
Article:
Hodgson, Robert and Coughlan, Diarmuid (2026) Schrodinger's Pricing:Conceptual and Practical Challenges of Conditional PAS in the NICE Technology Appraisal of Lorlatinib for Untreated ALK-Positive Advanced Non-small-cell Lung Cancer (Review of TA1103): An External Assessment Group Perspective. Pharmacoeconomics. ISSN: 1179-2027

https://doi.org/10.1007/s40273-026-01593-5

PharmacoEconomics
https://doi.org/10.1007/s40273-026-01593-5

RESEARCH LETTER

Schrodinger's Pricing: Conceptual and Practical Challenges of Conditional PAS in the NICE Technology Appraisal of Lorlatinib for Untreated ALK-Positive Advanced Non-small-cell Lung Cancer (Review of TA1103): An External Assessment Group Perspective

Robert Hodgson[1] · **Diarmuid Coughlan**[1]

Received: 23 December 2025 / Accepted: 18 January 2026

1 Introduction

Patient access schemes (PAS) are confidential commercial arrangements made between pharmaceutical companies and the National Health Service (NHS), allowing companies to provide discounts on a pharmaceutical technology's list price. These schemes are commonly proposed as part of a National Institute for Health and Care Excellence (NICE) technology appraisal, aiming to enhance the drug's cost effectiveness and support a positive recommendation.

Patient access schemes discounts most commonly take the form of a simple fixed or percentage reduction applied to the list price [1] and are typically applied across all indications for which the technology is recommended [2]. Indication-specific PAS discounts are less common and are generally only permitted where applying a single PAS discount across all indications would result in significant commercial harm to the manufacturer [2]. Conditional PAS discounts are a type of PAS discount offered conditionally on a positive NICE recommendation, rather than on outcomes or real-world performance. They are typically used when a technology already has an agreed PAS discount for another indication. When a positive recommendation is made under a conditional PAS, the discount applies to both the new and any existing indications.

Conditional PAS discounts create a unique conceptual challenge in economic modelling, particularly when the existing indication occupies a different position in the treatment pathway (e.g. first- vs second-line treatment) and forms part of the treatment sequence in the comparator arm. At the point of appraisal, two prices can be considered "true" simultaneously: the current applied to the existing indication in the comparator arm, and the conditional PAS discount applied to the intervention applied in the new indication. In reality, however, only one PAS price will ever apply following a positive recommendation. Like Schrödinger's cat, this exposes the tension between the modelled counterfactual and real-world NHS practice.

In this commentary, we reflect on observations and key learnings from an External Assessment Group (EAG) perspective on the application of a conditional PAS in the NICE appraisal of lorlatinib for untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) [TA1103] [3].

2 Lorlatinib for Untreated ALK-Positive Advanced NSCLC (Review of TA909)

NICE invited Pfizer to submit evidence on the clinical and cost effectiveness of lorlatinib for previously untreated ALK-positive advanced NSCLC. The comparators defined in the NICE scope were alectinib and brigatinib, both standard first-line treatment options in the NHS. Lorlatinib is already recommended by NICE (TA628) [4] for patients with previously treated ALK-positive advanced NSCLC and is currently used in the NHS as a second-line treatment option alongside pemetrexed-based chemotherapy, see Fig. 1.

As indicated in Fig. 1, if lorlatinib were recommended in the first-line setting, patients would no longer have access to other ALK inhibitors in the second-line setting, leaving pemetrexed-based chemotherapy as the only subsequent treatment option. Consequently, the company's decision problem can be conceptualised as a comparison

✉ Robert Hodgson
rob.hodgson@york.ac.uk

[1] Centre for Reviews and Dissemination, University of York, York YO10 5DD, UK

Published online: 24 February 2026

of alternative treatment sequences, including scenarios in which lorlatinib is reserved for use after either alectinib or brigatinib.

In the second-line setting, the NICE recommendation for lorlatinib was subject to a simple PAS discount. For the first-line appraisal, Pfizer proposed a revised conditional PAS, larger than the existing second-line discount. However, the availability of this larger discount was contingent on a positive first-line recommendation. The conditional PAS offered by Pfizer was not indication specific; as such, approval of lorlatinib for first-line use would mean that the revised (conditional) PAS applies across both first- and second-line indications.

To capture this conditionality in the economic analysis, the company applied the conditional PAS to first-line treatment while retaining the existing PAS for second-line use. This approach sought to represent the world as it is currently in the comparator arm while representing the counterfactual world in the intervention arm.

3 NICE Perspective

As part of the appraisal process, the EAG raised concerns about applying different PAS discounts for lorlatinib in each arm of the model. The NICE technical team noted that NICE's methods guide [5] does not specify the approach that the committee should take in these circumstances and also acknowledged that there were potential limitations associated with both approaches. In response, the NICE technical team explained that this issue had been considered at a recent internal workshop and advised that applying the conditional PAS to the intervention arm alone appropriately reflected the decision problem. Applying the current PAS to the comparator arm captured the cost of existing care, that is, the scenario that would persist if first-line lorlatinib were not recommended, and therefore appropriately represented the displaced treatment. The technical team's position was therefore aligned with the company's modelling approach.

In its deliberations, the committee noted that it would be helpful for NICE to publish formal guidance on how to address such issues in future appraisals. However, taking into account the NICE technical advice and the specific circumstances of the PAS arrangements in this appraisal, the committee concluded that the company's approach, in which the conditional PAS is applied to the intervention arm and the existing PAS to the comparator arm, was appropriate for decision making [3].

4 EAG Perspective

The EAG raised several concerns about the use of different PAS discounts in each arm of the economic model and considered that the decision framework adopted by both the company and the NICE technical team was conceptually flawed. The EAG advanced a number of arguments in support of this position.

First, it argued that the approach introduces a temporal dimension into what should be a contemporaneous comparison. The NICE Single Technology Appraisal process is designed to assess the relative clinical and cost effectiveness of competing options at a single point in time. Framing the comparison as a "before versus after" scenario

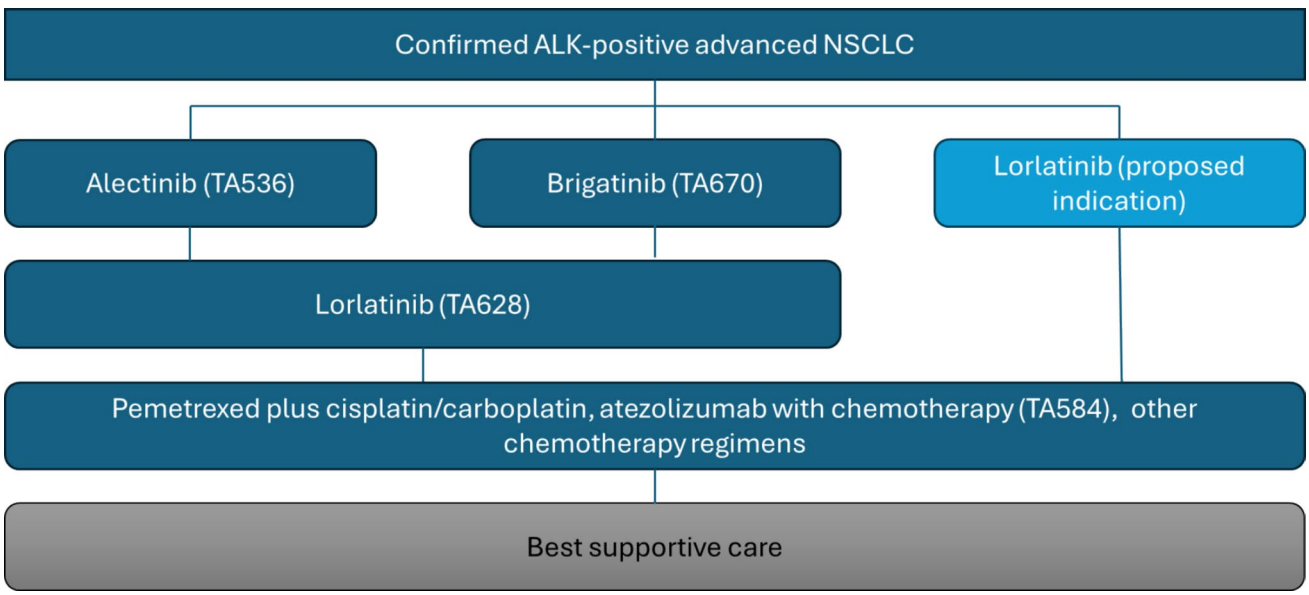

Fig. 1 Proposed positioning of lorlatinib in the clinical pathway. *ALK* anaplastic lymphoma kinase, *NSCLC* non-small-cell lung cancer

deviates from this principle, introduces inconsistency and risks undermining fairness in decision making.

Second, the approach explicitly assumes that second-line use of lorlatinib would cease following a positive recommendation for its first-line use. This assumption, however, incorrectly depicts the NICE process and likely future NHS practice. If lorlatinib were recommended for use in the first line, it would remain available for second-line use under existing NICE guidance. Moreover, clinical advice received by both the EAG and heard at the NICE committee meeting made it clear that first-line lorlatinib would not fully displace second-line use because of the adverse event burden associated with lorlatinib and uncertainties about its effectiveness relative to sequential treatment with multiple ALK inhibitors. A positive recommendation would therefore create a new treatment landscape in which lorlatinib is available in both lines of therapy.

The EAG argued that the committee should consider the decision within this broader context, emphasising that the company's approach risks producing guidance that invalidates itself. Because the conditional PAS would also apply in the second-line setting, a positive recommendation would substantially change the cost effectiveness of the current standard of care (alectinib or brigatinib followed by lorlatinib), thereby eroding the basis on which the guidance was issued. The EAG further highlighted that adopting technologies whose cost effectiveness relies on assumptions that no longer hold once adoption occurs risks inefficient and inconsistent allocation of NHS resources [6]. Guidance that is self-invalidating in this manner is therefore fundamentally at odds with the incremental logic that underpins NICE's technology appraisal framework. The EAG therefore advised the NICE committee to adopt a consistent approach in which the conditional PAS discount was applied to both the intervention and comparator arms of the model.

5 Recommendations

The use of conditional PAS discount prices within an economic model represented a rare instance in which the NICE technical team and the EAG were not aligned. Nevertheless, both parties agreed that the most appropriate course of action was to bring the issue to the NICE committee, allowing open discussion in a public forum and ensuring transparency so that stakeholders could clearly understand how the committee reached its conclusion.

In its deliberations, the committee acknowledged that formal guidance from NICE would be helpful for addressing similar issues in future appraisals. However, based on the technical team's advice and the specific circumstances of the PAS arrangements in this case, the committee concluded that applying the conditional PAS to the intervention arm and the existing PAS to the comparator arm was appropriate for decision making.

While the EAG respects the committee's conclusion, it considers that further work is required to determine the most appropriate way to handle such situations. Formal guidance from NICE, either as a position statement or a module update to the methods guide, would allow broader consultation and give stakeholders an opportunity to contribute outside the context of a live appraisal. Addressing the issue through a separate dedicated process would also enable more thorough consideration of the methodological principles involved, free from the time constraints and competing priorities inherent in the appraisal of a specific technology.

6 Key Learnings

- Conditional PAS implementation within an Single Technology Appraisal may introduce temporal and conceptual inconsistencies into economic modelling, potentially leading to inefficient and inconsistent resource allocation.
- NICE should consider issuing formal guidance to ensure consistent handling of conditional or multi-indication or multi-line PAS discounts.
- Greater transparency and broader consultation are needed to establish an approach that balances methodological integrity with practical feasibility. A conditional PAS creates methodological inconsistencies and conceptual confusion by introducing temporal elements into an Single Technology Appraisal.

7 Conclusions

The appraisal of lorlatinib for untreated ALK-positive advanced NSCLC raises important questions about the interpretation and implementation of conditional PAS discounts in NICE appraisals. While the committee accepted the company's approach in this case, the EAG remains concerned about the broader implications for decision making. Formal guidance on this issue would support greater consistency, transparency and methodological robustness in future NICE evaluations.

Funding This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number NIHR131946. Please visit the health technology assessment programme website for further project information (https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm). This summary of the EAG report was compiled after NICE issued the Final Guidance. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of NICE or the Department of Health.

Declarations

Conflicts of Interest/Competing Interests Robert Hodgson and Diarmuid Coughlan have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The data that support this commentary are available on the NICE website: https://www.nice.org.uk/guidance/ta1103.

Code Availability Not applicable.

Authors' Contributions RH was responsible for leading the critical review of the cost-effectiveness evidence and the writing of the EAG report. DC performed the critical review of the cost-effectiveness evidence and conducted EAG's additional analyses. All authors contributed to the conception and design of this manuscript. This manuscript was initially drafted by RH with input from DC. All authors had the chance to comment on draft versions of the manuscript and provided their approval for the final version to be published. RH acts as the overall guarantor for the article.

References

1. NICE. Patient access schemes and pricing agreements. 2026. Available from: https://www.nice.org.uk/what-nice-does/patient-access-schemes-and-pricing-agreements. Accessed 5 Jan 2026.
2. England NHS. NHS commercial framework for new medicines. 2026. Available from: https://www.england.nhs.uk/long-read/nhs-commercial-framework-for-new-medicines/. Accessed 5 Jan 2026.
3. National Institute for Health and Care Excellence. [TA1103] Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer. London: National Institute for Health and Care Excellence; 2025. https://www.nice.org.uk/guidance/ta1103" Overview | Lorlatinib for ALK-positive advanced non-small-cell lung cancer that has not been treated with an ALK inhibitor | Guidance | NICE.
4. National Institute for Health and Care Excellence. [TA628] Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer. London: National Institute for Health and Care Excellence; 2020. https://www.nice.org.uk/guidance/ta628" Overview | Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer | Guidance | NICE.
5. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. London: National Institute for Health and Care Excellence; 2022. https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2#the-reference-case-framework"4 Economic evaluation|NICE technology appraisal and highly specialised technologies guidance: the manual | GuidancelNICE.
6. Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technol Assess. 2015;19(14):1–503 (**v-vi**).