Cost-effectiveness of First-line Lorlatinib for ALK-positive Advanced Non-small-cell Lung Cancer in the UK

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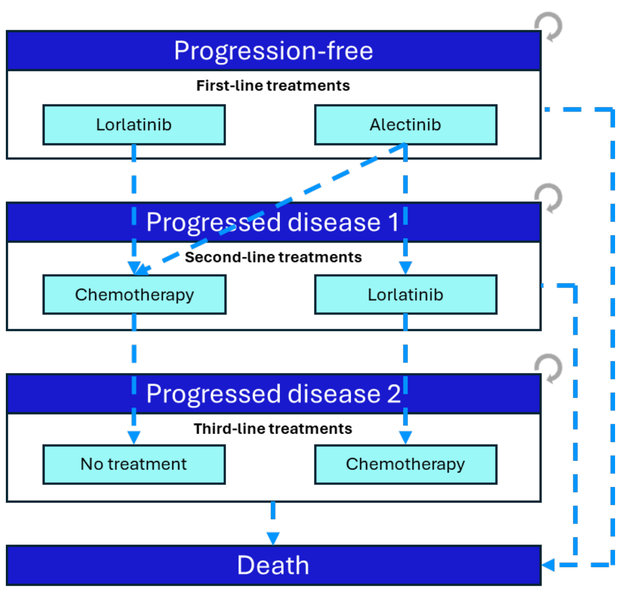
Background and objectives

- The 5-year update of the CROWN trial, a randomized controlled trial for first-line (1L) lorlatinib versus crizotinib, in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (aNSCLC), showed that the median progression-free survival (PFS) was not reached in the lorlatinib arm, thus representing the longest PFS achieved with any targeted monotherapy in aNSCLC and across all metastatic solid tumours[1]
- This study evaluated the cost-effectiveness of 1L lorlatinib versus alectinib, the most widely used ALK tyrosine kinase inhibitor (TKI) in untreated patients with ALK-positive aNSCLC, using a UK National Health Service (NHS) perspective
- The 5-year data cut update of the cost-effectiveness study includes structural changes to achieve a better reflection of the treatment path in NHS practice. It also allows for better differentiation of the costs and benefits of subsequent treatment options, as well as providing greater transparency. All assumptions are aligned with the National Institute for Health and Care and Excellence (NICE) committee's preferences expressed during its second meeting (committee's base case), although some assumptions are conservative for lorlatinib

Methods

- In the NICE appraisal of lorlatinib for untreated ALK-positive aNSCLC (Technology Appraisal [TA] 909),[2] the 18-month data cut informed the use of a pseudo-state-transition model using three health states – progression-free (PF), progressed disease (PD) and death. This approach addressed limitations highlighted by the External Assessment Group (EAG) at the clarification stage, including short overall survival follow-up and the use of subsequent treatments in the alectinib and lorlatinib trials (ALEX and CROWN, respectively) [1,3], which are not aligned with UK clinical practice. During the ALEX trial, lorlatinib was not available as a second-line (2L) treatment, which is an extended treatment option in the UK.[4] On the other hand, CROWN included several TKIs as subsequent treatments that are not available in the UK after 1L lorlatinib
- During the review of TA909 (ID 6434)[5], which incorporated the 5-year data cut, the NICE committee requested an update in the model structure to explicitly model the costs and health benefits of both 1L and 2L treatments in both treatment arms
- A cost-effectiveness model with a pseudo-state-transition structure was developed with four mutually exclusive health states: PF, PD1, PD2 and death. PD1 health state allows to explicitly model the costs and health benefits of 2L therapies after progression of 1L treatment. Transitions from PF to PD1 were estimated based on PFS extrapolations, while the remaining transitions were derived using constant transition probabilities. Alive states were further separated into on- and off-treatment
- The four-health state model incorporates different treatment sequences for 1L lorlatinib compared with 1L alectinib. Lorlatinib can only be followed by chemotherapy, while alectinib can be followed by lorlatinib or chemotherapy (Figure 1) Therefore, lorlatinib is both the intervention in the 1L setting and part of the treatment sequence in the comparator arm. Alectinib outputs are weighted by the proportion of patients who receive lorlatinib and chemotherapy as a 2L treatment. The NICE committee's preference was to assume that 42.2% of patients received 2L lorlatinib after 1L alectinib

Figure 1. Model structure



- As shown in Table 1, the transition probabilities for lorlatinib followed by chemotherapy were derived using the 5-year CROWN trial and the chemotherapy arm of TA628 (2L lorlatinib submission);[3] and for alectinib followed by lorlatinib using the hazard ratios (HRs) from the indirect treatment comparison (ITC) applied to the lorlatinib PFS curve (based on CROWN), Study 1027[6] (2L lorlatinib Phase IV trial) and Study 1001 EXP3B:5[7] (2L lorlatinib single-arm Phase II trial – data described in TA628[4]). Alectinib followed by chemotherapy transition probabilities were estimated using HRs from the ITC and assuming the same post-second progression survival as 1L lorlatinib

Table 1. Efficacy sources

Sequence	PFS	Time-to-second progression	Post-second progression survival
1L lorlatinib → 2L chemotherapy	CROWN PFS	CROWN time-to-second progression	TA628 2L PDC post-progression survival
1L alectinib → 2L chemotherapy	Lorlatinib CROWN PFS + ITC	CROWN time-to-second progression	TA628 2L PDC post-progression survival
1L alectinib → 2L lorlatinib → 3L chemotherapy	Lorlatinib CROWN PFS + ITC	Study 1027 PFS	Study 1001 EXP3B:5 2L lorlatinib post-progression survival

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

- Central nervous system (CNS) progression was included as an intercurrent event rather than a unique health state. Previous NICE TAs used a four-health state based on CNS progression. However, due to the lack of evidence on CNS progression after the 1L treatment discontinuation, the updated four-health state model structure could not incorporate the effect of brain metastases as a separate health state
- According to the product characteristics, treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity.[8] In the UK, treatment beyond progression is standard clinical practice for ALK TKIs in aNSCLC. The time-on-treatment curve was assumed to be equal to the PFS curve, and treatment beyond progression was modelled as a one-off cost based on the mean time on treatment beyond progression (5.7 months for lorlatinib and 3.5 months for alectinib) and the percentage of patients that received treatment beyond progression (75.6% for lorlatinib and 54.2% for alectinib). Time on treatment assumptions were aligned with the NICE committee's preferences

Results

- Considering the proportion of patients that receive lorlatinib and chemotherapy after 1L alectinib, at list price, the weighted incremental cost-effectiveness ratio (ICER) was £81,292 per quality-adjusted life year (QALY)
- The scenario analysis showed that the ICER versus the specific sequence of alectinib followed by lorlatinib was £34,649, while the ICER versus alectinib followed by chemotherapy was £95,562. If the same proportion of patients and duration of treatment beyond progression are considered, the ICER versus alectinib followed by chemotherapy decreases to £19,583

Discussion

- As the pseudo-state transition relies on the PFS extrapolations to estimate overall survival, the comparison of 1L lorlatinib followed by chemotherapy versus 1L alectinib followed by lorlatinib or chemotherapy is subject to an inherent uncertainty caused by low observed progression rates in the CROWN lorlatinib arm. Median survival was not reached in the lorlatinib arm, with only 55 observed PFS events (n = 149)[1]
- The pseudo-state-transition model using the four health states addresses the uncertainties caused by the immature overall survival (OS) data from CROWN and misalignment between subsequent treatments in the CROWN and ALEX trials and those used by the NHS, by using the best available evidence. Matching-adjusted indirect comparisons could not be conducted for post-progression survival due to the small number of progressed patients in the lorlatinib arm
- Despite its label, CROWN 5-year data show a time-to-discontinuation considerably shorter than PFS (not seen in the ALEX trial for alectinib)[9]. The base-case modelling approach, which assumes time-to-discontinuation equal to PFS, represents a conservative assumption for lorlatinib, as it includes additional acquisition costs without any health benefits, including no survival benefit from longer treatment. Similarly, assuming treatment beyond progression adds additional drug costs, while assuming no additional health benefit despite applying a longer treatment duration beyond progression to a higher percentage of patients, which biases against lorlatinib as a more effective treatment option. These assumptions are contrary to the NICE view of the hierarchy of evidence, where the trial-derived data is the best source of evidence
- Given its ability to cross the blood–brain barrier, and therefore increased potency and effect on brain metastasis, several base case assumptions on equivalent efficacy are conservative for lorlatinib. These include lorlatinib post-second-progression survival, which is assumed to be equal to post-progression survival in the chemotherapy arm after 1L ceritinib/crizotinib of TA628 (lorlatinib for previously treated ALK-positive advanced NSCLC). Additionally, both alectinib followed by chemotherapy post-second progression survival and time-to-second progression are assumed to be equivalent to those from the lorlatinib arm, which leads to a significantly higher ICER compared to the sequence 1L alectinib and 2L chemotherapy

Conclusion

- The four-health state model structure allows for a robust approach to model cost-effectiveness of alternative treatment sequences in ALK-positive aNSCLC and overcomes the limitations of immature OS data in CROWN and misalignment in subsequent treatment in CROWN and ALEX clinical trials and NHS practice
- When the committee's preferred assumptions for lorlatinib were applied, some of which were conservative, the ICER for lorlatinib compared with alectinib in the 1L setting was within the range that NICE considers a cost-effective use of NHS resources once the confidential discounts for lorlatinib and alectinib were applied

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References: **1**. Solomon et al. *J Clin Oncol*. 2024; JCO2400581. **2**. NICE. 2023. https://www.nice.org.uk/guidance/ta909. Accessed: September 20, 2025. **3**. Camidge et al. *J Thorac Oncol*. 2019; 14: 1233–1243. **4**. NICE. 2020 https://www.nice.org.uk/guidance/ta628/documents/committee-papers. Accessed: September 20, 2025. **5**. NICE.2024 https://www.nice.org.uk/guidance/indevelopment/gid-ta11570/documents. Accessed: September 20, 2025. **6**. Bearz et al. *Journal of Thoracic Oncology*. 2025; 20: S61. **7**. Solomon et al. *The Lancet Oncology*. 2018; 19: 1654–1667. **8**. BNF. 2025. https://bnf.nice.org.uk/drugs/lorlatinib-specialist-drug/#important-safety-information. Accessed: September 20, 2025. **9**. NICE. 2018. https://www.nice.org.uk/guidance/ta536. Accessed: September 20, 2025

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