some of the committee's concerns. Further PFS data is collected through the CROWN clinical trial.
CMT4	Time to intracranial progression	The open-label design of CROWN may have biased investigator-assessed outcomes, such as this.	Low	SACT and CROWN clinical trial	Whilst this is not directly mentioned in the managed access proposal provided by the company, the managed access team have met with the company and data collection on this was discussed.	Low	CDF data collection is limited to a 5 year timeframe (and the company in this case have suggested up to three years.) The company submission shows immature data at 80 months, which SACT data could only somewhat verify. Furthermore, specific site progression is not recorded in SACT as standard. Whilst no RWE collection would be feasible, the company wishes that limitation of bias is considered in the context of the protocol design and that ITCs have shown that lorlatinib has better in reducing the risk of intracranial progression than NHS-relevant comparators. Further data from CROWN will continue to be collected and include data cuts on time to intracranial progression.

CMT5	Overall survival	OS data is immature, with the latest OS data cut from March 2020 after a median of 20 months of follow up. Although the PFS benefit with lorlatinib was deemed significant, it is unclear whether this translates to a benefit in OS.	Unclear	CROWN clinical trial	Yes	High	Further data cuts are planned and more mature OS data could be collected during a period of managed access.
CMT6	Network meta-analysis	The company performed a Bayesian NMA to compare 1L lorlatinib to alectinib and brigatinib. This showed that lorlatinib showed PFS and time to intracranial progression benefits over NHS comparators alectinib and brigatinib. However, OS benefit was short (although not statistically relevant.) Furthermore, treatment sequencing in the trials of the NMA did not correspond to NHS practice, the violation of the proportional hazards assumption and the immaturity of the CROWN OS data mean that the NMA OS estimates were uncertain.	Unclear	Committee judgement required	No	Low	Whilst further OS data collection through CROWN could address some uncertainty, there are further issues with the NMA analysis and outcome data that cannot be addressed through further data collection.
CMT7	Model structure	The company used a 3-state model to evaluate the cost effectiveness of lorlatinib. This, however, is likely to be unable to fully account for lorlatinib 2L. The committee has asked for a 4-state model. The committee has also stated other preferences for the model for the company to adopt in its submission.	Unclear	Further data submission ahead of ACM2	No	Low	The company have stated that managed access would allow further data collection of further mature data, which could be used to populate the 4HS model.

CMT8	Managed Access	The CDF lead at ACM1 stated that the NHS would collect observational data on lorlatinib as well as comparators alectinib and brigatinib, which could be collated and analysed for the resubmission at the end of managed access	Unclear	N/A	Whilst this is not directly mentioned in the managed access proposal provided by the company, the managed access team have met with the company and data collection on this was discussed.	Medium	Survival data for alectinib and brigatinib could be collected through SACT. However, the data for the comparator treatments would be more mature and not comparable to the SACT-collected lorlatinib data, as the latter would be too immature. The RWE data for alectinib and brigatinib would then have to be compared to trial data, which would introduce a different uncertainty. The company have suggested that the indirect treatment comparisons versus alectinib and brigatinib can be updated with updated CROWN data that would be collected during managed access. Current ITC uses immature OS CROWN data for lorlatinib.

Data Collection

What data sources are available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	
Rating	**Rationale**
Yes	Further data collection would be possible through the CROWN clinical trial as well as real world evidence generation through SACT.

Existing or proposed clinical trials	
Name and registry ID of trial	CROWN
Is trial proposed for managed access?	Yes
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT03052608
Start date	Apr-17
Anticipated completion date	Dec-28
Data cut presented to committee	Oct-23
Data collection timeline	The data cuts are events led, so subject to change but further data cuts, especially for OS are planned
Description of trial	Phase 3, randomised, open-label study of lorlatinib monotherapy versus crizotinib monotherapy in the first-line treatment of people with advanced ALK-positive non-small cell lung cancer, n=296
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/35605188/

NHS registry data	
Name of registry	SACT
Is registry proposed for managed access?	By the managed access team, with verbal agreement from the company
Mandated data collection?	SACT is a mandated data set, but sometimes additional data fields will be added, so capture that information here, alongside a consideration of that additional burden.
Available to use?	Yes
Data items already collected	Detail if SACT items will help resolve uncertainties. The full list will be provided in in SOP/template - or we can provide link to SACT page list.
Issues raised by committee or stakeholders	N/A
Data collection timeline (future data cuts, proposed end of data collection…)	Data cuts are events driven, with further data cuts expected and SACT data cuts could be aligned to the expected trial data cut schedule. The latest data cut would be at the end of 2028.

Data collected in clinical practice

SACT

Is RWE data collection within managed access feasible?		
Overall Rating	**Rationale/comments**	
High		The SACT dataset could collect some useful information, in particular time on treatment and subsequent treatment as well as some information on the patient population (in combination with Blueteq criteria)

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHS England's SACT dataset is an established mandatory dataset
Prior experience with managed access	High	NHS England's SACT Team have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	0
If required, ease that new data items can be created / modified	Not applicable	No additional data items to be included
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice
Data completeness	High	NHS England's SACT Team have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHS Digital follow-up with trusts where data is missing
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS England's SACT Teaml have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly

Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk
Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHS England's SACT Team's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSE, SACT, blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSD to link blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	0
Analyses		
How easily could collected data be incorporated into an economic model	High	0
Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	0
Existing analytical capacity	High	Established analytical capacity
Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	0
Security assurance	Yes	0
Existing relevant ethics/research approvals	Not applicable	0
Patient consent	Yes	No prior patient consent required
Funding		

Existing funding	Yes	Established partnership between NHS Englands CDF team and SACT team (part of NDRS)
Additional funding required for MA	No	0
If yes, has additional funding been agreed in principle	Not applicable	0
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. No additional data items created
Are any of the clinical assessments not validated for use or accepted clinical practice	No	See above
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. No additional data items created
Burden		
Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Existing mandated data set. No additional burden of data collection within managed access
Other additional burden	No	0

Other issues

SACT

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	It is expected that there are no substantive issues

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	Data collection in clinical practice through existing mandated data set. No additional burden of data collection within managed access
	Expected overall additional system burden from data collection?	Low	As above
	Do stakeholders consider any additional burden to be acceptable	Not applicable	0
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	0

		Rating	Rationale / comments

Patient Safety	Have patient safety concerns been identified during the evaluation?	No	No additional patient safety concerns identified
	Is there a clear plan to monitor patient safety within a MA?	Yes	No additional patient safety concerns identified
	Are additional patient safety monitoring processes required	No	No additional patient safety concerns identified

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	It the event of negative NICE guidance at the end of managed access it is expected, in line with principles of the Innovative Medicines Fund and Cancer Drugs Fund, that patients will continue to be able to receive the treatment until such time that the patient and the treating clinician determines it is no longer clinically appropriate.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	0

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	0
	Will implementation subject the NHS to irrecoverable costs?	No	0
	Is there an existing service specification which will cover the new treatment?	Yes	0

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	It is expected that the entire eligible patient population, as recommended by NICE, will be able to access the medicine. Detailed blueteq criteria will be developed by NHSE prior publication of any positive draft final NICE guidance

	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	-

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	As above
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	0
	Any issues from registry specific questions	No	0
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	0
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	0
	Any issues from registry specific questions	No	0

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	There are not expected to be any equality issues from a recommendation for use with managed access compared to a recommendation for routine use.

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	It is expected that a data collection agreement could be agreed within normal FAD development timelines (35 days) if committee make a recommendation for use in managed access