Review proposal of lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (TA909)

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (TA909) was published in July 2023. Lorlatinib was not recommended, within its marketing authorisation, for routine use in the NHS.

Proposal

A review of this guidance should be planned into the appraisal work programme, the review will be conducted through the STA process. We will consult on this proposal.

Rationale for review

Lorlatinib for untreated ALK-positive advanced non-small-cell-lung cancer (NSCLC) was appraised by NICE in 2023 ([TA909](https://www.nice.org.uk/guidance/ta909)). Lorlatinib was not recommended for use in routine commissioning. The committee cited a number of key uncertainties as their rationale for why it could not be recommended for use in routine commissioning. These included subsequent treatments in the key clinical trial for lorlatinib ([CROWN trial](https://pubmed.ncbi.nlm.nih.gov/36535300/)) differing from those expected in NHS practice, immaturity of progression-free survival and overall survival data, approach to modelling of central nervous system (CNS) metastases among those in the progressed disease (PD) health state and survival extrapolation. The committee agreed that lorlatinib was not suitable for managed access as both the EAG and the company’s estimates of cost-effectiveness were above the threshold NICE considers a cost-effective use of NHS resources.

The company have highlighted that more mature evidence from the CROWN trial is now available for the committee and will address key uncertainties that arose during the original appraisal. In particular, it has the potential to better inform the magnitude of the PFS benefit compared to comparators, subsequent treatments and survival extrapolation.

Summary of new evidence and implications for review (to be confirmed)

## The technology

|  |  |
| --- | --- |
| **Intervention(s)** | Lorlatinib |
| **Population(s)** | Adults with untreated ALK-positive advanced NSCLC |
| **Comparators** | * Alectinib * Brigatinib |
| **Outcomes** | The outcome measures to be considered include:   * overall survival * progression-free survival * response rates * adverse effects of treatment * health-related quality of life. |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.  The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.  Costs will be considered from an NHS and Personal Social Services perspective.  The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. |
| **Related NICE recommendations** | **Related technology appraisals:**  [Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor](https://www.nice.org.uk/guidance/TA670) (2021). NICE Technology Appraisal 670. Review date: 2024.  [Alectinib for untreated ALK-positive advanced non-small-cell lung cancer](https://www.nice.org.uk/guidance/ta536) (2018). NICE Technology Appraisal 536. Review date: August 2021.  [Ceritinib for untreated ALK-positive non-small-cell-lung cancer](https://www.nice.org.uk/guidance/ta500) (2018). NICE Technology Appraisal 500. Review date: January 2021.  [Crizotinib for untreated anaplastic lymphoma kinase- positive advanced non-small-cell lung cancer](https://www.nice.org.uk/guidance/ta406) (2016). NICE Technology Appraisal 406. Review date: September 2019.  **Related NICE guidelines:**  [Lung cancer: diagnosis and management (2019](https://www.nice.org.uk/guidance/NG122)). NICE guideline 122.  **Related quality standards:**  [Lung cancer in adults (2019).](https://www.nice.org.uk/guidance/QS17) NICE Quality Standard 17. |
| **Related National Policy** | The NHS Long Term Plan (2019) [NHS Long Term Plan](https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/)  NHS England (2023) [Manual for prescribed specialist services (2023/2024)](https://www.england.nhs.uk/wp-content/uploads/2017/10/PRN00115-prescribed-specialised-services-manual-v6.pdf). |

## Has there been any change to the price of the technology(ies) since the guidance was published?

No

## Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

No

## Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

A number of uncertainties were identified in the original guidance.

The company suggests that they will be able to address the following key uncertainties:

* concerns over subsequent treatments
* magnitude of the PFS benefit compared to comparators
* modelling of survival

Other uncertainties identified in the original guidance include:

* Modelling of CNS metastases (including proportion of people with CNS metastases at baseline, how non-CNS PD to CNS PD transition is modelled and the rates informing this transition)
* No NMA for adverse events despite evidence suggesting high rates with lorlatinib (compared with other ALK TKIs)

## Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

Related NICE guidance relevant to this appraisal relate to the comparators and are listed in the scope. Ceritinib and crizotinib were both comparators in original scope but committee accepted that these were only rarely used in untreated ALK patients in the NHS and that alectinib and brigatinib are the main comparators. It is possible that more recent studies are available for inform the indirect comparison for these treatments.

## Questions for consultation

Where do you consider lorlatinib will fit into the existing care pathway for untreated ALK-positive advanced NSCLC?

Do you consider that the use of lorlatinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

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 proposed remit and scope may need changing in order to meet these aims.  In particular, please tell us if the proposed remit and scope:

* could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which lorlatinib is be licensed;
* could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE’s health technology evaluation processes is available at <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation>).

Equality issues

Stakeholders commented that people with ALK positive NSCLC having treatment at small district general hospitals are very likely to be disadvantaged as the oncologists in these hospitals are less likely to specialise in lung cancer or have any experience in ALK positive NSCLC. The committee agreed this reflected an implementation issue and cannot be addressed in a NICE technology appraisal recommendation.

Proposal/decision paper sign off

Gavin Kenny – Programme Manager, Technology Appraisals and Highly Specialised Technologies

14 June 2024

# Contributors to this paper

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Appendix A – Information from existing guidance

Original remit

To appraise the clinical and cost effectiveness of lorlatinib within its marketing authorisation for untreated ALK-positive advanced non-small cell lung cancer.

Current guidance

Lorlatinib is not recommended, within its marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults who have not had an ALK inhibitor.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

| **Options** | **Consequence** | **Selected – ‘Yes/No’** |
| --- | --- | --- |
| A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process. | A review of the appraisal will be planned into the NICE’s work programme. | Yes |
| The decision to review the guidance should be deferred to specify date or trial. | NICE will reconsider whether a review is necessary at the specified date. | No |
| The guidance should be Cross referred into an on-going clinical guideline. | The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.  This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal. | No |
| The guidance should be updated in an on-going clinical guideline[[1]](#footnote-2). | Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.  Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation). | No |
| The guidance remains relevant, and an update is not needed. | The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. | No |
| The guidance should be withdrawn | The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS.  The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved. | No |

Appendix C –

# Relevant Institute work

## Published

[Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor](https://www.nice.org.uk/guidance/TA670) (2021). NICE Technology Appraisal 670. Review date: 2024.

[Alectinib for untreated ALK-positive advanced non-small-cell lung cancer](https://www.nice.org.uk/guidance/ta536) (2018). NICE Technology Appraisal 536. Review date: August 2021.

[Ceritinib for untreated ALK-positive non-small-cell-lung cancer](https://www.nice.org.uk/guidance/ta500) (2018). NICE Technology Appraisal 500. Review date: January 2021.

[Crizotinib for untreated anaplastic lymphoma kinase- positive advanced non-small-cell lung cancer](https://www.nice.org.uk/guidance/ta406) (2016). NICE Technology Appraisal 406. Review date: September 2019.

[Lung cancer: diagnosis and management (2019](https://www.nice.org.uk/guidance/NG122)). NICE guideline 122.

# Details of changes to the marketing authorisation for the technology

## Marketing authorisation and price considered in original appraisal

There are no changed to the marketing authorisation or price that are relevant to this appraisal.

## Proposed marketing authorisation (for this appraisal) and current price

Lorlatinib as monotherapy 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.

The list price of lorlatinib 30x100 mg and 90x25 mg tablets is £5,283 (excluding VAT; BNF online accessed April 2024).

# Registered and unpublished trials

| **Trial name and registration number** | **Details** |
| --- | --- |
| CROWN trial (ongoing)  [NCT03052608](https://clinicaltrials.gov/study/NCT03052608) | * Primary completion 2020 * Estimated final completion 2028   RCT comparing lorlatinib with crizotinib (n= 296)   * 104 centres in 23 countries worldwide. * Eligible participants were aged 18 years and older or aged 20 years and older (depending on local regulations) with advanced, ALK-positive non-small-cell lung cancer, had received no previous systemic treatment for metastatic disease, had at least one extracranial measurable target lesion (according to the Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1), and had an Eastern Cooperative Oncology Group performance status score of 0–2. * Significant improvement in primary endpoint (progression-free survival) |

# References

Solomon, B.J., et al (2023) Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. *The Lancet respiratory medicine. 11(4*):354-366.

1. Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the [guide to the processes of technology appraisal](https://www.nice.org.uk/process/pmg19/chapter/reviews#updating-technology-appraisals-in-the-context-of-a-clinical-guideline). [↑](#footnote-ref-2)