Single Technology Appraisal

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

Committee Papers

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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 (review of TA909) [ID6434]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Pfizer:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Clarification response Appendix 1
   c. Clarification response Appendix 2

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. ALK Positive UK
   b. Roy Castle Lung Cancer Foundation
   c. British Thoracic Oncology Group

4. **Expert personal perspectives** from;
   a. Debra Montague, Chair ALK Positive UK – patient expert, nominated by ALK Positive UK
   b. Shobhit Baijal, Consultant Medical Oncologist – clinical expert, nominated by British Thoracic Oncology Group
   c. Professor Alastair Greystoke, Professor of Oncology and Honorary Consultant in Medical Oncology – clinical expert, nominated by Pfizer

5. **External Assessment Report** prepared by prepared by CRD and CHE Technology Assessment Group, University of York

6. **External Assessment Report – factual accuracy check**

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

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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]

Document B

Company evidence submission

11 September 2024

File name	Version	Contains confidential information	Date
ID6434 Lorlatinib Document B.docx	Final	Yes	11 September 2024

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Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

In this template any information that should be provided in an appendix is listed in a box.

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Contents

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Tables and figures

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Abbreviations

Abbreviations	Definition
AE	Adverse event
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
CNS AEs	Central nervous system adverse events
CrI	Credible interval
CSR	Clinical study report
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule associated protein-like 4
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-VAS	EQ-5D visual analogue scale
HCRU	Healthcare resource use
HR	Hazard ratio
HRQL	Health-related quality of life
IC-CR	Intracranial complete response
IC-DOR	Intracranial duration of response
ICER	Incremental cost-effectiveness ratio
IC-OR	Intracranial objective response
IC-TTP	Intracranial time to progression
IC-TTR	Intracranial time to tumour response
INV	Investigator assessment
IQR	Interquartile range
ITT	Intention-to-treat
MAIC	Matching-adjusted indirect comparison
MIMS	Monthly Index of Medical Specialities
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reached
NSCLC	Non-small-cell lung cancer

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Abbreviations	Definition
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumour version 1.1
ROS1	ROS proto-oncogene 1
RTK	Receptor tyrosine kinase
SAS	Safety analysis set
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TPR	Translocated promotor region
TTD	Time to deterioration
WTP	willingness to pay

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B.1. Decision problem, description of the technology and clinical care pathway

Decision problem

- The submission covers lorlatinib's full marketing authorisation for this indication, as monotherapy '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 company submission is aligned with the final National Institute for Health and Care Excellence (NICE) scope and is informed by the pivotal Phase III trial CROWN, mainly the results of the October 2023 unplanned 5-year data cut-off, and a network meta-analysis (NMA) comparing lorlatinib with the relevant comparators, second generation ALK tyrosine kinase inhibitors (TKIs) alectinib and brigatinib. This expands on the data provided in the initial appraisal of lorlatinib in ALK-positive advanced NSCLC, TA909, providing further robust evidence for the efficacy of lorlatinib and addressing concerns raised in the original appraisal[1]

Description of the technology

- Lorlatinib (Lorviqua®) is a third generation small molecular inhibitor of ALK and ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase (RTK) specifically designed to cross the blood–brain barrier to achieve high central nervous system (CNS) exposure; and to prevent development and maintain potency against a broad spectrum of *ALK* resistance mutations
- Lorlatinib is a once daily oral medication

Disease overview and clinical burden

- Lung cancer is the third most common cancer and the most common cause of cancer deaths in the UK
- Lung cancer is often diagnosed at an advanced inoperable stage
- ALK fusion oncogenes are direct drivers of lung tumourigenesis
- Patients with ALK-positive advanced NSCLC experience higher symptom burden and poorer survival compared with ALK-wildtype advanced NSCLC patients

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- The risk of developing brain metastases is much higher in ALK-positive advanced NSCLC compared with other lung cancers
- Patients with ALK-positive advanced NSCLC are younger and often non-smokers compared with other lung cancers

Humanistic burden

- Symptoms of ALK-positive advanced NSCLC such as pain, fatigue, loss of appetite and shortness of breath lead to significant health-related quality of life (HRQL) burden and mental health decline
- Brain metastases can further impact HRQL in advanced NSCLC
- NSCLC negatively affects carer HRQL, especially as patients' fitness status declines, and when brain metastases are present
- Patient testimonies show the considerable physical, mental and financial burden of living with ALK-positive advanced NSCLC for patients, their carers and families

Economic and societal burden

- Multiple studies have shown that patients with advanced NSCLC incur high healthcare resource use (HCRU) and costs; the burden is increased further with ALK-positive NSCLC since patients are more likely to be of working age, have dependents, or be carers than those with ALK-negative disease
- The presence of brain metastases further impacts the economic burden of NSCLC due to the additional symptoms and associated care needs of patients

Clinical pathway of care

- Alectinib, followed by brigatinib, is the most commonly used first-line treatment option for ALK-positive advanced NSCLC; however, durability of response is limited, and many patients never receive second-line therapy
- Lorlatinib will provide an additional option for first-line treatment of ALK-positive advanced NSCLC

Unmet need

- ALK-positive advanced NSCLC is an aggressive type of lung cancer with a need for more effective treatment options

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B.1.1. Decision problem

The submission covers lorlatinib's full marketing authorisation for this indication, as monotherapy 'for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor'.[2] The key evidence in this submission is based on the results of the unplanned 5-year data cut-off of the Phase III CROWN study.

The company submission is aligned with the final NICE scope.[3] The case for clinical effectiveness and cost-effectiveness will be made versus the selected comparators (alectinib and brigatinib). Alectinib is considered the major comparator due to market share (around 80%) relative to brigatinib in the UK as verified by UK clinical experts.[4]

A detailed outline of the decision problem for this evaluation is presented in Table 1, including the rationale for any amendments.

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Table 1: The decision problem

	Final scope issued by NICE – 10 July 2024	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	n/a
Intervention	Lorlatinib	Lorlatinib	n/a
Comparator(s)	• Alectinib • Brigatinib	• Alectinib • Brigatinib	Based on market share data and clinical opinion, alectinib is considered the main comparator (around 80% market share). Brigatinib is considered a minor comparator but comparisons are provided for completeness.[4, 5]
Outcomes	• OS • PFS • Response rates • Adverse effects of treatment • HRQL	• OS • PFS • Response rates • Intracranial outcomes • Adverse effects of treatment • Discontinuation rate due to adverse events • HRQL	Intracranial endpoints were reported as secondary outcomes in the CROWN study and are reported because preventing and treating brain metastases are a priority in the treatment of ALK-positive NSCLC
Economic analysis	Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	n/a
Subgroups to be considered	none	none	n/a

Key: ALK, anaplastic lymphoma kinase; CNS, central nervous system; HRQL, health-related quality of life; OS, overall survival; NSCLC, non-small-cell lung cancer; PFS, progression-free survival.

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Source: NICE [ID6434], Solomon et al. 2023, Solomon et al. 2024.[3, 6, 7]

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B.1.2. Description of the technology being evaluated

Lorlatinib (previously PF-06463922, [Lorviqua®]) is a third generation small molecular inhibitor of ALK and ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase (RTK) specifically designed to cross the blood–brain barrier to achieve high CNS exposure, providing a major advantage when compared to earlier generations of ALK inhibitors. This is because brain metastases occur in 25–40% of ALK-positive advanced NSCLC patients and further compromise patients' quality of life and reduce survival.[8-10] In the first-line setting, lorlatinib has the potential to eliminate rare pre-existing subclones that harbour *ALK* resistance mutations or delay the emergence of such resistant subclones[10] In the second-line setting, lorlatinib retains potency against a broad spectrum of *ALK* resistance mutations, including *G1202R*, the most common secondary *ALK* mutation identified in patients prescribed second generation ALK inhibitors.

A description of the technology being appraised (lorlatinib) is provided in Table 2. A link to the Summary of Product Characteristics (SmPC) and UK public assessment report for lorlatinib is provided in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Lorlatinib (Lorviqua®)
Mechanism of action	Lorlatinib (previously PF-06463922) is a selective small molecule inhibitor of ALK and ROS1 RTKs, that is capable of crossing the blood–brain barrier.[11] ALK is a member of the insulin receptor superfamily of receptors and is expressed in a number of adult human tissues, including the brain, small intestine, testis, prostate and colon.[12] ALK activates multiple cellular signalling pathways and is thought to play a role in the development and function of the nervous system. Rearrangements, mutations or amplifications of ALK have been identified in a number of tumour types and play an essential role in the regulation of tumour cell survival, growth and metastasis.[13, 14] Lorlatinib has shown potent growth-inhibitory activity and induced cell death in vitro.[2] In vivo, lorlatinib has demonstrated a marked reduction in the number of ALK or ROS1 fusion variant tumour cells in mice. Lorlatinib was specifically designed to cross the blood–brain barrier and has demonstrated CNS penetration in animal models and anti-CNS metastases effect in people with ALK-positive advanced NSCLC.[2, 15] Lorlatinib has shown in vitro to be active against resistance mutations in the ALK gene that can arise spontaneously or due to

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	use of first and second generation inhibitors.[16] When used first-line, lorlatinib has a potential to prevent development of these resistance mutations.[7]
Marketing authorisation/CE mark status	MHRA marketing authorisation for lorlatinib in this indication was granted on 23 September 2021.[17]
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	Of relevance to this submission, lorlatinib holds an MHRA marketing authorisation for the following indication[17]: • Lorlatinib as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor Lorlatinib also holds a marketing authorisation for the following indication, which was appraised in TA628:[15, 17] • Lorlatinib as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after prior treatment with an ALK inhibitor
Method of administration and dosage	The recommended dose of lorlatinib is 100 mg taken orally once daily.[18] Lorlatinib may be taken with or without food.
Additional tests or investigations	No additional tests are required to receive lorlatinib in UK clinical practice. ALK testing is routinely performed in the NHS during the diagnosis of NSCLC.[19]
List price and average cost of a course of treatment	The list price of lorlatinib is £5,283.00 per 30 x 100 mg tablets and £7,044.00 per 120 x 25 mg tablets.[18]
Patient access scheme (if applicable)	There is an active patient access scheme of [redacted]. A further PAS has been proposed and submitted to PASLU of [redacted]. Cost-effectiveness analyses have been provided at the proposed PAS.
Key: ALK, anaplastic lymphoma kinase; CNS, central nervous system; MHRA, Medicines and Healthcare Products Regulatory Agency, NSCLC, non-small-cell lung cancer; ROS1, ROS proto-oncogene 1; RTK, receptor tyrosine kinase. **Source**: British National Formulary, 2021; EMA, 2022; Entrez Gene, 2024; Gainor et al. 2016; MHRA, 2021; NHS, 2024;NICE 2017; NICE, 2020; NICE, 2021; Soda et al. 2007; Zhao et al. 2015.[2, 12-20]	

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

Lung cancer is often diagnosed at an advanced inoperable stage.

Lung cancers are malignant tumours that form in the respiratory tissues, usually in the cells lining the air passages.[21] In the UK, 90.3% of lung cancers are classified as NSCLC, which can be further histologically categorised into subtype (squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma) and pathologic stage of disease (Stage I – localised to Stage IV – metastatic).[21]

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Due to the usually asymptomatic nature of the early stages of lung cancer, it is typically diagnosed at an advanced stage. In the UK, the majority of lung cancers present as inoperable locally advanced (Stage IIIb: 8%) or metastatic (Stage IV: 53%) disease with no curative treatment options.[22]

ALK fusion oncogenes are direct drivers of lung tumourigenesis.

ALK gene fusions are almost exclusively found in adenocarcinoma NSCLC which makes up approximately 40% of NSCLC cases.[23, 24] The rate of ALK alterations (referred to as ALK-positive throughout this document) ranges between 3–7% of patients. Patients with ALK-positive NSCLC are predominantly younger and less likely to have a history of smoking than patients with wildtype ALK.

ALK is a member of the insulin receptor superfamily of receptors that normally plays an important role in the development and function of the brain and the nervous system.[13, 25] However, formation of ALK fusion proteins plays an essential role in the regulation of tumour cell survival, growth and metastasis.[14] The most common form of ALK fusion protein is the echinoderm microtubule associated protein-like 4 (EML-4)-ALK variant where mutations in chromosome 2p23 cause fusion of the 5' end of the *EML-4* gene and 3' end of the *ALK* gene, giving one of eight possible fusion products.[24] Figure 1 shows the three most common *EML4-ALK* gene fusions – accounting for 80-90% of fusion proteins – however, there are at least 28 known rearrangements of the *ALK* gene.[24, 26]

Effectiveness of second generation ALK tyrosine kinase inhibitors (TKIs) in first-line treatment is limited due to drug resistance; patients harbouring specific EML4-ALK variant subtypes and/or a TP53 mutation are especially difficult to treat and have worse outcomes.[27-29]

NHS England recommends that ALK status testing should be conducted for all patients with non-squamous NSCLC at diagnosis.[19]

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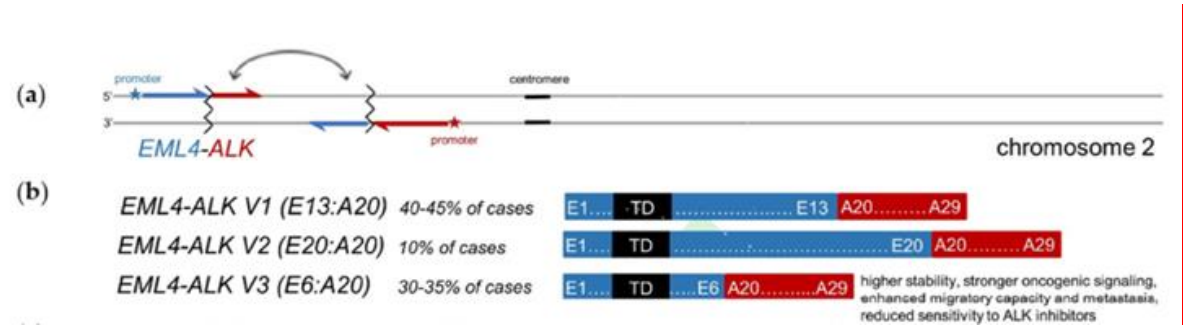
Figure 1: Schematic of the formation of EML-4-ALK fusion proteins



Source: Elysad et al. 2021.[26]

Lung cancer is the third most common cancer and the most common cause of cancer deaths in the UK.

Lung cancer is one of the most common cancers in the UK.[30] Table 3 shows calculated estimates for the incidence of ALK-positive advanced NSCLC patients in England and Wales using 2024 National Lung Cancer Audit incidence figures for lung cancer in 2022 and estimated percentages for NSCLC, advanced and ALK-positive lung cancers as proportions of the total lung cancer population and the number of patients who do not receive chemotherapy during genetic testing.[20, 21, 24, 31] The estimated number of patients who do not receive chemotherapy during genetic testing in England is 334; and in Wales the estimate is 20.

Table 3: Estimated number of ALK-positive advanced NSCLC cases in the UK, England and Wales

Type/Stage of lung cancer	England	Wales
All new cases of lung cancer	36,886	2,211
All new cases of NSCLC[a]	34,303	2,056
All new cases of adenocarcinoma NSCLC[b]	13,721	822
All new cases of Stage IIIb/IV adenocarcinoma NSCLC[c]	8,370	501
All new cases of ALK-positive Stage IIIb/IV NSCLC[d]	418	25
Proportion of patients not initiating chemotherapy while awaiting genetic test results confirming ALK-positive status (80%)[20]	334	20

Key: ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer.
Notes: [a]90.3% of lung cancer cases are NSCLC; [b] Assuming adenocarcinoma makes up 40% of NSCLC cases; [c] Assuming 61% of NSCLC cases are Stage IIIb/IV; [d] Assuming ALK-positive is found in 5% (range 3–7%) of cases.
Source: Cancer Research UK, 2022; National Lung Cancer Audit, 2024 Zappa et al. 2016; NICE – TA670 EAG Report.[20, 21, 31]

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B.1.3.2. Clinical burden

Patients with ALK-positive advanced NSCLC experience higher symptom burden, higher risk of brain metastases and poorer survival compared with ALK-wildtype advanced NSCLC patients.

Lung cancer is commonly diagnosed at an advanced stage (61% of diagnoses)[22], when it has severe symptom burden[32, 33] and poor survival prognosis, with 5-year overall survival of < 10%.[34]

Patients with ALK-positive advanced NSCLC have an increased clinical burden and poorer prognosis relative to other patients with lung cancer. One study reported that median OS was 12.3 months in ALK-positive patients (n = 26) compared with 29.63 months (p = 0.001) in patients with epidermal growth factor receptor (EGFR) mutations (n = 46) and 19.33 months (p = 0.016) in patients without ALK or EGFR alterations (n = 46).[35]

In Stage IV patients, additional symptoms develop that are specific to the site of metastasis. A common site of metastasis in ALK-positive NSCLC is the brain, as seen in 20–40% of patients not treated with a ALK inhibitor.[36] The brain metastases pose higher symptom burden as patients are less able to carry out daily tasks and often require more care due to cognitive symptoms such as memory problems, changes to mood and personality, seizures, confusion, headaches and sickness and weakness in the limbs.[32] These symptoms mean that ALK-positive NSCLC patients with brain metastases have higher care needs than patients without brain metastases. Patients with brain metastases can struggle to live independently, with impacts on the ability to drive and financial security.[37]

Patients with brain metastases also have a poor prognosis, a 2023 estimated post-progression survival of NSCLC patients who develop brain metastases was approximately 27.5 months from onset of treatment for brain metastasis.[38]

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B.1.3.3. Humanistic burden

Symptoms of ALK-positive advanced NSCLC such as pain, fatigue, loss of appetite and shortness of breath lead to significant health-related quality of life (HRQL) burden and mental health decline.

Lung cancer symptoms can have a negative impact on both patients' and their caregivers' quality of life (QoL), well-being and social functioning. This negative impact on QoL increases as the severity of symptoms increases. A 2013 cross-sectional study of 1,213 patients in France and Germany investigated the driving symptoms of HRQL in advanced lung cancer using the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale.[39] The study found that severity of fatigue, loss of appetite, pain and shortness of breath all had a significant negative impact on HRQL in patients with advanced stage lung cancer.[39] A second study measured progression of anxiety and depression in lung cancer patients using the Hospital Anxiety and Depression Scale (HADS) from 2003–2005 in 106 patients with lung cancer.[40, 41] Depression scores showed a significant increase and anxiety scores showed a non-significant increase over 12-months. Probable diagnoses of clinical anxiety was 13% at 12-months and probable depression was 17%.[40]

Brain metastases can further impact HRQL in advanced NSCLC.

A 2018 United States (US) study conducted in 145 patients with advanced NSCLC showed that patients with advanced NSCLC and baseline brain metastases have significantly greater deterioration over time in the domains of social, emotional, cognitive, and physical functioning compared with patients without baseline brain metastases.[25] This was demonstrated by significantly greater decline from baseline in all European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) measures except Global Health Status, all the Lung Cancer Module of the M.D. Anderson Symptom Inventory (MDASI-LC) measures and the Rotterdam Activity Level Scale (RALS) among people with baseline brain metastases than those without them. A study of 498 patients with metastatic NSCLC found that 29 patients with brain metastases had significantly poorer HRQL, as measured by EQ-5D, than patients with other sites of metastases such as contralateral lung, adrenal glands and liver, except those with bone metastasis.[42]

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NSCLC negatively affects carer HRQL, especially as patients' fitness status declines, and when brain metastases are present.

A European study of carer HRQL in advanced NSCLC reported negative impacts on carer HRQL, which was negatively correlated with the Eastern Cooperative Oncology Group Performance Status (ECOG PS) of the patient they were providing care for.[43]

The carer burden is also increased when patients have brain metastases as the cognitive symptoms mean patients require more care, while symptoms such as memory loss can be distressing to carers.[44]

Patient testimonies show the considerable physical, mental and financial burden of living with ALK-positive advanced NSCLC for patients, their carers and families.

In a recent qualitative study of UK and US patients with ALK-positive advanced NSCLC, UK patients worried about the lack of effective treatment options in the UK and development of brain metastases, which can mean loss of their driving licence and independence.[37]

Patient groups consulted during previous technology appraisals (TA628 and TA670) highlighted that ALK-positive advanced NSCLC comes with considerable physical and mental burden as well as functional changes as they come to terms with a terminal diagnosis.[15, 20] ALK-positive patients are often younger in comparison to lung cancer patients in general and patients experience debilitating symptoms and often have to give up work and change their lifestyles dramatically. This means that families lose income and spend more on childcare because of regular and emergency appointments. The constant threat of disease progression as 'all current treatments ultimately fail' carries considerable anxiety and depression, and if symptoms worsen, patients often worry that their disease has progressed. Patient groups express the burden ALK-positive advanced NSCLC has on carers and families, including dependents such as young children.[15, 20] Patient HRQL and carer burden are significantly worse when brain metastases are present.[1]

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B.1.3.4. Economic and societal burden

Multiple studies have shown patients with advanced NSCLC incur high HCRU and costs.[45-49] The burden is increased further with ALK-positive NSCLC as patients are more likely to be of working age, have dependents, or be carers than those with ALK-negative disease, thus ALK-positive disease leads to higher productivity loss in the population.[45, 46]

Presence of brain metastases further impacts the economic burden of NSCLC due to the additional symptoms and associated care needs of patients.

Le et al. (2023) adapted Spain's cost category to estimate the annual costs of managing brain metastases in patients with ALK-positive advanced NSCLC who received first-line TKIs in the UK.[47] They found a direct relationship between higher cumulative incidence of brain metastasis progression and higher cost burden. In the base case analysis, management costs were £4,893 per patient-year for those without brain metastases and £13,732 per patient-year for those with brain metastases. The cost difference of £8,838 per patient-year was driven by radiotherapy (£4,150), surgical resection (£1,138), and medical visits (£1,084). Additionally, medical oncology hospitalisations were higher among those with brain metastases (20%) versus those without brain metastases (10%).[47]

A 2023 retrospective claims study of patients with ALK-positive NSCLC treated with second and third generation ALK TKIs with brain metastases diagnoses found diagnosis of brain metastases was associated with a higher cost burden compared with costs before the diagnosis of brain metastases.[48] Increases in the mean total per patient per month medical costs after diagnosis of brain metastases were observed for patients who were diagnosed with brain metastases at least 3-months after NSCLC (n = 41) in PharMetrics (n = 21; difference, $3,219.60; p = 0.02), Optum (n = 9; difference, $3,735.80; p = 0.13), and MarketScan (n = 11; difference, $2,081.80; p = 0.12) databases.[48] While various ALK TKIs penetrate the CNS and target brain metastases, there are no consistent guidelines outlining the preferred treatment approach for patients with brain metastases.[49]

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B.1.3.5. Clinical pathway of care

B.1.3.5.1. Current pathway of care

Alectinib, followed by brigatinib, is the most commonly used first-line treatment option for ALK-positive advanced NSCLC; however, durability of response is limited, and many patients never receive second-line therapy.

The treatment pathway for ALK-positive advanced NSCLC has seen a major shift since the introduction of ALK targeted therapies, summarised in Table 4. NICE guidelines recommend a range of first and second generation ALK inhibitors as first-line treatment options (Table 5). However, the second generation inhibitor alectinib is used in the vast majority of patients as confirmed by UK clinicians.[4] Brigatinib is a minor comparator given that it is not used in most patients in first-line. This is because second generation ALK inhibitors offer important progression-free survival (PFS) and OS advantages over first generation crizotinib, and thus have replaced the use of crizotinib in the first-line setting.[20, 50] However, second generation ALK inhibitors have considerable limitations, mainly the development of drug resistance and a limited ability to cross the blood–brain barrier to target brain metastases.[26-29, 51, 52] Patients harbouring specific *EML4-ALK* variant subtypes and/or a tumour protein P53 (*TP53*) mutation are especially difficult to treat and have worse outcomes.[27-29]

Lorlatinib, a third generation ALK inhibitor, was specifically designed to overcome these challenges. UK clinicians (n = 15) during clinical engagements including an advisory board (n=9) and Delphi panel (n=9; of which three clinicians were included in the prior advisory board) suggested that given the superior efficacy of lorlatinib at preventing progression (overall and intercranial) versus second generation ALK inhibitors (alectinib and brigatinib) many clinicians and patients would use it as a first-line treatment.[4, 5]

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Table 4: Summary of ALK inhibitors currently recommended by NICE for first-line treatment of ALK-positive advanced NSCLC

ALK inhibitor	Generation	EMA approval for first-line ALK-positive advanced NSCLC	NICE recommendation for first-line ALK-positive advanced NSCLC	Potential limitations
Crizotinib	First	October 2012	TA406 – 2016[53]	• Low/no usage in NHS practice • Patients can develop treatment resistance leading to relapse[54] • Progression often occurs within 1-year[55] • Low penetration into the CNS[56] • Largely overtaken by second generation ALK inhibitors
Ceritinib	Second	February 2015	TA500 - 2018[57]	• Low usage in NHS practice (1–2%)[20] • Limited efficacy against CNS metastases[20] • Concerning tolerability profile[58]
Alectinib	Second	February 2017	TA536 – 2018[50]	• Risk of developing ALK resistance mutations within the first 3 months of treatment[16, 59] • Associated with clinically relevant AEs[60]
Brigatinib	Second	November 2018	TA670 - 2021[20]	• Risk of developing ALK resistance mutations[16] • Associated with clinically relevant AEs[61]

Key: AEs, adverse events; ALK, anaplastic lymphoma kinase; CNS, central nervous system; EMA, European Medical Association; NICE, National Institution for Health and Care Excellence; NSCLC, Non-small-cell lung cancer.
Source: Costa et al. 2011; EMA crizotinib; EMA ceritinib; EMA alectinib; EMA brigatinib; Gainor, 2016; Khan et al. 2019; Makimoto et al. 2019; NICE TA406, 2016; NICE TA500, 2018; NICE TA536, 2018; NICE TA670, 2021; Solomon et al. 2014; Soria et al. 2017.[20, 50, 53-57, 60-63]

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A summary of the full current pathway of care as recommended by NICE for the treatment of ALK-positive advanced NSCLC is presented in Table 5.

Table 5: Summary of NICE recommended ALK inhibitor treatment for ALK-positive advanced NSCLC

Line of treatment	NICE recommendation
First-line	Initial treatment options are: • Brigatinib [TA670] • Alectinib [TA536] • Ceritinib [TA500] • Crizotinib [TA406]
Second-line	• For people who have disease progression after initial treatment with brigatinib [TA670], alectinib [TA536] or ceritinib [TA500], the only recommended treatment option is lorlatinib [TA628] • For people who have disease progression after initial treatment with crizotinib [TA406], recommended treatment options are: – Brigatinib [TA571] – Ceritinib [TA395]
Third-line	• For people who have had initial treatment with crizotinib [TA406] and who have disease progression after follow-up treatment with brigatinib [TA571] or ceritinib [TA395], the only recommended treatment option is lorlatinib [TA628] • For people who have disease progression after treatment with lorlatinib [TA628], recommended treatment options are: – platinum doublet chemotherapy [TA181] – atezolizumab and bevacizumab, carboplatin and paclitaxel [TA584]
Source: NICE Guideline NG122, 2024.[64]	

B.1.3.5.2. Anticipated positioning in the treatment pathway

Lorlatinib will provide an additional option for first-line treatment of ALK-positive advanced NSCLC.

Lorlatinib is a third generation ALK inhibitor specifically designed to cross the blood–brain barrier and prevent the development of ALK resistance mutations. In 2022, the European Medicines Agency approved the use of lorlatinib for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.[2] Lorlatinib also has international recommendations for the first-line treatment of ALK-positive advanced NSCLC including in a Category 1

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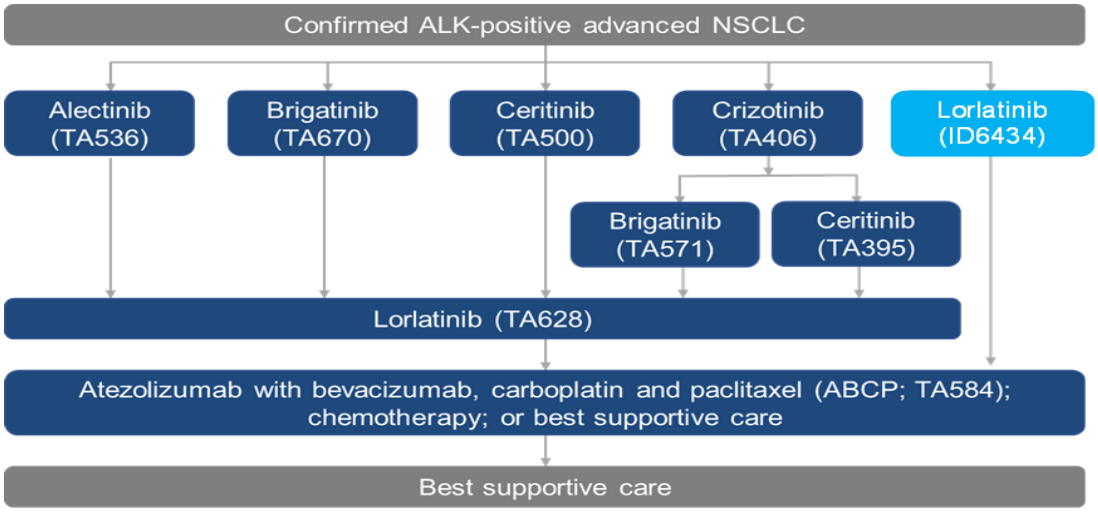
recommendation from the US National Comprehensive Cancer Network and the European Society of Medical Oncology.[65, 66]

The anticipated positioning of lorlatinib within NICE treatment guidelines for ALK-positive advanced NSCLC is presented in Figure 2. Lorlatinib is currently recommended by NICE in the second-line setting (TA628), and the introduction of lorlatinib to the first-line setting has the potential to displace its second-line use.[15] This type of displacement and change to the treatment sequence has been seen in previous appraisals including TA536, TA500 and TA670, where addition of second generation ALK inhibitors to the first-line treatment options displaced their use in the second-line setting.[20, 50, 57] Research suggests that up to a third of patients do not receive second-line treatment, mainly due to health and fitness deterioration.[51, 67] Therefore, treating patients upfront with the most effective progression-delaying treatment (and so longest duration treatment) is in line with current treatment paradigms. This shift in treatment sequencing and 'treating with the most effective therapy first' is supported by advice from UK clinicians (n = 15 clinicians).[4, 5] Advisors would welcome an additional option for patients in first-line setting and acknowledged that many clinicians and patients would like to use the most effective option first, in terms of delaying progression and intracranial progression.[4, 5]

Figure 2: Proposed positioning of lorlatinib in the NICE clinical pathway



Key: ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer.
Notes: Lorlatinib in the first-line position (ID6434) is the subject of this evaluation. Alectinib is the most frequently used ALK inhibitor currently (up to 80%), followed by brigatinib, based on market share data and clinical advice.
Source: NICE technology appraisals: 395, 406, 500, 536, 571, 395, 571, 584, 628, 670.[15, 20, 50, 53, 57, 68]

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B.1.3.6. Unmet need

ALK-positive advanced NSCLC is an aggressive type of lung cancer with a need for more effective treatment options.

Lung cancer is the third most common cancer and the most common cause of cancer deaths in the UK.[30] ALK-positive advanced NSCLC is a type of lung cancer that affects younger patients and is characterised by higher symptom burden and poorer survival prognosis relative to other non-small-cell lung cancers.[35]

Patients with advanced NSCLC commonly experience severe respiratory symptoms, weight loss and fatigue that negatively affects their HRQL and as patient fitness declines, they require increased care.[39, 43] Furthermore, brain metastases are common in ALK-positive advanced NSCLC and patients with brain metastases experience an onset of distressing cognitive symptoms that further impacts prognosis and HRQL and increases economic and carer burden.[32, 36, 42, 44, 69, 70]

Second generation ALK inhibitors alectinib and brigatinib provide improved intracranial outcomes compared with first generation ALK inhibitors but still have significant limitations in preventing brain metastases onset and progression, which are among the most devastating aspects of the disease. They also have limited treatment effect durability due to development of ALK resistance mutations with many patients not able to receive second-line treatment.[16, 26-29, 51, 52, 54, 56, 59] This was validated by clinical experts who emphasised this as a priority for patients and clinicians, and one of the key reasons why they would like to use lorlatinib in the first-line setting.[4] Furthermore, in a US cohort study where 30% of patients had brain metastases at baseline, an additional 20% of patients with ALK-positive NSCLC treated with a second generation inhibitor developed brain metastasis after 5 years.[52]

Therefore, patients with ALK-positive advanced NSCLC need new treatment options that prolong survival, reduce symptom burden, prevent development of new brain metastases and control existing brain metastases, as well as provide long-lasting treatment benefit by preventing the emergence of treatment resistant mutations in the ALK genes.

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B.1.4. Equality considerations

Some socio-economic and ethnic groups, and underserved communities have their cancer diagnosed later than the general population and so receive treatment later (this is likely to include ALK-positive NSCLC). These groups are disproportionately impacted by the negative quality of life and economic impacts of disease progression and in particular impact of disease progression in the brain.[1] As discussed previously, brain metastases have further negative impacts on a patient's ability to live independently and can increase carer burden relative to patients without brain metastases.[42, 44]

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B.2. Clinical effectiveness

Summary of clinical effectiveness evidence

- Evidence for the efficacy of lorlatinib in first-line ALK-positive advanced NSCLC is provided by the Phase III CROWN trial
- CROWN is an ongoing multinational, multicentre, randomised, open-label, parallel, two-arm Phase III trial of lorlatinib versus crizotinib in patients with ALK-positive advanced NSCLC who have received no previous systemic treatment for metastatic disease.[7] Patients were randomised 1:1 to receive oral once daily lorlatinib 100 mg (n = 149) or oral twice daily (BID) crizotinib 250 mg (n =147)[7]
- CROWN was assessed as methodologically robust and well-reported, and was considered to be at low risk of bias using the risk of bias checklist recommended by NICE
- This submission focuses on the latest, 5-year data cut-off, from October 2023.[7] Data from the 3-year data cut-off (September 2021)[6], including the primary outcome of PFS by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumour version 1.1 (RECIST v1.1), was previously presented in TA909 and is presented in Appendix M1 for reference. Data from the 18-month data cut-off (March 2020) is presented for OS, as OS has not yet reached maturity at the 5-year data cut-off[7]

Primary efficacy outcome

- PFS by BICR assessment using RECIST v1.1 was reported up to the 3-year data cut-off
- Median PFS by BICR was not reached (NR, [95% confidence interval (CI): NR, NR]) in the lorlatinib arm and was 9.3 months (95% CI: 7.6, 11.1) in the crizotinib arm[6]
- This resulted in a substantial 73% reduction in risk of progression or death between the lorlatinib arm and crizotinib arm (hazard ratio [HR] 0.27; 95% CI: 0.18, 0.39)[6]

Key secondary efficacy outcomes

- At the latest 5-year data cut-off, the median follow-up for PFS by investigator assessment (INV) (RECIST v1.1) was 60.2 months (95% CI: 57.4 to 61.6) for

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lorlatinib and 55.1 months (95% CI: 36.8 to 62.5) for crizotinib.[7] Median PFS was not reached for lorlatinib (95% CI: 64.3, NR) and was 9.1 months (95% CI: 7.4, 10.9) for crizotinib. There was an 81% reduction in the risk of progression or death in favour of lorlatinib (HR: 0.19; [95% CI: 0.13, 0.27])[7]

- Overall survival (OS) data has not reached maturity at the 5-year data cut-off[7], so OS is presented for the 18-month data cut-off.[10] At that time, only 51 death events had occurred. The HR for OS 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]).[7, 10] Further OS analyses are planned when 70% and 100% of the 198 OS events required for the final OS analysis have occurred
- Objective response rate (ORR, RECIST v1.1; by INV) at the 5 year data cut-off showed a meaningful improvement in ORR with lorlatinib versus crizotinib (81% versus 63%)[6, 7 6, 7]
- Duration of response (DOR, RECIST v1.1, by INV) at the 5 year data cut-off showed a numerical improvement in the median DOR with lorlatinib versus crizotinib (not evaluable [NE] versus 9.2 months, respectively)[6, 7]

Intracranial outcomes

- Intracranial time to progression (IC-TTP; by INV) at the 5 year data cut-off was meaningfully longer with lorlatinib versus crizotinib (NE vs 16.4 months)[6, 7]
- In patients with measurable and/or non-measurable baseline brain metastasis, intracranial objective response rate (IC-ORR; by INV) and intracranial duration of response (IC-DOR; by INV)[6, 7] improved with lorlatinib compared with crizotinib, at the 5-year data cut-off[6, 75]

HRQL

- Lorlatinib demonstrated consistent longitudinal patient-reported outcomes (PRO) data at 18 and 36 months of follow-up, showing improvement in global QoL versus crizotinib and no deterioration in cognitive or emotional functioning over time compared with crizotinib[71, 72]
  - Consistent with the 18-month results, lorlatinib's overall QoL after 36 months of follow-up was preserved regardless of baseline brain metastasis status as demonstrated by longitudinal PRO data[71]

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- Lorlatinib demonstrated improvement in emotional functioning and no significant or clinically meaningful deterioration in cognitive functioning, irrespective of presence of CNS adverse events (CNS AEs)[71]
  - Consistent with previous data showing that CNS AEs with lorlatinib were mostly Grade 1 or 2, and more than half of all CNS AEs resolved without intervention or with lorlatinib dose interruption, these longitudinal PRO data demonstrate that occurrence of CNS AEs did not result in a clinically meaningful difference in patient-reported QoL[71]

Subgroups

- Lorlatinib's PFS benefit was demonstrated across all pre-defined subgroups, gender, preference of baseline brain metastasis, ethnicity, age and smoking status and among people with poor prognostic factors (*EML4::ALK* variant 3a/b and TP53-positive patients)[6, 7, 73]

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence of the efficacy and safety of treatments for patients with ALK-positive advanced NSCLC.[74] The SLR was initially conducted for all lines of therapy in 2017 and was updated to focus on therapies in the first-line setting in April 2021, and then updated again in February 2024. In total, the SLR identified 145 records reporting on 12 unique randomised controlled trials (RCTs, four of which were relevant to the decision problem) and 71 records reporting on 44 unique non-RCTs.[74] Full details of the SLR search strategy, study selection process and results can be found in Appendix D.1.1. and D.1.2.

B.2.2. List of relevant clinical effectiveness evidence

The clinical value of lorlatinib in first-line ALK-positive advanced NSCLC is supported by the pivotal open-label, Phase III RCT, CROWN.[6, 7, 10] A summary of the overall trial design for CROWN is presented in Table 6.

Table 6: Clinical effectiveness evidence: CROWN

Study	CROWN

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<table>
<tr><td>Study design</td><td colspan="2">Multinational, multicentre, randomised, open-label, parallel, two-arm Phase III trial.</td></tr>
<tr><td>Population</td><td colspan="2">Patients with ALK-positive advanced NSCLC who had received no previous systemic treatment for metastatic disease.</td></tr>
<tr><td>Intervention(s)</td><td colspan="2">Lorlatinib 100 mg, oral once daily.</td></tr>
<tr><td>Comparator(s)</td><td colspan="2">Crizotinib 250 mg, oral twice daily.</td></tr>
<tr><td>Indicate if study supports application for marketing authorisation</td><td>Yes</td><td rowspan="2">CROWN is the pivotal Phase III trial for lorlatinib in patients with previously untreated ALK-positive advanced NSCLC. This trial informed the marketing authorisation application for lorlatinib in this indication and considers a population directly relevant to the decision problem addressed in this submission.</td></tr>
<tr><td>Indicate if study used in the economic model</td><td>Yes</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="2">Primary outcome
• PFS by BICR assessment (RECIST v1.1)
Secondary outcomes
• PFS by INV (RECIST v1.1)
• OS
• Response rates (all RECIST v1.1)
– ORR by BICR and INV
– DOR by BICR and INV
– TTR based on BICR assessment
• IC outcomes (all modified RECIST v1.1)
– IC-TTP by BICR and INV
– IC-OR by BICR and INV
– IC-DOR by BICR and INV
– IC-TTR by BICR and INV
• Adverse effects of treatment
– AEs
– Treatment discontinuation due to AEs
– Deaths
– SAEs
– AEs of special interest
• HRQL as assessed by EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L</td></tr>
<tr><td>All other reported outcomes</td><td colspan="2">• Subsequent anti-cancer therapies
• Probability of first event being a CNS progression, non-CNS progression, or death based on BICR (RECIST v1.1 and modified RECIST v1.1)
• Biomarkers
• PK</td></tr>
<tr><td colspan="3">Key: AE, adverse event; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; CAN, circulating nucleic acid; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life</td></tr>
</table>

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Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Lung Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5 dimensions 5 levels; HRQL, health-related quality of life; IC, intracranial; IC-DOR, intracranial duration of response; IC-OR, intracranial objective response; IC-TTP, intracranial time to progression; IC-TTR, intracranial time to tumour response; INV, investigator assessment; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1; SAE, serious adverse event; TTR, time to tumour response.
Source: Shaw et al. 2020, Solomon et al. 2023, Solomon et al. 2024. [6, 7, 10, 75]

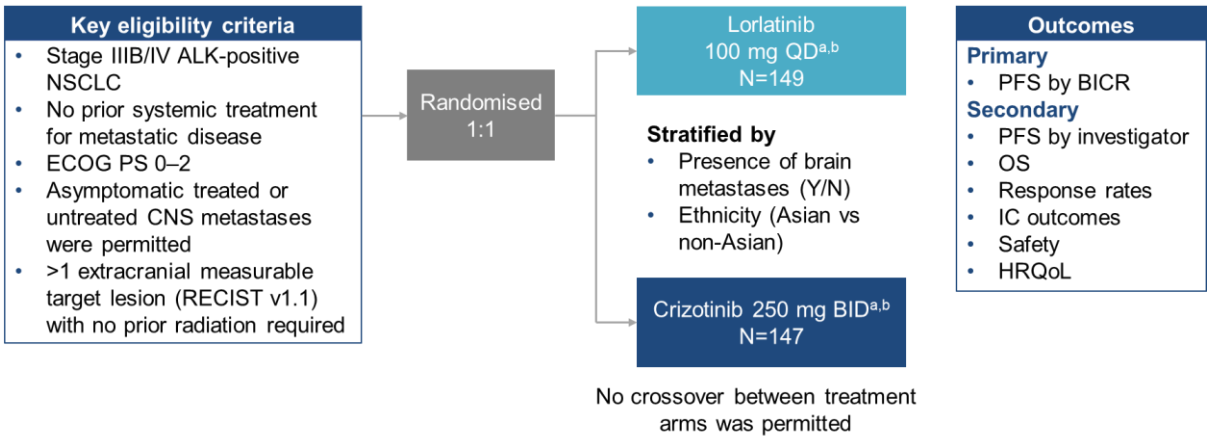
B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Summary of trial design and methodology

CROWN is an ongoing Phase III, multinational, multicentre, randomised, open-label, parallel, two-arm study in which patients with previously untreated ALK-positive advanced NSCLC were randomised 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy.[6, 7, 10]

Summaries of the CROWN study design and methodology are presented in Figure 3 and Table 7.

Figure 3: CROWN study design



Key: ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; BID, twice daily; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRQL, health-related quality of life; IC, intracranial; N, no; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1; Y, yes.
Notes: [a] Study treatment continued until confirmed disease progression assessed by BICR, patient refusal, patient lost to follow-up, unacceptable toxicity, or study termination by the sponsor, whichever comes first. [b] Defined as time from randomisation to RECIST v1.1-defined progression or death due to any cause.
Source: Pfizer Inc. CROWN Interim Study Report 1, 2020.[75]

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Table 7: Summary of methodology for CROWN

CROWN (NCT03052608)	
Location	Multinational (104 sites in 23 countries: Argentina [2 sites]; Australia [1]; Belgium [1]; Canada [2]; China [9]; Czechia [2]; France [8]; Germany [3]; Hong Kong [3]; India [3]; Italy [13]; Japan [17]; Korea [5]; Mexico [3]; The Netherlands [1]; Poland [4]; Russia [4]; Singapore [2]; Spain [10]; Taiwan [4]; Turkey [1]; UK [3]; US [3])
Trial design	Phase III, multinational, multicentre, randomised, open-label, parallel two-arm study
Duration of study and follow-up	• Study treatment beyond progression was allowed. Participants who develop radiological disease progression but are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with the treatment they have been assigned to, provided that the treating physician has determined that the benefit/risk for doing so is favourable • Survival follow-up will be performed every four months up to three years, then every six months thereafter
Method of randomisation	• Patients were randomised 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy and allocated to treatment arms using an interactive response technology system (interactive web-based response) • Patients were stratified according to presence of brain metastases (Yes versus No) and ethnic origin (Asian versus non-Asian)
Trial drugs and method of administration	• *Arm A:* Lorlatinib monotherapy at the recommended Phase II dose of 100 mg QD, administered as 4 x 25 mg oral tablets • *Arm B:* Crizotinib monotherapy at the registered starting dose of 250 mg BID, administered as 1 x 250 oral capsules/BID
Permitted and disallowed concomitant medication	The following concomitant therapies were disallowed, or caution warranted: • Other anti-tumour/anti-cancer drugs, including anti-cancer systemic chemotherapy or biological therapy • Select vitamin or herbal supplements, including herbal remedies with anti-cancer properties or known to potentially interfere with major organ function or study drug metabolism (e.g., hypericin) • Investigational agents or experimental pharmaceutical products other than lorlatinib • Radiation therapy, with exception of palliative radiotherapy to specific sites of disease if considered medically necessary by the treating physician • Surgical procedures • Lorlatinib specific – Strong or moderate CYP3A inhibitors and inducers – Sensitive CYP2B6 substrates – CYP3A substrates with a narrow therapeutic index – CYP2C19 inhibitors – CYP2C8 inhibitors

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CROWN (NCT03052608)	
	– P-gp substrates with a narrow therapeutic index • Crizotinib specific – Potent CYP3A inhibitors and inducers – CYP3A substrates – CYP3A4 substrates with a narrow therapeutic index Permitted concomitant therapies included: • Treatment considered necessary for the patient's well-being (at the discretion of the treating physician) • Medications solely for supportive care (e.g., antiemetics, analgesics, megestrol acetate for anorexia, bisphosphonates or RANK-ligands for metastatic bone disease or osteoporosis) are allowed • There are no prohibited therapies during the post-treatment follow-up phase
Primary outcomes[a]	**PFS based on BICR assessment (RECIST v1.1):** time from randomisation to the date of the first documentation of objective progression of disease or death due to any cause, whichever occurs first.
Secondary outcomes[a]	• **PFS based on INV (RECIST v1.1):** PFS derived using the local radiologist's/investigator's assessment. An expedited BICR review was performed for investigator assessed disease progression • **OS:** time from date of randomisation to date of death due to any cause. Patients last known to be alive will be censored at date of last contact • Response rates – **ORR based on BICR and on INV (RECIST v1.1):** CR or PR per RECIST v1.1 recorded from randomisation until disease progression or death due to any cause. Repeat assessments performed no less than four weeks after the criteria for response are first met – **DOR based on BICR and on INV (RECIST v1.1):** time from the first documentation of objective tumour response (CR or PR) to the first documentation of objective tumour progression or death due to any cause, whichever occurs first – **TTR based on BICR assessment (RECIST v1.1):** time from the date of randomisation to the first documentation of OR (CR or PR) which is subsequently confirmed • IC outcomes – **IC-TTP based on BICR and on INV (modified RECIST v1.1):** time from randomisation to the date of the first documentation of objective progression of IC disease, based on either new brain metastases or progression of existing brain metastases – **IC-OR based on BICR and on INV (modified RECIST v1.1):** OR only based on IC disease in the subset of patients with at least one IC lesion – **IC-DOR based on BICR and on INV (modified RECIST v1.1):** time from the first documentation of IC-OR (CR or PR) to the date of first documentation of IC objective progression of disease or

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CROWN (NCT03052608)	
	death due to any cause in the subset of patients with an IC-DOR of CR or PR – **IC-TTR based on BICR and on INV (modified RECIST v1.1):** time from the date of randomisation to the first documentation of IC-OR (CR or PR) • **Adverse effects of treatment:** AEs were classified using the MedDRA classification system. The severity of the toxicities were graded according to the NCI CTCAE v4.03 whenever possible • **HRQL:** assessed by EORTC QLQ-C30 and its corresponding module for lung cancer (QLQ-LC13) and the EQ-5D-5L questionnaires on Day 1 of each treatment cycle, at end of treatment and at post-treatment follow-up. Cycle durations were four weeks (28 days) and were always considered four weeks irrespective of any dose delays/dosing interruptions or missed doses which may affect nominal days of each cycle.
Pre-specified subgroup analyses	The following subset analyses were performed for PFS and ORR by BICR assessment on the FAS: • Randomisation stratification factors: – Presence of brain metastases (Yes, No) – Ethnic origin (Asian, non-Asian) • Other baseline characteristics: – Age (<65 years, ≥65 years) – Gender (male, female) – Smoking status (never versus current/former) – ECOG PS (0/1 versus 2) – Extent of disease (locally advanced versus metastatic) – Histology (adenocarcinoma versus non-adenocarcinoma).
Key: AE, adverse event; BICR, blinded independent central review; BID, twice daily; CR, complete response; CT, computed tomography; CYP, cytochrome; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Lung Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5 dimensions 5 levels; FAS, full analysis set; HRQL, health-related quality of life; IC, intracranial; IC-DOR, intracranial duration of response; IC-OR, intracranial objective response; IC-TTP, intracranial time to progression; IC-TTR, intracranial time to tumour response; INV, investigator assessment; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; P-gp, P-glycoprotein; PR, partial response; QD, once daily; RANK, receptor activator of nuclear factor kappa-B; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1; TTR, time to tumour response; UK, United Kingdom; US, United States. **Notes:** [a] Tumour assessments included all known or suspected disease sites. Imaging included chest, abdomen, brain and pelvis CT or MRI scans. **Source:** Pfizer Inc. CROWN Interim Study Report 1, 2020.[75]	

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B.2.3.2. Eligibility criteria

A summary of the key eligibility criteria for CROWN is presented in Table 8.

Table 8: Eligibility criteria for CROWN

Inclusion criteria	• Diagnosis: – Study population: Patients with histologically or cytologically confirmed diagnosis of locally advanced or metastatic ALK-positive NSCLC where ALK status is determined by the FDA-approved Ventana ALK (D5F3) CDx Assay – Tumour requirements: At least one extracranial measurable target lesion per RECIST v.1.1 that has not been previously irradiated. CNS metastases are allowed if: • Asymptomatic: either not currently requiring corticosteroid treatment, or on a stable or decreasing dose of ≤ 10 mg QD prednisone or equivalent • Previously diagnosed and treatment has been completed with full recovery from the acute effects of radiation therapy or surgery before randomisation, and if corticosteroid treatment for these metastases has been withdrawn for at least four weeks with neurological stability • No prior systemic NSCLC treatment, including molecularly targeted agents, angiogenesis inhibitors, immunotherapy, or chemotherapy. Adjuvant/neoadjuvant NSCLC treatment only allowed if completed more than 12 months before randomisation • ECOG PS 0, 1, or 2 • Age ≥ 18 years (or ≥ 20 years as required by local regulation) • Adequate function of bone marrow, pancreas, kidney and liver
Exclusion criteria	• Major surgery within four weeks before randomisation. Minor surgical procedures (e.g. port insertion) are not excluded, but sufficient time should have passed for adequate wound healing • Radiation therapy within two weeks before randomisation, including stereotactic or partial brain irradiation. Patients who complete whole brain irradiation within four weeks before randomisation or palliative radiation therapy outside of the CNS within 48 hours before randomisation will also not be included in the study • Gastrointestinal abnormalities, including inability to take oral medication; requirement for intravenous alimentation; prior surgical procedures affecting absorption including total gastric resection or lap band; active inflammatory gastrointestinal disease, chronic diarrhoea, symptomatic diverticular disease; treatment for active peptic ulcer disease in the past six months; malabsorption syndromes • Disease besides NSCLC that may interfere with the study
Key: ALK, anaplastic lymphoma kinase; CDx, companion diagnostic; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDA, Food and Drug Administration; NSCLC, non-small-cell lung cancer; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1. **Source:** Pfizer Inc. CROWN Interim Study Report 1, 2020.[75]	

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B.2.3.3. Baseline characteristics

A summary of the baseline characteristics of patients in the CROWN trial is shown in Table 9. The baseline patient demographics were well-balanced between treatment arms, with no major differences with respect to gender, race, presence of brain metastases or other clinically important characteristics. Across both treatment arms, the median age of patients was 57 years, 41% patients were male and 26% had brain metastases.[10] There were numerically slightly fewer female patients in the lorlatinib arm compared with the crizotinib arm. Patient baseline characteristics were generally aligned with characteristics of patients with ALK-positive NSCLC in routine UK clinical practice, including the proportion of patients with brain metastases (n = 9 clinicians from the advisory board).[4] However, CROWN included a higher proportion of patients with Asian heritage, compared with UK clinical practice, which is a common feature of NSCLC trials and according to clinicians is not a significant treatment effect modifier.

Table 9: Baseline characteristics of patients in the ITT population in CROWN

Characteristic	Lorlatinib (N = 149)[a]	Crizotinib (N = 147)[a]
Age		
Mean, years (SD)	59.1 (13.1)	55.6 (13.5)
Median	61	56
Interquartile range	51, 69	45, 66
Sex		
Female, n (%)	84 (56)	91 (62)
Male, n (%)	65 (44)	56 (38)
Race or ethnic group[b]		
White, n (%)	72 (48)	72 (49)
Asian, n (%)	65 (44)	65 (44)
Black, n (%)	0	1 (1)
Missing, n (%)	12 (8)	9 (6)
ECOG PS score[c]		
0, n (%)	67 (45)	57 (39)
1, n (%)	79 (53)	81 (55)
2, n (%)	3 (2)	9 (6)
Smoking status[d]		

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Characteristic	Lorlatinib (N = 149)[a]	Crizotinib (N = 147)[a]
Never smoked, n (%)	81 (54)	94 (64)
Previous smoker, n (%)	55 (37)	43 (29)
Current smoker, n (%)	13 (9)	9 (6)
Current stage of disease[e]		
IIIA, n (%)	1 (1)	0
IIIB, n (%)	12 (8)	8 (5)
IV, n (%)	135 (91)	139 (95)
Other, n (%)[e]	1 (1)	0
Histologic type		
Adenocarcinoma, n (%)	140 (94)	140 (95)
Adenosquamous carcinoma, n (%)	6 (4)	5 (3)
Large-cell carcinoma, n (%)	0	1(1)
Squamous-cell carcinoma	3 (2)	1 (1)
Use of previous anti-cancer drug therapy[f]		
n (%)	12 (8)	9 (6)
Previous brain radiotherapy		
n (%)	9 (6)	10 (7)
Brain metastases at baseline		
n (%)	38 (26)	40 (27)

Key: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; SD, standard deviation.
Notes: [a] Percentages may not total 100 because of rounding. [b] Race or ethnic group was reported by the investigator. [c] ECOG PS scores range from 0 to 5, with higher scores indicating greater disability. [d] Smoking status was not reported for one patient in the crizotinib group. [e] The disease stage in one patient who had locally advanced disease at trial entry was defined according to the AJCC, version 8.0, instead of AJCC, version 7.0, as required by the protocol. This stage was therefore classified as 'other.'. [f] According to the protocol, previous adjuvant or neoadjuvant anti-cancer therapy was allowed if it had been completed more than 12 months before randomisation. One patient who had received previous chemotherapy for metastatic disease was reported as having a protocol violation.
Source: Shaw et al. 2020.[10]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Statistical analysis

A summary of the statistical analyses of the CROWN trial are provided in Table 10.

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Table 10: Summary of statistical analyses in CROWN

CROWN (NCT03052608)	
Hypothesis objective	The primary objective was to demonstrate that lorlatinib is superior to crizotinib in prolonging PFS by BICR assessment per RECIST v1.1: • H_0: $HR_{PFS} \geq 1$ • H_A: $HR_{PFS} < 1$, where HR_{PFS} is the HR (arm A / arm B) of PFS A key secondary objective of the study was to demonstrate that lorlatinib is superior to crizotinib in prolonging OS
Statistical analysis	Statistical analysis of endpoints • The primary endpoint was PFS which was defined as the time from randomisation to the date of the first documentation of objective progression of disease or death due to any cause, whichever occurred first • PFS data were censored on the date of the last adequate tumour assessment (before any new anti-cancer treatment) for patients who did not have an event (PD or death), for patients who started new anti-cancer treatment before an event, or for patients with an event after two or more missing tumour assessments. Patients who did not have a baseline tumour assessment, or who did not have any post-baseline tumour assessments were censored on the day of randomisation, with a duration of 1 day, unless death occurred on or before the time of the second planned tumour assessment, in which case the death was considered an event • The primary analysis of PFS was performed on the FAS, based on BICR assessment. A stratified log-rank test (one-sided) was used to compare PFS time between the two treatment arms at the interim and/or final analyses with the overall significance level preserved at 0.025 (one-sided). The stratification factors used to conduct the stratified log-rank test for the primary analysis included the two randomisation stratification factors and a sensitivity analysis was also performed • PFS, OS, IC-TTP and DOR times associated with each treatment arm were summarised using the Kaplan–Meier method. CIs for the 25th, 50th, and 75th percentiles were reported. The Cox proportional hazards model was fitted to compute the treatment HRs and the corresponding 95% CIs for PFS, OS and IC-TTP. For DOR, the median and 95% CI for the median were also calculated Analysis plan • PFS interim analysis was planned based on the BICR-assessed PFS primary endpoint in the FAS and safety evaluation in the SAS, to allow early stopping of the study for efficacy only and to assess the safety of lorlatinib. A Lan-DeMets (O'Brien-Fleming) α-spending function was used to determine the non-binding futility boundary • Interim analysis was performed after 127 PFS events based on BICR assessments (72% of the 177 events planned for the final analysis of PFS) had occurred (data cut-off 20 March 2020) • In interim analysis, if the primary PFS endpoint was statistically significant favouring lorlatinib, the secondary OS endpoint would be analysed using a hierarchical testing procedure. Further OS analyses

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CROWN (NCT03052608)	
	are planned when 70% and 100% (final OS analysis) of the 198 OS events have occurred. A Lan-DeMets (O'Brien-Fleming) α-spending function would be used
Sample size, power calculation	• In the CROWN trial 296 patients were randomised • The sample size was determined based on the assumption of a HR of 0.611 under the alternative hypothesis (under an exponential model, assumes median PFS of 11 months in the crizotinib arm and 18 months in the lorlatinib arm). A total of 177 PFS events are required to have at least 90% power to detect a HR of 0.611 using a one-sided stratified log-rank test at a significance level of 0.025 (one-sided), and a 2-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries • This sample size would also allow comparison of OS between the two treatment arms, provided that superiority of lorlatinib over crizotinib with respect to PFS has been demonstrated. If the true HR is 0.70 under the alternative hypothesis (under an exponential model, assumes median OS of 48 months on the crizotinib arm and 68.6 months on the lorlatinib arm), a total of 198 deaths will be required to have 70% power using a one-sided stratified log-rank test at a significance level of 0.025 (one-sided), and a 3-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries at the interim analysis • The sample size further assumes a 15% drop-out rate within each treatment arm at 30 months and 120 months for PFS and OS, respectively. It also assumes a non-uniform patient accrual over approximately 15 months and follow-up after the last patient is randomised of approximately 18 months for PFS and approximately 110 months for OS
Data management	• This study used an E-DMC comprised of at least three members with at least one having appropriate medical qualifications and one statistician • The E-DMC were responsible for ongoing monitoring of the safety of patients in the study and the evaluation of efficacy at the interim analysis according to the charter. The recommendations made by the E-DMC to alter the conduct of the study were forwarded to Pfizer for final decision. Pfizer would then forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate
Patient withdrawals	Patients could withdraw from the study at any time at their own request, or they could be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site

Key: ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; E-DMC, External Data Monitoring Committee; FAS, full analysis set; H0, null hypothesis; HA, alternative hypothesis; HR, hazard ratio; HR_{PFS}: Hazard ratio progression-free survival; IC-TTP, intracranial time to progression; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1; SAS, safety analysis set; TKI, tyrosine kinase inhibitors.
Source: Pfizer Inc. CROWN Interim Study Report 1, 2020.[75]

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B.2.4.2. Analysis sets

A summary of the analysis sets for the CROWN trial is presented in Table 11.

Table 11: Analysis sets in CROWN

Analysis set	Description	Applicable endpoint
Full analysis set (n = 296)	Included all patients who were randomised. Patients were classified according to the treatment assigned at randomisation.	Primary population for evaluating all efficacy endpoints and patient characteristics.
Safety analysis set (n = 291)	Included all patients who received at least one dose of study drug. Patients were classified according to the treatment assigned at randomisation unless the incorrect treatment(s) were received throughout the dosing period, in which case patients will be classified according to the first study treatment received.	Primary population for evaluating treatment administration/compliance and safety. Efficacy endpoints were also assessed in this population.
Patient-reported outcomes analysis set (n = 285)	Defined as patients from the full analysis set who completed a baseline (last PRO assessment before randomisation day) and at least one post-baseline PRO assessment.	Primary population for the analysis of change from baseline scores and TTD in patient-reported pain, dyspnoea, or cough.

Key: PRO, patient-reported outcome; TTD, time to deterioration.
Source: Pfizer Inc. CROWN Interim Study Report 1, 2020.[75]

B.2.4.3. Patient disposition

A CONSORT diagram of patient flow is presented in Figure 4. In total, 296 patients were enrolled in the CROWN trial.[7] These patients were randomly assigned at a 1:1 ratio to the lorlatinib arm (n = 149) and the crizotinib arm (n = 147). All 149 patients in the lorlatinib arm received treatment, however five patients in the crizotinib arm did not receive treatment. At the data cut-off for Interim Analysis 3, 74 patients remained on lorlatinib and seven remained on crizotinib. The most common reason for discontinuation was disease progression in both arms (36 on lorlatinib and 104 on crizotinib).[7]

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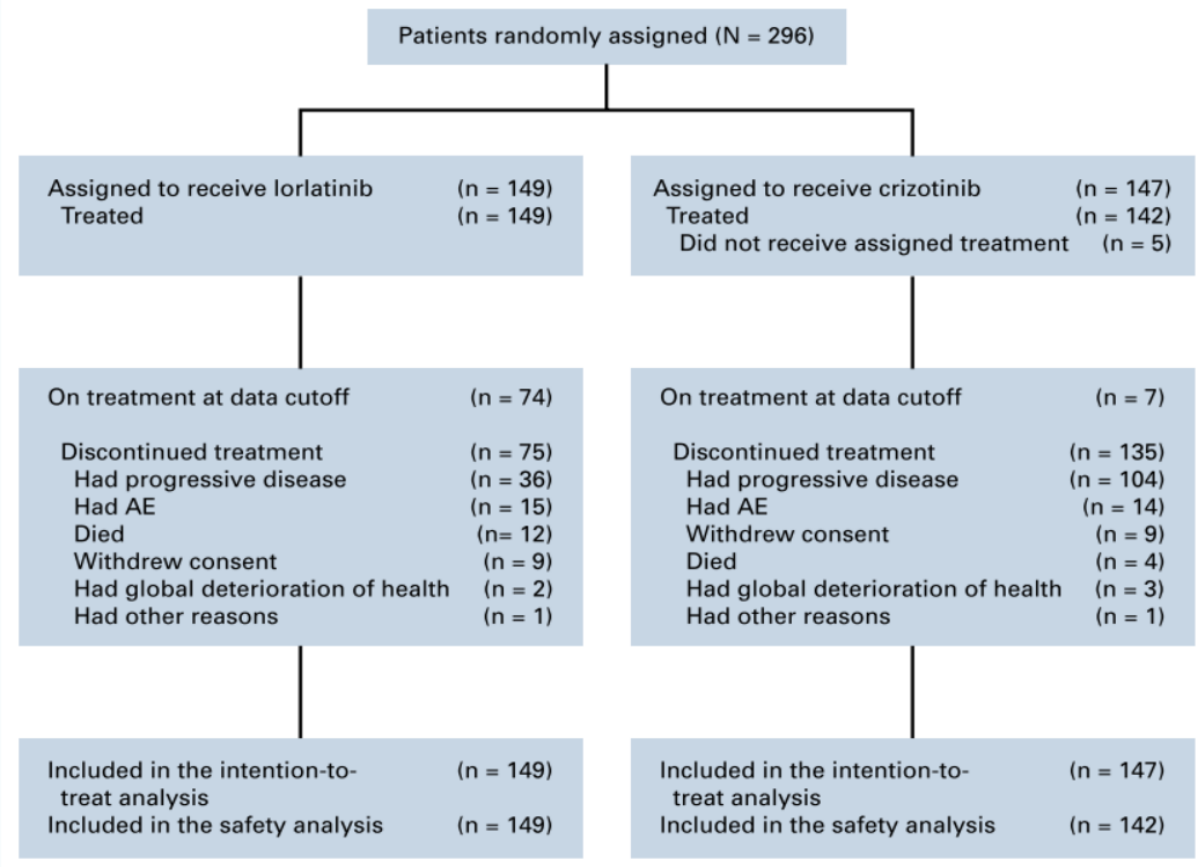
Figure 4: CONSORT Diagram for CROWN at Interim Analysis 3



Key: AE, adverse events.
Source: Solomon et al. 2024.[7]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the CROWN trial, based on the CROWN protocol, clinical study report (CSR) and Shaw et al. 2020 publication, using the risk of bias checklist recommended by NICE is provided in Table 12. CROWN was methodologically robust, well-reported and considered to be at low risk of bias.[10, 75]

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Table 12: Quality assessment of the CROWN trial

Question	CROWN trial
1. Was randomisation carried out appropriately?	Yes
2. Was the concealment of treatment allocation adequate?	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	No
5. Were there any unexpected imbalances in drop-outs between groups?	No
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

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B.2.6. Clinical effectiveness results of the relevant trials

Three different data cut-offs are available for the pivotal Phase III CROWN trial, corresponding to up to 5 years of follow-up for selected outcomes (Table 13). This submission focuses on the latest, 5-year data cut-off, from October 2023 (median PFS follow-up 60.2 months [95% CI: 57.4 to 61.6] for lorlatinib and 55.1 months [95% CI: 36.8 to 62.5] for crizotinib).[7] Data from the 3-year data cut-off (September 2021), including primary outcomes of PFS by BICR (RECIST v1.1) is presented in Appendix M1 and other 3-year outcomes are presented in Solomon et al. 2023.[6] Data from 18-month data cut-off (March 2020) is presented for OS, as OS has not yet reached maturity at the 5-year data cut-off.[7] Other 18-month outcomes are presented in Shaw et al. 2020.[10]

A summary of outcomes and respective data cut-offs presented is provided in Table 13.

Table 13: Summary of data cut sources for outcomes in the CROWN trial

Outcome	Data cut-off presented in submission
Primary outcome	
PFS by BICR (RECIST v1.1)	Appendix M1: September 2021 data cut-off (3-year follow-up)[a]
Secondary Outcomes	
PFS by INV (RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]
OS	March 2020 data cut-off (18-month follow-up)[c,d]
Response rates (ORR, DOR and TTP) by BICR (RECIST v1.1)	Appendix M1: September 2021 data cut-off (3-year follow-up)[a]
Response rates (ORR and DOR) by INV (RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]
Intracranial Outcomes	
IC-TTP by BICR (modified RECIST v1.1)	Appendix M1: September 2021 data cut-off (3-year follow-up)[a]
IC-TTP by INV (modified RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]
IC-OR by BICR (modified RECIST v1.1)	Appendix M1: September 2021 data cut-off (3-year follow-up)[a]
IC-OR by INV (modified RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]
HRQL (all measures)	September 2021 data cut-off (3-year follow-up)[b]
Adverse events (all event types)	October 2023 data cut-off (5-year follow-up)[c]

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Key: BICR, blinded independent central review; DOR, duration of response; HRQL, health-related quality of life; IC, intracranial; INV, investigator assessment; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1; TTP, time to progression.
Notes: [a] unplanned data cut; [b] unplanned data cut using INV as BICR was stopped by this date (per protocol); [c] planned, primary analysis set; [d] the number of deaths required to achieve 70% power has not yet been met and therefore OS data were not analysed.
Source: Shaw et al. 2020; Solomon et al. 2023; Solomon et al. 2024.[6, 7, 10]

B.2.6.1. Progression-free survival per INV (RECIST v1.1)

PFS by INV (RECIST v1.1) was assessed at the 5-year October 2023 data cut-off.[7] Median follow-up for PFS was 60.2 and 55.1 months for lorlatinib and crizotinib arms, respectively. Median PFS was not reached for lorlatinib (95% CI: 64.3, NR) and was 9.1 months (95% CI: 7.4, 10.9) for crizotinib (Table 14 and Figure 5). There was an 81% reduction in the risk of progression or death in favour of lorlatinib (HR: 0.19; [95% CI: 0.13, 0.27];). The 4- and 5-year PFS rate was 63% and 60% (95% CI: 51 to 68) with lorlatinib, respectively, and 10% and 8% (95% CI: 3, 14) with crizotinib.[7]

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Table 14: Summary of PFS by INV (RECIST v1.1), FAS, October 2023 data cut-off

Variable	Lorlatinib (N = 149)	Crizotinib (N = 147)
Patients with event		
n (%)	55 (36.9)	115 (78.2)
Type of event		
PD, n (%)	46 (30.9)	110 (74.8)
Death, n (%)	9 (6.0)	5 (3.4)
Patients censored		
n (%)	94 (63.1)	32 (21.8)
Reason for censoring		
No adequate baseline assessment, n (%)	1 (0.7)	0
Start of new anti-cancer therapy, n (%)	7 (4.7)	9 (6.1)
Event after ≥ 2 missing or inadequate post-baseline assessments, n (%)	5 (3.4)	3 (2.0)
Withdrawal of consent, n (%)	9 (6.0)	12 (8.2)
Lost to follow-up, n (%)	2 (1.3)	1 (0.7)
No adequate post-baseline tumour assessment, n (%)	0	0
Ongoing without an event, n (%)	70 (47.0)	7 (4.8)
Probability of being event free		
At 24 months, (95% CI)[a]	0.699 (0.615, 0.768)	0.147 (0.090, 0.216)
At 36 months, (95% CI)[a]	0.645 (0.558, 0.719)	0.101 (0.054, 0.164)
At 48 months, (95% CI)[a]	0.629 (0.542, 0.704)	0.101 (0.054, 0.164)
At 60 months, (95% CI)[a]	0.599 (0.509, 0.678)	0.075 (0.034, 0.137)
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[b]	16.4 (11.1, 32.9)	5.5 (3.7, 7.1)
Median, (95% CI)[b]	NR (64.3, NR)	9.1 (7.4, 10.9)
Q3, (95% CI)[b]	NR (NR, NR)	16.4 (12.7, 19.6)
Comparison versus crizotinib, stratified analysis[c]		
HR (95% CI)[d]	0.19 (0.133, 0.272)	

Key: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRT, interactive response technology; NR, not reached; PD, progressive disease; PFS, progression-free survival; Q, quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.
Notes: [a] CIs were derived using the log-log transformation with back transformation to original scale. [b] CIs were calculated using the Brookmeyer and Crowley method. [c] Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomisation from IRT. [d] HR based on Cox proportional hazards model; under proportional hazards, HR < 1 indicates a reduction in hazard rate in favour of lorlatinib compared to crizotinib stratification values.
Source: Pfizer Inc. CROWN Interim Study Report 3, 2023; Solomon et al. 2024.[7, 76]

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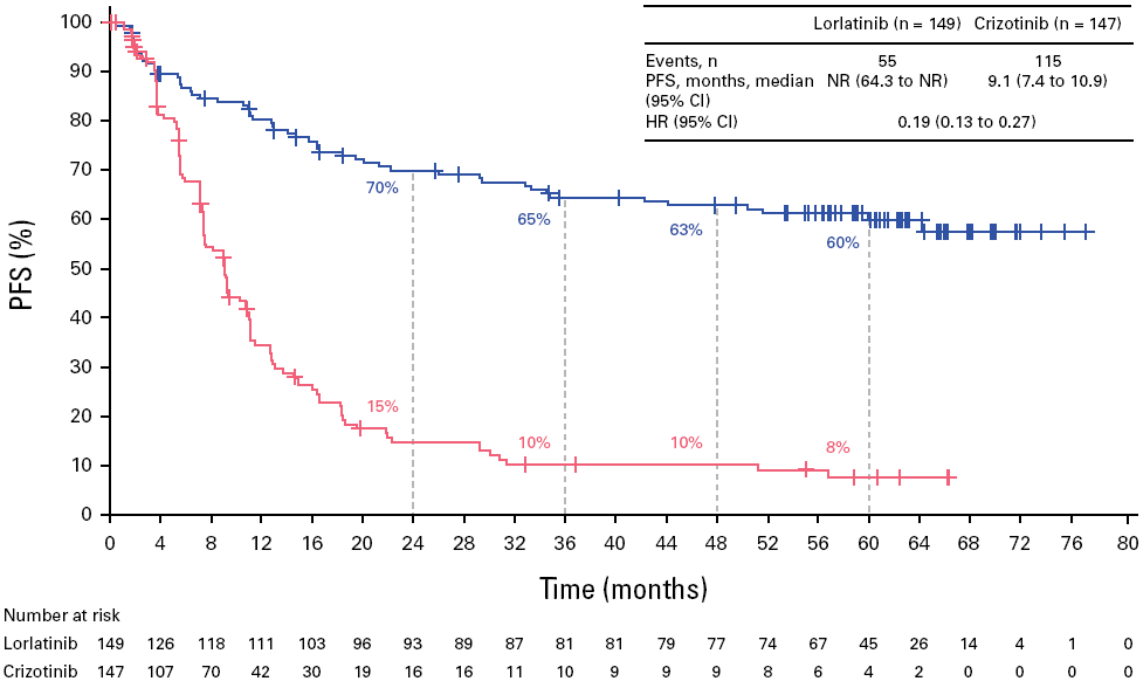
Figure 5: Kaplan–Meier curve of PFS by INV (RECIST v1.1) from CROWN, FAS, 5-year follow-up (October 2023 data cut-off)



Key: CI, confidence interval; HR, hazard ratio; INV, investigator assessment; NR, not reached.
Source: Solomon et al. 2024.[7]

B.2.6.2. Overall survival

As per the protocol, a total of 198 deaths are required to achieve 70% power using a one-sided stratified log-rank test, which has not yet been met in the CROWN trial. As such, OS data were not analysed as of the October 2023 or September 2021 data cut-off, and therefore, only OS data from the March 2020 data cut-off are presented here.

At the March 2020 data cut-off, the majority of patients in both treatment arms were still alive, and only 51 (26%) of the total 198 deaths required for the final OS analysis had occurred (Table 15).[10] The efficacy boundary for OS was not crossed. The HR for OS showed a 28% reduction in the risk of death in the lorlatinib arm compared with the crizotinib arm (HR: 0.72 [95% CI: 0.41, 1.25]). Deaths had occurred in 15.4% and 19.0% of patients in the lorlatinib and crizotinib arms, respectively. The median OS was not evaluable in either treatment arm. Despite the immaturity of OS data, the HR is in favour of lorlatinib. In the Kaplan–Meier curve shown in Figure 6, a separation between the curves can be seen from 10 months, indicating an

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improvement in OS in the lorlatinib arm, and is sustained until substantial censoring occurs at later time points due to the immaturity of the data.[10]

Due to the immaturity of the trial data, no robust conclusions can yet be drawn from the OS data.[10] However, clinical advice suggests that although long-term OS is uncertain, given the lack of death and progression events it can be expected that the long PFS will translate to a long OS, with potentially a ‘decadal’ median OS (i.e. at least 10 years).[4] Further OS analyses are event-driven, planned when 70% and 100% of the 198 OS events needed for the final OS analysis have occurred, and therefore their date is unknown.

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Table 15: Summary of OS, FAS, March 2020 data cut-off

Variable	Lorlatinib (N = 149)	Crizotinib (N = 147)
Patients with event		
n (%)	23 (15.4)	28 (19.0)
Patients censored		
n (%)	126 (84.6)	119 (81.0)
Reason for censoring		
Withdrawal of consent, n (%)	4 (2.7)	18 (12.2)
Lost to follow-up[a], n (%)	0	2 (1.4)
Alive, n (%)	122 (81.9)	99 (67.3)
Probability of being event free		
At 12 months, (95% CI)[b]	0.898 (0.837, 0.937)	0.866 (0.795, 0.913)
At 24 months, (95% CI)[b]	0.833 (0.748, 0.891)	0.763 (0.670, 0.833)
At 36 months, (95% CI)[b]	NE (NE, NE)	NE (NE, NE)
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[c]	28.2 (24.7, NE)	NE (17.4, NE)
Median, (95% CI)[c]	NE (NE, NE)	NE (NE, NE)
Q3, (95% CI)[c]	NE (NE, NE)	NE (NE, NE)
Comparison versus crizotinib, stratified analysis[d]		
HR[e]	0.72	
95% CI[e]	0.41, 1.25	
Follow-up probability		
At 12 months (95% CI)[b]	0.979 (0.936, 0.993)	0.872 (0.805, 0.918)
At 24 months (95% CI)[b]	0.306 (0.229, 0.387)	0.277 (0.199, 0.360)
At 35 months (95% CI)[b]	NE (NE, NE)	NE (NE, NE)
Kaplan–Meier estimates of duration of follow-up (months)		
Quartiles		
Q1, (95% CI)[c]	16.4 (15.4, 17.3)	15.0 (13.9, 16.9)
Median, (95% CI)[c]	20.0 (19.2, 21.5)	19.8 (17.8, 20.7)
Q3, (95% CI)[c]	24.9 (23.5, 26.8)	24.2 (23.0, 26.3)

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRT, interactive response technology; NE, not evaluable; OS, overall survival; Q, quartile.
Notes: [a] Included patients deemed to be lost to follow-up by the investigator and patients with last follow-up >365 days before data cut-off (20th March 2020). [b] CIs were derived using the log-log transformation with back transformation to original scale. [c] CIs were calculated using Brookmeyer and Crowley method. [d] Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomisation from IRT stratification values. [e] HR based on Cox proportional hazards model; under proportional hazards, HR <1 indicates a reduction in hazard rate in favour of lorlatinib compared to crizotinib.
Source: Shaw et al. 2020. [10]

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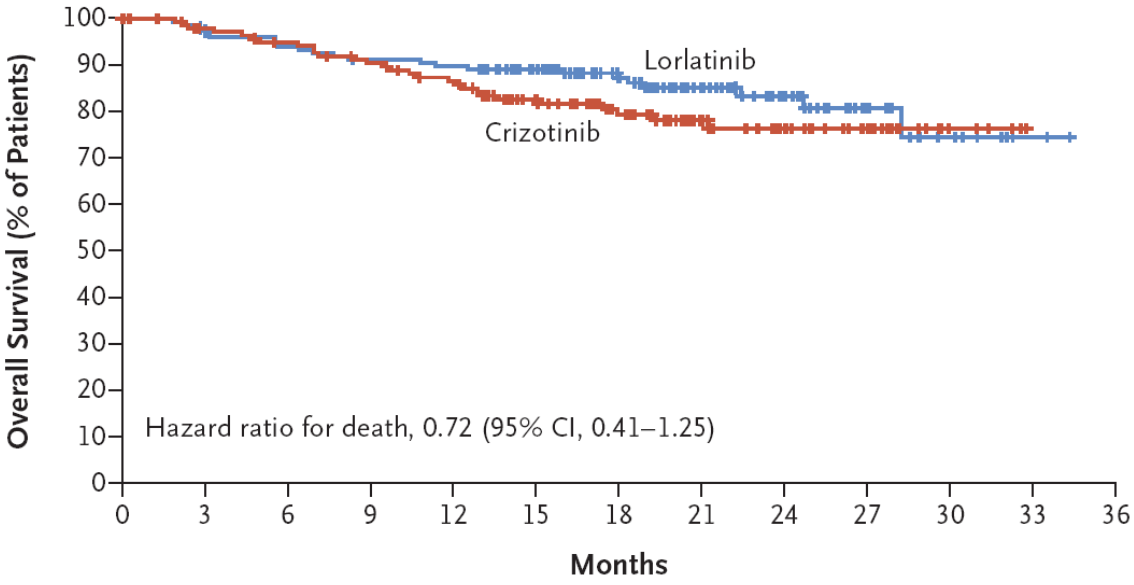
Figure 6: Kaplan–Meier curve for OS in CROWN, FAS, (March 2020 data cut-off)



No. at Risk																			
Lorlatinib	149	148	141	138	135	133	131	122	101	85	63	50	38	27	13	8	4	1	0
Crizotinib	147	139	133	127	122	116	111	97	85	68	55	40	31	22	12	5	3	0	0

Key: CI, confidence interval; FAS, full analysis set; OS, overall survival.
Source: Shaw et al. 2020.[10]

B.2.6.3. Response rates

B.2.6.3.1. Objective response rate based on INV (RECIST v1.1)

At the October 2023 data cut-off, the proportion of patients with a confirmed objective response by INV was 81% (95% CI: 73, 87) with lorlatinib and 63% (95% CI: 54, 70) with crizotinib (Table 16). In total, 120 patients in the lorlatinib arm achieved an objective response compared to 92 in the crizotinib arm.[7]

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Table 16: Summary of best overall response and OR (confirmed) based on INV (RECIST v1.1), FAS, October 2023 data cut-off

Variable	Lorlatinib (N = 149)	Crizotinib (N = 147)
Confirmed best overall response		
CR, n (%)	15 (10)	3 (2)
PR, n (%)	105 (70)	89 (61)
Stable disease, n (%)	16 (11)	38 (26)
PD, n (%)	8 (5)	7 (5)
NE, n (%)	5 (3)	10 (7)
OR (CR + PR)		
n (%)	120 (81)	92 (63)
95% CI[a]	73, 87	54, 70
Comparison versus crizotinib, stratified analysis[b]		
Odds ratio (95% CI)[c]	2.43 (1.43, 4.43)	

Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; FAS, full analysis set; INV, investigator assessment; IRT, interactive response technology; NE, not evaluable; OR, objective response; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.
Notes: [a] Clopper-Pearson method used. [b] Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomisation from IRT stratification values. [c] Odds ratio was estimated using Mantel-Haenszel method. Odds Ratio >1 indicates better outcome for lorlatinib relative to crizotinib; exact CI was calculated.
Source: Pfizer Inc. CROWN Interim Study Report 3, 2023; Solomon et al. 2024.[7, 76]

B.2.6.3.2. Duration of response based on INV (RECIST v1.1)

At the October 2023 data cut-off, the median DOR was NR (95% CI: NR, NR) with lorlatinib and 9.2 months (95% CI: 7.5, 11.1) with crizotinib (Table 17). In the lorlatinib arm, 74% of patients had a DOR ≥ 2 years compared with 15% of patients in the crizotinib arm; 66% and 10%, respectively, had a DOR ≥ 3 years; 60% and 9% had a DOR ≥ 4 years; and 26% and 2% had a DOR of ≥ 5 years.[7] Probability of being event free at 5 years was 68.8% (95% CI: 58.9%, 76.8%) in the lorlatinib arm and 9.5% (95% CI: 3.9%, 18.2%) in the crizotinib arm.

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Table 17: Summary of DOR based on INV (RECIST v1.1) – Patients with confirmed CR or PR in the FAS, October 2023 data cut-off

Variable	Lorlatinib (N = 120)	Crizotinib (N = 92)
Patients with event		
n (%)	35 (29.2)	75 (81.5)
Type of event		
PD, n (%)	29 (24.2)	74 (80.4)
Death, n (%)	6 (5.0)	1 (1.1)
Patients censored		
n (%)	85 (70.8)	17 (18.5)
Reason for censoring		
No adequate baseline assessment, n (%)	0	0
Start of new anti-cancer therapy	4 (3.3)	4 (4.3)
Event after ≥ 2 missing or inadequate post-baseline assessments, n (%)	3 (2.5)	2 (2.2)
Withdrawal of consent, n (%)	8 (6.7)	3 (3.3)
Lost to follow-up, n (%)	0	0
No adequate post-baseline tumour assessment, n (%)	0	0
Ongoing without an event, n (%)	70 (58.3)	8 (8.7)
Probability of being event free		
At 24 months, (95% CI)[a]	0.810 (0.726, 0.871)	0.190 (0.113, 0.283)
At 36 months, (95% CI)[a]	0.746 (0.655, 0.816)	0.136 (0.071, 0.222)
At 48 months, (95% CI)[a]	0.727 (0.634, 0.800)	0.136 (0.071, 0.222)
At 60 months, (95% CI)[a]	0.688 (0.589, 0.768)	0.095 (0.039, 0.182)
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[b]	33.1 (17.9, NR)	5.6 (5.3, 7.4)
Median, (95% CI)[b]	NR (NR, NR)	9.2 (7.5, 11.1)
Q3, (95% CI)[b]	NR (NR, NR)	16.6 (12.9, 28.2)
DOR (months)		
Range (min, max)	1.9, 75.3	1.1, 62.7
Response duration		
≥ 24 months, n (%)	89 (74.2)	14 (15.2)
≥ 36 months, n (%)	79 (65.8)	9 (9.8)
≥ 48 months, n (%)	72 (60.0)	8 (8.7)
≥ 60 months, n (%)	31 (25.8)	2 (2.2)

Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; FAS, full analysis set; INV, investigator assessment; Max, maximum; Min, minimum; NR, not reached; PD, progressive disease; PR, partial response; Q, quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.
Notes: [a] CIs were derived using the log-log transformation with back transformation to original scale. [b] CIs were calculated using Brookmeyer and Crowley method.
Source: Pfizer Inc. CROWN Interim Study Report 3, 2023; Solomon et al. 2024.[7, 76]

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B.2.6.4. Intracranial outcomes

Lorlatinib is effective in controlling pre-existing brain metastases as well as in protecting against the development of new brain metastases in patients with ALK-positive NSCLC.

B.2.6.4.1. Intracranial time to progression based on INV (modified RECIST v1.1)

At the October 2023 data cut-off, IC-TTP by INV was substantially longer with lorlatinib than with crizotinib, with an HR of 0.06 (95% CI: 0.03, 0.12) (Table 18 and Figure 7). Median IC-TTP was NE (95% CI: NE, NE) with lorlatinib and 16.4 months (95% CI: 12.7, 21.9) with crizotinib.[7, 76] Furthermore, 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.[7, 76]

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Table 18: Summary of IC-TTP based on INV (modified RECIST v1.1), FAS, October 2023 data cut-off

Variable	Lorlatinib (N = 149)	Crizotinib (N = 147)
Patients with event		
n (%)	9 (6.0)	65 (44.2)
Patients censored		
n (%)	140 (94.0)	82 (55.8)
Reason for censoring		
No baseline assessment, n (%)	0	0
No adequate baseline assessment	1 (0.7)	0
Start of new anti-cancer therapy, n (%)	34 (22.8)	47 (32.0)
Event after ≥ 2 missing or inadequate post-baseline assessments, n (%)	0	1 (0.7)
Death without progression, n (%)	18 (12.1)	12 (8.2)
Withdrawal of consent, n (%)	10 (6.7)	13 (8.8)
Lost to follow-up, n (%)	3 (2.0)	2 (1.4)
Ongoing without an event, n (%)	74 (49.7)	7 (4.8)
Probability of being event free		
At 24 months, (95% CI)[a]	0.942 (0.882, 0.972)	0.370 (0.260, 0.480)
At 36 months, (95% CI)[a]	0.922 (0.854, 0.959)	0.248 (0.147, 0.362)
At 48 months, (95% CI)[a]	0.922 (0.854, 0.959)	0.248 (0.147, 0.362)
At 60 months, (95% CI)[a]	0.922 (0.854, 0.959)	0.207 (0.104, 0.333)
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[b]	NE (NE, NE)	7.6 (5.8, 10.7)
Median, (95% CI)[b]	NE (NE, NE)	16.4 (12.7, 21.9)
Q3, (95% CI)[b]	NE (NE, NE)	31.4 (27.4, NE)
Comparison versus crizotinib, stratified analysis[c]		
HR (95% CI)[d]	0.06 (0.029, 0.120)	

Key: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IC-TTP, intracranial time to progression; INV, investigator assessment; IRT, interactive response technology; NE, not evaluable; Q, quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.
Notes: [a] CIs were derived using the log-log transformation with back transformation to original scale. [b] CIs were calculated using the Brookmeyer and Crowley method. [c] Stratified by ethnic origin (Asian/Non-Asian) at randomisation from IRT. [d] HR based on Cox proportional hazards model; under proportional hazards, HR < 1 indicates a reduction in hazard rate in favour of lorlatinib compared to crizotinib stratification values.
Source: Pfizer Inc. CROWN Interim Study Report 3, 2023; Solomon et al. 2024.[7, 76]

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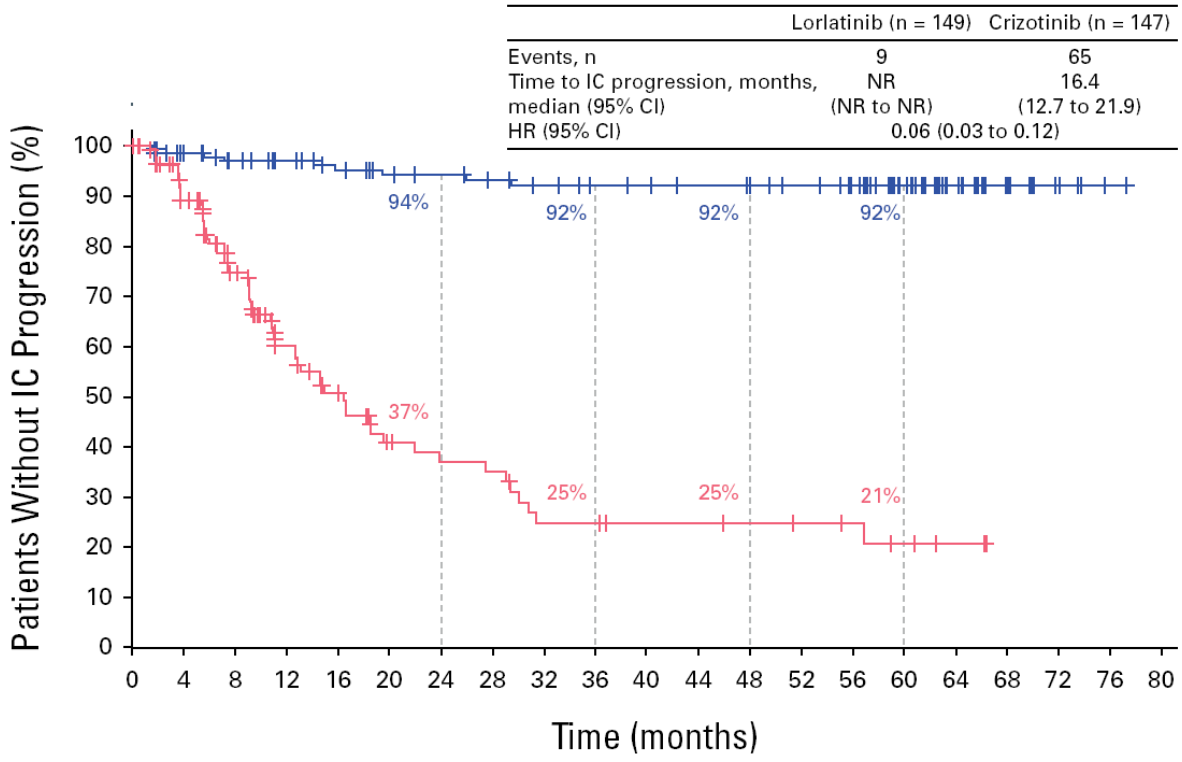
Figure 7: Kaplan–Meier plot of time to intracranial progression by INV using modified RECIST v1.1 in the FAS, October 2023 data cut-off



Key: CI, confidence interval; IC, intracranial; INV, investigator assessment; NR, not reached.
Source: Solomon et al. 2024.[7]

B.2.6.4.2. Intracranial objective response and duration of response based on INV (modified RECIST v1.1)

At the October 2023 data cut-off in patients with measurable and/or non-measurable baseline brain metastases (n = 35 patients in the lorlatinib arm and n = 38 in the crizotinib arm), IC-OR was greater with lorlatinib than with crizotinib (60% versus 11%, respectively; Table 19).[7, 76] Intracranial complete response was reported in 49% and 5% of patients, respectively. Median duration of intracranial response was NR (95% CI: NR, NR) and 12.8 months (95% CI: 7.5, NR), respectively (Table 20).[7, 76]

In patients with measurable baseline brain metastases (n = 12 patients in the lorlatinib arm and n = 6 in the crizotinib arm), IC-OR was greater with lorlatinib than with crizotinib (92% versus 33%, respectively; Table 19).[7, 76] Intracranial complete response was reported in 58% and 0% of patients, respectively. Median duration of

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intracranial response was NR (95% CI: NR, NR) and 10.2 months (95% CI: 7.5, NR), respectively (Table 20).[7, 76]

Table 19: Summary of best IC overall response and OR (confirmed) based on INV (modified RECIST v1.1), patients with brain metastases at baseline, FAS, October 2023 data cut-off

Variable	Patients with any measurable or non-measurable brain metastases at baseline		Patients with at least one measurable brain metastasis at baseline	
	Lorlatinib (n = 35)	Crizotinib (n = 38)	Lorlatinib (n = 12)	Crizotinib (n = 6)
Confirmed best overall response				
CR, n (%)	17 (49)	2 (5)	7 (58)	0
PR, n (%)	4 (11)	2 (5)	4 (33)	2 (33)
Stable disease, n (%)	0	4 (11)	0	4 (67)
Non-CR/Non-PD, n (%)	13 (37)	22 (58)	NA	NA
PD, n (%)	1 (3)	5 (13)	1 (8)	0
NE, n (%)	0	3 (8)	0	0
OR (CR+PR)				
n (%)	21 (60)	4 (10)	11 (92)	2 (33)
95% CI[a]	42, 76	3, 25	62, 100	4, 78
Comparison versus crizotinib, stratified analysis[b]				
Odds ratio (95% CI)[c]	12.02 (3.23, 54.92)		15.00 (0.99, 786.47)	

Key: CI, confidence interval; CR, complete response; FAS, full analysis set; IC, intracranial; INV, investigator assessment; IRT, interactive response technology; NR, not reached; OR, objective response; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.
Notes: [a] Clopper-Pearson method used. [b] Stratified by ethnic origin (Asian/Non-Asian) at randomisation from IRT stratification values. [c] Odds ratio was estimated using Mantel-Haenszel method. Odds Ratio > 1 indicates better outcome for lorlatinib relative to crizotinib; exact CI was calculated.
Source: Pfizer Inc. CROWN Interim Study Report 3, 2023; Solomon et al. 2024.[7, 76]

Table 20: Summary of IC-DOR based on INV (RECIST v1.1) – Patients with brain metastases at baseline and confirmed CR or PR in the FAS, October 2023 data cut-off

Variable	Patients with any measurable or non-measurable brain metastases at baseline		Patients with at least one measurable brain metastasis at baseline	
	Lorlatinib (n = 21)	Crizotinib (n = 4)	Lorlatinib (n = 11)	Crizotinib (n = 2)
Patients with event				

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Variable	Patients with any measurable or non-measurable brain metastases at baseline		Patients with at least one measurable brain metastasis at baseline	
	Lorlatinib (n = 21)	**Crizotinib (n = 4)**	**Lorlatinib (n = 11)**	**Crizotinib (n = 2)**
n (%)	2 (9.5)	3 (75.0)	2 (18.2)	2 (100)
Type of event				
PD, n (%)	0	3 (75)	0	2 (100)
Death, n (%)	2 (9.5)	0	2 (18.2)	0
Patients censored				
n (%)	19 (90.5)	1 (25)	9 (81.8)	0
Reason for censoring				
Start of new anti-cancer therapy	4 (19)	1 (25)	2 (18.2)	0
Lost to follow-up, n (%)	1 (4.8)	0	1 (9.1)	0
Ongoing without an event, n (%)	14 (66.7)	0	6 (54.5)	0
Probability of being event free				
At 24 months, (95% CI)[a]	0.905 (0.67, 0.975)	NE (NE, NE)	0.818 (0.447, 0.951)	NE (NE, NE)
At 36 months, (95% CI)[a]	0.905 (0.67, 0.975)	NE (NE, NE)	0.818 (0.447, 0.951)	NE (NE, NE)
At 48 months, (95% CI)[a]	0.905 (0.67, 0.975)	NE (NE, NE)	0.818 (0.447, 0.951)	NE (NE, NE)
At 60 months, (95% CI)[a]	0.905 (0.67, 0.975)	NE (NE, NE)	0.818 (0.447, 0.951)	NE (NE, NE)
Kaplan–Meier estimates of time to event (months)				
Quartiles				
Q1, (95% CI)[b]	NR (NR, NR)	7.5 (7.5, NE)	NR (3.9, NR)	7.5 (7.5, NE)
Median, (95% CI)[b]	NR (NR, NR)	12.8 (7.5, NE)	NR (NR, NR)	10.2 (7.5, NE)
Q3, (95% CI)[b]	NR (NR, NR)	14.7 (7.5, NE)	NR (NR, NR)	12.8 (7.5, NE)
DOR (months)				
Range (min, max)	3.9, 71.9	4.7, 14.7	3.9, 66.2	7.5, 12.8
Response duration				
≥ 24 months, n (%)	17 (81.0)	0	8 (72.7)	0
≥ 36 months, n (%)	15 (71.4)	0	8 (72.7)	0
≥ 48 months, n (%)	12 (57.1)	0	7 (63.6)	0
≥ 60 months, n (%)	3 (14.3)	0	2 (18.2)	0

Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; FAS, full analysis set; INV, investigator assessment; Max, maximum; Min, minimum; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; Q, quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.

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Variable	Patients with any measurable or non-measurable brain metastases at baseline		Patients with at least one measurable brain metastasis at baseline	
	Lorlatinib (n = 21)	Crizotinib (n = 4)	Lorlatinib (n = 11)	Crizotinib (n = 2)
Notes: [a] CIs were derived using the log-log transformation with back transformation to original scale. [b] CIs were calculated using Brookmeyer and Crowley method. **Source:** Pfizer Inc. CROWN Interim Study Report 3, 2023; Solomon et al. 2024.[7, 76]				

B.2.6.5. Health-related quality of life

HRQL was not assessed at the 5-year data cut-off. Data from the 3-year data cut-off is presented in Appendix M2.

Briefly, results showed lorlatinib demonstrated consistent longitudinal patient-reported outcomes (PRO) data at 18 and 36 months of follow-up, showing improvement in global QoL versus crizotinib and no deterioration in cognitive or emotional functioning over time compared with crizotinib.[71, 72] Consistent with the 18-month results, lorlatinib's overall QoL after 36 months of follow-up was preserved regardless of baseline brain metastasis status as demonstrated by longitudinal PRO data.[71]

Lorlatinib demonstrated improvement in emotional functioning and no significant or clinically meaningful deterioration in cognitive functioning, irrespective of presence of CNS AEs.[71] Consistent with previous data showing that CNS AEs with lorlatinib were mostly Grade 1 or 2, and more than half of all CNS AEs resolved without intervention or with lorlatinib dose interruption, these longitudinal PRO data demonstrate that occurrence of CNS AEs did not result in a clinically meaningful difference in patient-reported QoL.[71]

B.2.7. Subgroup analysis

B.2.7.1. Progression-free survival by INV

At the October 2023 data cut-off, PFS benefit in the lorlatinib arm compared with the crizotinib arm was consistently observed across all pre-specified subgroups based on baseline patient demographics and disease characteristics, supporting the robustness of PFS findings within the study population (Appendix E).[6, 7, 73]

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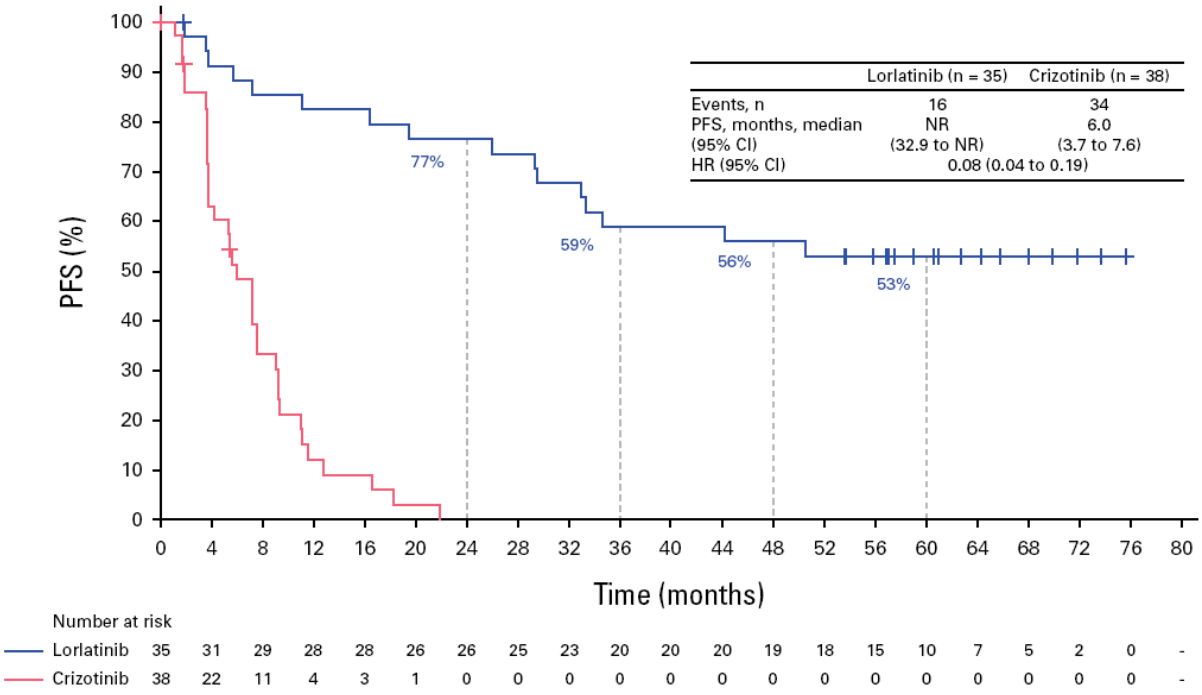
Among patients with baseline brain metastases (measurable and/or non-measurable; n = 35 in the lorlatinib group and n = 38 in the crizotinib group), the HR for disease progression or death with lorlatinib versus crizotinib was 0.08 (95% CI: 0.04, 0.19; Figure 8).[7] Median PFS was NR (95% CI: 32.9, NR) with lorlatinib and 6.0 months (95% CI: 3.7, 7.6) with crizotinib. Five-year PFS was 53% (95% CI, 35 to 68) with lorlatinib and not evaluable with crizotinib as all patients progressed or died or were censored within 2 years.[7]

Figure 8: Kaplan–Meier curve for PFS by INV in patients with baseline brain metastasis in CROWN, October 2023 data cut-off



Key: CI, confidence interval; INV, investigator assessment; NR, not reached; PFS, progression-free survival.
Source: Solomon et al. 2024.[7]

Among patients without baseline brain metastases (n = 114 in the lorlatinib group; n = 109 in the crizotinib group), the HR for disease progression or death with lorlatinib versus crizotinib was 0.24 (95% CI: 0.16, 0.36).[7] Median PFS was NR (95% CI, 64.3, NR) with lorlatinib and 10.8 months (95% CI: 9.0, 12.8) with crizotinib (Figure 9). Five-year PFS was 63% (95% CI: 52, 71) with lorlatinib and 10% (95% CI: 5, 18) with crizotinib.[7]

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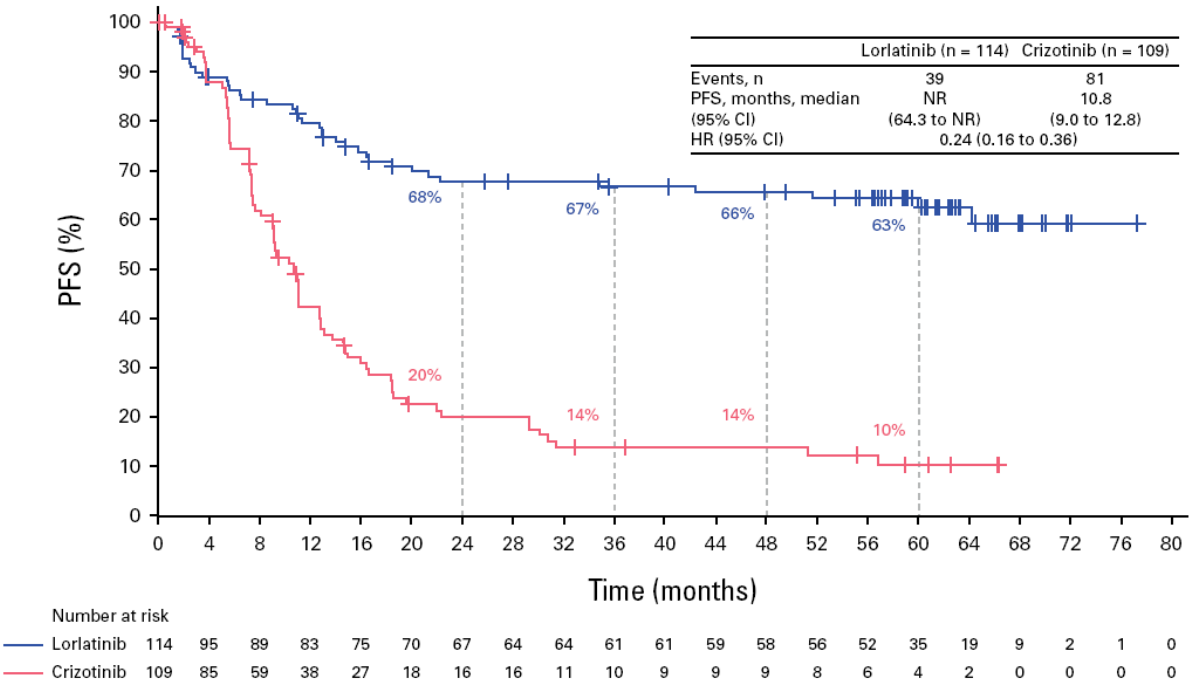
Figure 9: Kaplan–Meier curve for PFS by INV in patients without baseline brain metastasis in CROWN, October 2023 data cut-off



Key: CI, confidence interval; INV, investigator assessment; NR, not reached; PFS, progression-free survival.
Source: Solomon et al. 2024.[7]

In subgroup of patients with *EML4::ALK* variant 3a/b treated with lorlatinib (n=18), median PFS was 60.0 months (95% CI, 33.3 to NR), and in the crizotinib subgroup (n=23), the median PFS was 5.6 months (95% CI, 5.3 to 7.6).[7]

In the TP53 mutation-positive subgroup treated with lorlatinib (n = 41), the median PFS was 51.6 months (95% CI: 16.4, NR) and in the TP-53 mutation negative subgroup treated with lorlatinib (n=56), the median PFS was NR (95% CI, 60.0, NR). For TP53 mutation-positive and -negative patients treated with crizotinib (n =100), the median PFS was 5.7 months (95% CI: 5.4, 7.2) and 9.1 months (95% CI: 7.6, 11.1), respectively.[7]

The subgroup analyses of PFS by INV at 5 years are aligned with the earlier subgroup analyses of PFS by BICR from the 3-year data cut-off, presented in Appendix E1.

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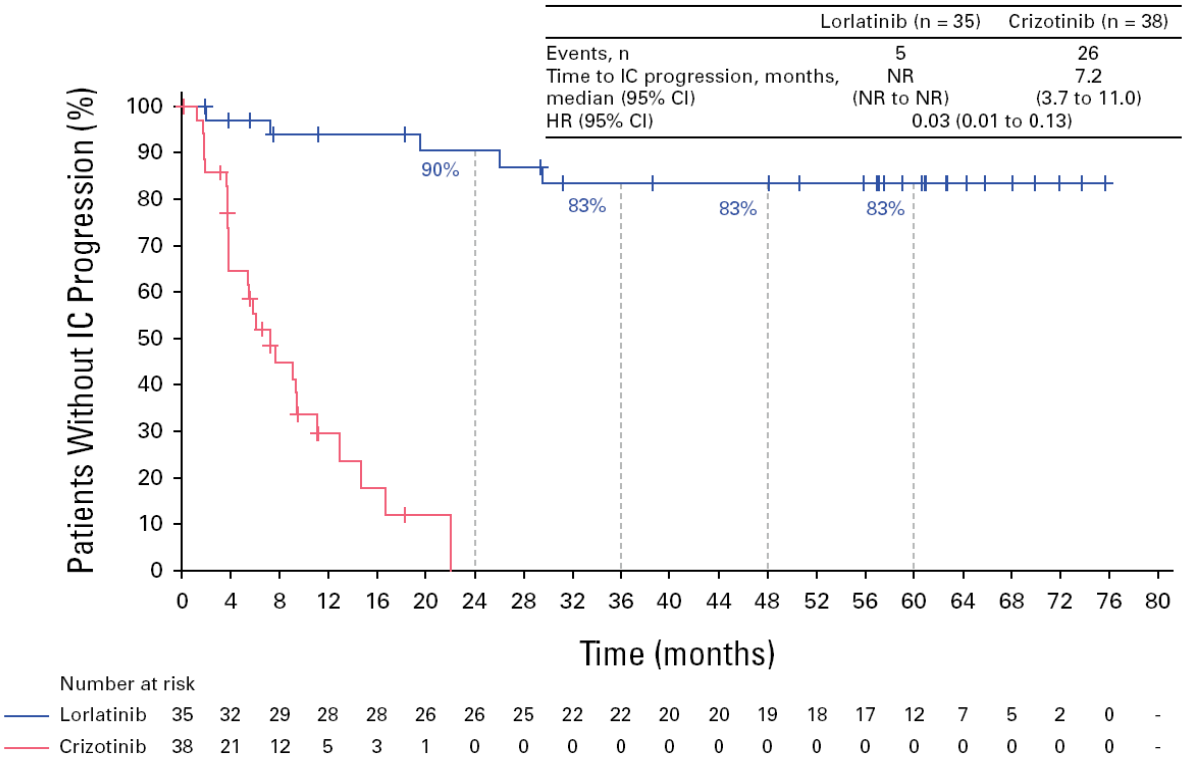
B.2.7.2. Time to intracranial progression (IC-TTP) based on INV (modified RECIST v1.1)

At the October 2023 data cut-off, among patients with baseline brain metastases, there were only five events of intracranial progression in the lorlatinib arm, all occurring in the first 3 years of treatment. The HR for IC-TTP favoured lorlatinib over crizotinib at 0.03 (95% CI: 0.01, 0.13; Figure 10).[7] 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. 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.[7]

Figure 10: Kaplan–Meier curve for intracranial time to progression in patients with baseline brain metastases in CROWN, October 2023 data cut-off



Source: Solomon et al. 2024.[7]

Among patients without baseline brain metastases, only four patients developed intracranial lesions in the lorlatinib arm, all of them occurring in the first 16 months of treatment. The HR for time to intracranial progression was 0.05 (95% CI, 0.02 to 0.13), favouring lorlatinib over crizotinib (Figure 11).[7] Median IC-TTP was NR (95%

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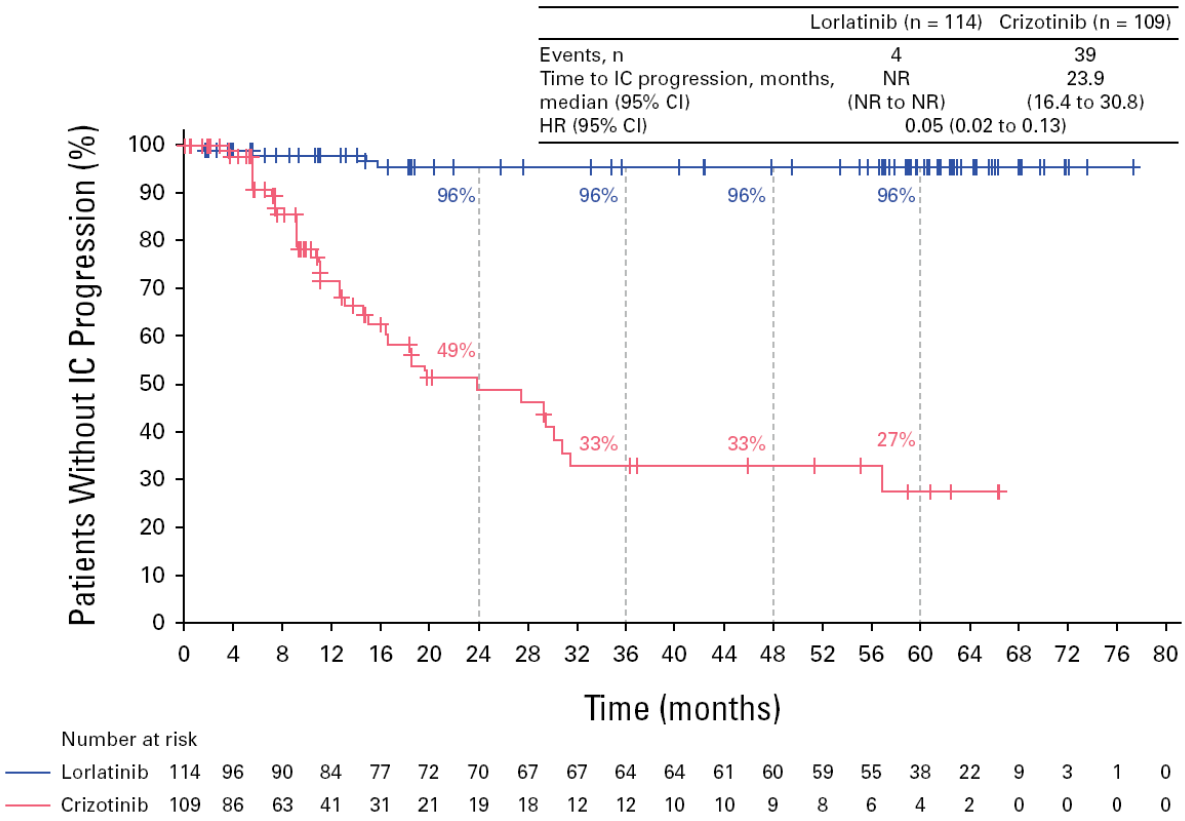
CI: NR, NR) in the lorlatinib arm and 23.9 months (95% CI: 16.4, 30.8) in the crizotinib arm. The probability of preventing development of brain metastases at 5-years was 96% (95% CI: 89, 98) with lorlatinib versus 27% (95% CI: 14, 43) with crizotinib.[7]

Figure 11: Kaplan–Meier curve for intracranial time to progression in patients without baseline brain metastasis in CROWN, October 2023 data cut-off



Source: Solomon et al. 2024.[7]

B.2.8. Meta-analysis

The main evidence for the use of lorlatinib for the first-line treatment of ALK-positive advanced NSCLC comes from the CROWN trial. A meta-analysis was not conducted as there was no other head-to-head comparison between lorlatinib and comparators within the scope of this submission. A network meta-analysis (NMA) was conducted to compare lorlatinib with ALK inhibitors included within the scope and is presented in Section B.2.9.

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B.2.8.1. Pooled analysis of overall survival from CROWN and Study 1001

Kaplan–Meier curves for OS from CROWN and the Phase II Study 1001 were pooled to strengthen the extrapolations of OS data for modelling purposes. Study 1001 is a Phase II open-label, single-arm trial of lorlatinib in patients with ALK-positive NSCLC with varying prior treatment exposure, including a cohort of 30 patients who were treatment naïve (referred to as EXP1 in Section B.3).[77] Baseline characteristics were similar between the treatment naïve arm of Study 1001 and the lorlatinib arm of CROWN (Section B.2.3.3 and Solomon et al 2018).[10, 78] Median duration of follow-up for OS in that group was 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%.[77] This overall survival data from 30 patients in a treatment naïve cohort was pooled with OS data from the CROWN Phase III trial presented in Section B.2.6.2. Pooled analysis of OS from CROWN and Study 1001 shows that median OS was not reached and 1-, 3- and 5-year OS rates were 89%, 77% and 73% (Figure 12 and Table 21).[79] With immature OS data in CROWN, this data supports the continued OS benefit of lorlatinib in patients with ALK-positive NSCLC.

Table 21: OS outcomes in CROWN, Study 100 and pooled analysis

OS outcome	CROWN – 18-month data cut-off (n = 149)[10]	Study 1001 (n = 30)[77]	CROWN + Study 1001 (n = 179)[79]
Median duration of follow-up		72.7 months (95% CI: 69.3, 76.3)	-
Median OS	Not estimable	NR (95% CI: NR, NR)	NR
1-year OS rate	90%	90%	89%
3-year OS rate	-	80%	77%
5-year OS rate	-	76%	73%

Key: CI, confidence interval; NR, not reached; OS, overall survival.
Source: Ou et al., manuscript in preparation; Pfizer Inc. Data on File, 2024; Shaw et al. 2020; Solomon et al. 2024.[7, 10, 77, 79]

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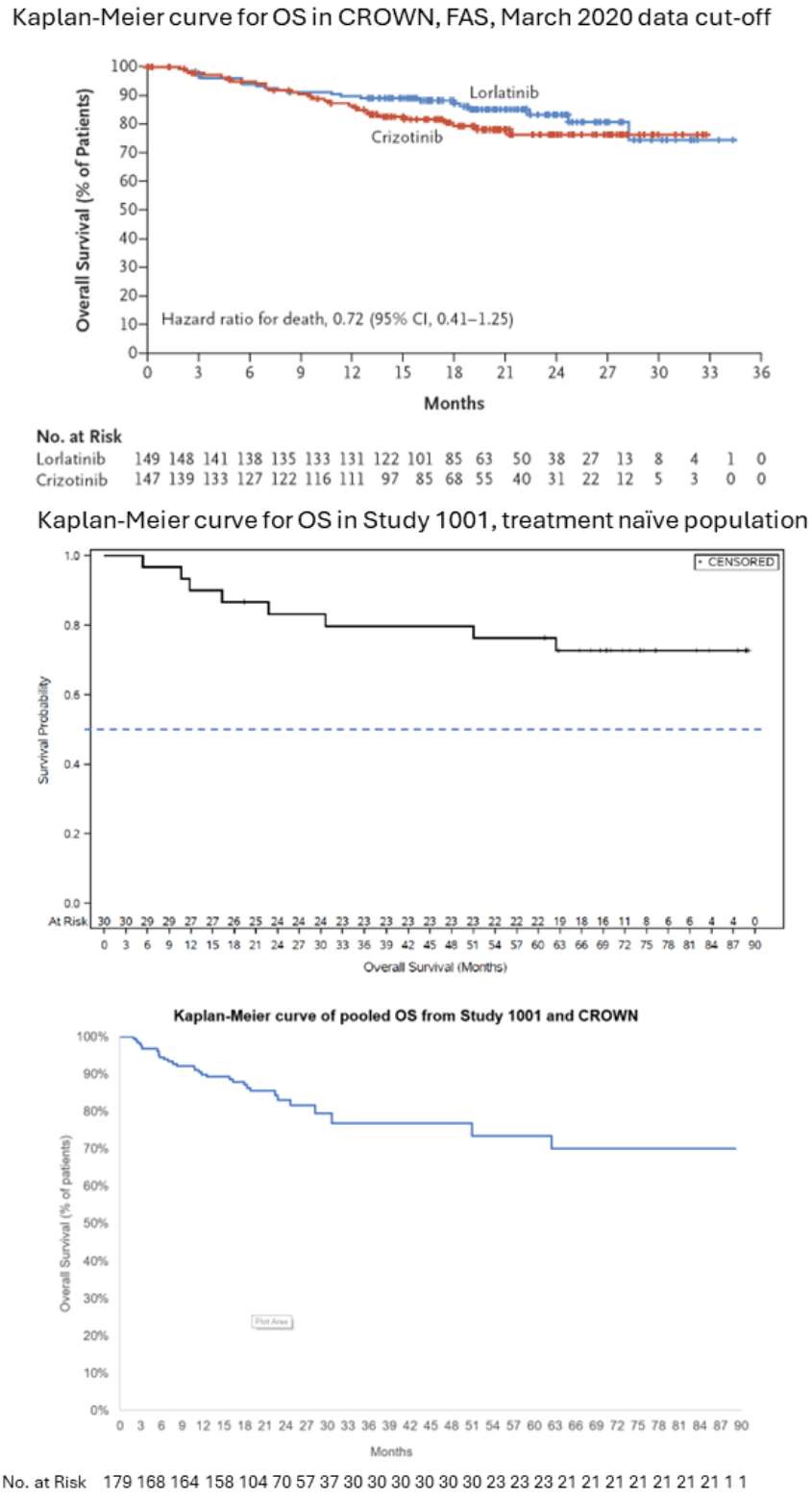
Figure 12: Kaplan–Meier curves for OS for CROWN (top); Study 1001 (middle); CROWN + Study 1001 pooled analysis (bottom)



Source: Shaw et al. 2020; Ou et al. (manuscript in preparation); Pfizer Inc. Data on File, 2004.[10, 77, 79]

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B.2.9. Indirect and mixed treatment comparisons

- An SLR identified 12 RCTs for inclusion within the NMA, four of which were relevant to the decision problem:
  - CROWN, lorlatinib versus crizotinib
  - ALEX, alectinib versus crizotinib
  - ALESIA, alectinib versus crizotinib (100% Asian patients)
  - ALTA-1L, brigatinib versus crizotinib
- A feasibility assessment was conducted and suitable levels of homogeneity, similarity and consistency of the trials was observed
- A standard Bayesian NMA was conducted to demonstrate the relative efficacy of all treatments

Results

- **PFS** for lorlatinib was significantly better than for all comparators
  - PFS by BICR, lorlatinib demonstrating a 41% and 44% reduction in the risk of progression or death versus alectinib (HR: 0.59 [95% credible interval [CrI]: 0.37, 0.95]) and brigatinib (HR: 0.56 [95% CrI: 0.34, 0.93]), respectively[80]
  - PFS by INV, lorlatinib demonstrated a 51% and 56% reduction in the risk of progression or death versus alectinib (HR: 0.49 [95% CrI: 0.32, 0.75]) and brigatinib (0.44 [95% CrI: 0.27, 0.72]), respectively[80]
- **OS**, no conclusions could be drawn due to the immaturity of the OS data in CROWN
  - HRs were 1.12 (95% CrI: 0.59, 2.11) for lorlatinib versus alectinib and 0.89 (95% CrI: 0.44, 1.78) for lorlatinib versus brigatinib[80]
- **IC-TTP** for lorlatinib was significantly better than with all comparators
  - IC-TTP by INV, lorlatinib demonstrating a 61% and 80% reduction in the risk of intracranial progression compared with alectinib (HR: 0.39 [95% CrI: 0.17, 0.89]) and brigatinib (HR: 0.20 [95% CrI: 0.07, 0.54]), respectively[80]

As the pivotal RCT for lorlatinib (CROWN, Section B.2.2) provides direct head-to-head evidence only versus crizotinib, a NMA was conducted to assess the comparative efficacy between lorlatinib, alectinib and brigatinib. The methodology and results of the NMA are presented below.

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B.2.9.1. Identification of comparator trials

As described in Section B.2.1 an SLR was conducted to identify relevant clinical evidence of the efficacy and safety of treatments for patients with ALK-positive advanced NSCLC.[74] Full details of the methodology and results of the SLR are presented in Appendix D.

Overall, a total of 12 RCTs (including CROWN) were included in the SLR and considered for inclusion within the NMA and only four were relevant to the decision problem (Table 22).[74] Non-RCTs were not considered for the NMA (see Section B.2.1 and Appendix D).

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Table 22: Overview of RCTs identified in the SLR and relevance for inclusion in the NMA

Study name	Trial name	Treatment 1	Treatment 2	Treatment line	Asian only population	OS available	PFS available	Relevant to decision problem
Solomon et al. 2024[7]; Solomon et al 2023[6]; Shaw et al 2020[10]	CROWN	Lorlatinib (100 mg QD)	Crizotinib (250 mg BID)	First-line	No	Yes	Yes	Yes
Mok 2020[81];Mok 2019[82]; Camidge 2019[83]; Peters 2017[84]	ALEX	Alectinib (600 mg BID)	Crizotinib (250 mg BID)	First-line	No	Yes	Yes	Yes
Zhou 2022[85]; Zhou 2019[86]; Zhou 2018[87]	ALESIA	Alectinib (600 mg BID)	Crizotinib (250 mg BID)	First-line	Yes	Yes	Yes	Yes
Hida 2017[88]	J-ALEX	Alectinib (300 mg BID)	Crizotinib (250 mg BID)	Mixed	Yes	No	Yes	No – not the licensed dose
Camidge 2021[89]; Popat 2018[90]	ALTA-1L	Brigatinib (180 mg QD)	Crizotinib (250 mg BID)	Mixed	No	Yes	Yes	Yes
Soria 2017[58]	ASCEND-4	Ceritinib (750 mg QD)	Chemotherapy	First-line	No	Yes	Yes	No – not a relevant comparator
Cho 2019[91]	ASCEND-8	Ceritinib (450 mg, 600 mg, 450 mg QD)		Mixed	No	No	Yes	No – not a relevant comparator
Solomon 2018[92]	PROFILE 1014	Chemotherapy	Crizotinib (250 mg BID)	First-line	No	Yes	Yes	No – not a relevant comparator
Wu 2018[93]	PROFILE 1029	Chemotherapy	Crizotinib (250 mg BID)	First-line	Yes	Yes	Yes	No – not a relevant comparator

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Study name	Trial name	Treatment 1	Treatment 2	Treatment line	Asian only population	OS available	PFS available	Relevant to decision problem
Salvaggi 2021[94]	eXalt3	Ensartinib(225 mg QD)	Crizotinib (250 mg BID)	Mixed	No	Yes	Yes	No – not a relevant comparator
Yang 2023[95]	Not reported	Envonalkib	Crizotinib	Mixed	Yes	Yes	Yes	No – not a relevant comparator
Shi 2024[96]	INSPIRE	Iruplinalkib (WX-0593)	Crizotinib	First-line	Yes	Yes	Yes	No – not a relevant comparator

Key: BID, twice a day; OS, overall survival; PFS, progression-free survival; QD, once a day; RCT, randomised controlled trial; SLR, systematic literature review.

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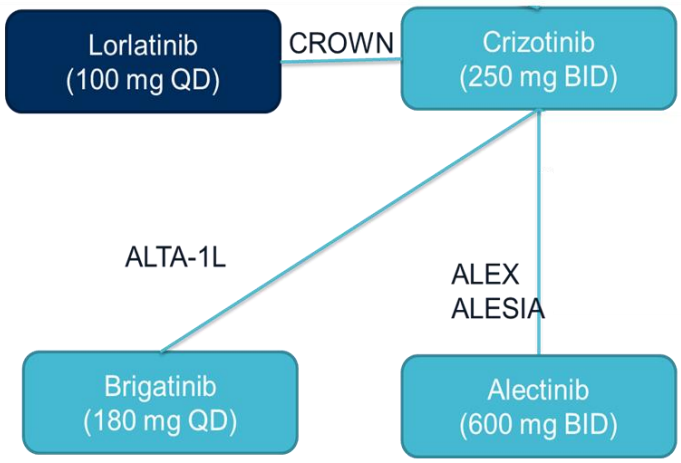
B.2.9.2. Feasibility assessment

A feasibility assessment was first conducted to investigate the homogeneity, similarity and consistency of the trials identified in the SLR, and therefore the appropriateness of conducting an NMA with these trials.[97]

Of the 12 RCTs, only four considered interventions relevant to the decision problem in this appraisal (Table 22). A relevant network could be formed from these four studies, as presented in Figure 13.[97]

Figure 13: Initial network of evidence from the RCTs identified in the SLR



Key: BID, twice daily; QD, once daily; RCT, randomised controlled trial; SLR, systematic literature review.
Source: Pfizer Inc., Data on file, 2024.[97]

B.2.9.2.1. Patient population

The patient population considered in the NMA was adults with untreated ALK-positive advanced NSCLC, in line with the scope of this decision problem and the patient population included in the pivotal CROWN trial.

In the four RCTs considered in the feasibility assessment, the proportion of Asian patients ranged from 36–100%; ALESIA only included Asian patients.

B.2.9.2.2. Inclusion and exclusion criteria

Overall, the inclusion criteria were generally comparable across the studies. Criteria relating to disease stage, ECOG PS, CNS metastases, tumour requirements and age were consistent across studies.[97]

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ALTA-1L included ALK inhibitor naïve patients but also patients with prior chemotherapy (24–36% of the intention-to-treat [ITT]). All other trials included at least 85% of patients who had no prior therapy, with the proportions of patients receiving prior chemotherapy ranging from 0–15%.[97]

A summary of the study inclusion and exclusion criteria is provided in Table 23. Details of the prior treatment received by patients in ALTA-1L are presented in Appendix D.1.3.1.1.

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Table 23: Summary of inclusion and exclusion criteria of RCTs considered in the NMA

Study name	Trial name	Disease stage	Line of treatment	ECOG PS	CNS metastases	Tumour requirement	Age
Solomon et al. 2024[7, 73]; Solomon et al 2023[6]; Shaw et al 2020[10]	CROWN	IIIB/IV ALK-positive NSCLC	ALK inhibitor naïve	0–2	Asymptomatic treated or untreated CNS metastases permitted	≥ 1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required	≥ 18 years (or ≥ 20 years as required by local regulation)
Mok 2020[81];Mok 2019[82]; Camidge 2019[83]; Peters 2017[84]	ALEX	IIIB/IV ALK-positive NSCLC	ALK inhibitor naïve	0–2	CNS metastases allowed if asymptomatic	Measurable disease by RECIST v1.1	≥ 18 years
Zhou 2022[85]; Zhou 2019[86]; Zhou 2018[87]	ALESIA	IIIB/IV ALK-positive NSCLC	ALK inhibitor naïve	0–2	CNS metastases allowed if asymptomatic	Measurable disease by RECIST v1.1	≥ 18 years
Camidge 2021[89]; Popat 2018[90]	ALTA-1L	IIIB/IV ALK-positive NSCLC	ALK inhibitor naïve +/- prior chemotherapy	0–2	Permitted if asymptomatic and neurologically stable with no increasing dose of steroids or anticonvulsants within 7 days before randomisation	≥ 1 measurable target lesion (RECIST v1.1)	≥ 18 years

Key: ALK, anaplastic lymphoma kinase positive; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small-cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.
Source: Pfizer Inc., Data on file, 2024.[97]

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B.2.9.2.3. Baseline characteristics

In general, while there was some variation in baseline characteristics across the trials, there were no clear outliers other than race.[97] Patients in the CROWN study were generally slightly older (median age of 61 for the lorlatinib arm and 56 for the crizotinib arm) than patients in the other trials (median ranges from 49–61). There were also slightly fewer male patients in the CROWN study (44% and 38% in the lorlatinib and crizotinib arms, respectively) compared with some other trials (proportion ranges from 42–59%). It was not considered that either of these differences were likely to affect the relative treatment effects. The proportion of patients who have never smoked ranged from 54–73%. The proportion of patients who had an ECOG PS score of 0 or 1 at baseline was similar across all studies (proportion ranges from 93%–98%).[97]

A summary of the most commonly presented baseline characteristics is presented in Table 24. There were slightly fewer patients with brain metastases at baseline in the CROWN study (26% and 27% in the lorlatinib and crizotinib arms, respectively) compared with some of the other trials (proportion ranges from 29–42%).[97] However, these differences were unlikely to be so great as to affect the relative treatment effects; this was confirmed by additional published MAICs using data from the September 2021, 3-year data cut-off, that adjusted for baseline characteristics including brain metastases (Section B.2.9.5).[97]

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Table 24: Summary of commonly reported patient baseline characteristics in the ITT populations of the RCTs considered in the NMA

Trial name	Treatment/ comparator	N	Age	Gender	Brain metastasis	Race	Smoking	ECOG PS	Prior treatment
			Median (range)	Male (%)	Proportion with brain metastasis (%)	Asian (%)	Never/current or former (%)	0 or 1 (%)	Prior chemotherapy (%)
CROWN[6, 7, 10]	Lorlatinib	149	61 (30, 90)	44	26	44	54/46	98	0
	Crizotinib	147	56 (26, 84)	38	27	44	64/35	94	0
ALEX[a81-84]	Alectinib	152	58 (25, 88)	45	42	45	61/40	93	0
	Crizotinib	151	54 (18, 91)	42	38	46	65/35	93	0
ALESIA[b85-87]	Alectinib	125	51 (43, 59)	51	35	100	67/33	97	6
	Crizotinib	62	49 (41, 59)	55	37	100	73/28	98	15
ALTA-1L[89, 90]	Brigatinib	137	58 (27, 86)	50	29	43	61/39	96	26
	Crizotinib	138	60 (29, 86)	59	30	36	54/46	96	27

Key: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; NMA, network meta-analysis.
Notes: [a] The ITT population of this study includes patients with prior crizotinib; therefore the treatment naïve population was used. [b] Studies excluded from the NMA.
Source: Pfizer Inc., Data on file, 2024.[97]

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B.2.9.2.4. Treatments

Treatments in studies considered for the NMA are presented in Table 25. All doses were comparable for studies that investigated the same treatments.[97] Only ALTA-1L allowed treatment crossover. In ALTA-1L, crossover was permitted after progression from crizotinib to brigatinib only.[89, 98] Out of 137 patients, 35 (25.5%) who were randomised to crizotinib crossed over to brigatinib. No method of adjustment for crossover was reported in the primary publication; the NICE appraisal for brigatinib (TA670) investigated multiple methods for adjusting OS but the committee considered the crossover adjustments were not robust and did not consider them as part of the preferred assumptions.[20] There was a high rate of post-crizotinib treatment with ALK inhibitors, including brigatinib, in CROWN and the other studies included in the NMA given that in most countries ALK inhibitor treatment after crizotinib is established. This further justifies including ALTA-1L results without adjustment for crossover (Table 25). [7, 81, 86, 98] As ALTA-1L was the only RCT identified in the SLR which included brigatinib, removing it from the network due to crossover would prevent a comparison of lorlatinib with brigatinib; as such, ALTA-1L was maintained in the network.[97]

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Table 25: Summary of treatments in studies considered in the NMA

Study name	Study drug	Patients (ITT)	Dose	Route of admin	Cross-over	Lorlatinib subsequent therapy	Alectinib subsequent therapy	Brigatinib subsequent therapy	Crizotinib subsequent therapy	Ceritinib subsequent therapy
CROWN[7, 73]	Lorlatinib	149	100 mg QD	Oral	No	3/46 (6.5%); 3/149 (2.0%)[a,b]	12/46 (26.1%); 12/149 (8.1%)[a,b]	1/46 (2.2%); 1/149 (0.7%)[a,b]	4/46 (8.7%); 4/149 (2.75)[a,b]	3/46 (6.5%); 3/149 (2.0%)[a,b]
	Crizotinib	147	250 mg BID	Oral	No	4/110 (3.6%); 4/147 (2.7%)[a]	68/110 (61.8%); 68/147 (46.3%)[a]	21/110 (19.1%); 21/147 (14.3%)[a]	5/110 (4.5%); 5/147 (3.4%)[a]	3/110 (2.7%); 3/147 (2.0%)[a]
ALEX[81-84]	Alectinib	152	600 mg BID	Oral	No	11/84 (13.1%); 11/152 (7.3%)[a]	2/84 (2.4%); 2/152 (1.3%)[a]	8/84 (9.5%); 8/152 (5.3%)[a]	11/84 (13.1%); 11/152 (7.3%)[a]	7/84 (8.3%); 7/152; (4.6%)[a]
	Crizotinib	151	250 mg BID	Oral	No	10/114 (8.8%); 10/151 (6.6%)[a]	24/114 (21.1%); 24/151 (15.8%)[a]	11/114 (9.6%); 11/151(72%)[a]	9/114 (7.9%); 9/151 (5.9%)[a]	24/114 (21.1%); 24/151 (15.8%)[a]
ALESIA[85-87]	Alectinib	125	600 mg BID	Oral	No	3/20 (15.0%); 3/125 (2.4%)[a]	1/20 (5.0%); 1/125 (0.8%)[a]	0/20 (0%); 0/125 (0%)[a]	4/20 (20%); 4/125 (3.2%)[a]	0/20 (0%); 0/125 (0%)[a]
	Crizotinib	62	250 mg BID	Oral	No	1/30 (3.3%); 1/62 (1.6%)[a]	4/30 (13.3%); 4/62 (6.5%)[a]	4/30 (13.3%); 4/62 (6.5%)[a]	1/30 (3.3%); 1/62 (1.6%)[a]	2/30 (6.7%); 2/62 (3.2%)[a]
ALTA-1L[89, 90]	Brigatinib	137	180 mg QD	Oral	Yes	22/74 (29.7%); 22/137 (16.2%)[a]	16/74 (21.6%); 16/137 (11.8%)[a]	2/74 (2.7%); 2/137 (1.5%)[a]	11/74 (14.9%); 11/137 (8.1%)[a]	4/74 (5.4%); 4/137 (2.9%)[a]
	Crizotinib	138	250 mg BID	Oral	Yes	21/101 (20.8%); 21/138 (15.3%)[a]	28/101 (27.7%); 28/138 (20.4%)[a]	80/101 (79.2%); 80/138 (58.4%)[a]	6/101 (5.9%); 6/138 (4.4%)[a]	5/101 (5.0%); 5/138 (3.6%)[a]

Key: BID, twice daily; ITT, intention-to-treat; QD, once a day.
Notes: [a] n/N (% over progressed patients); n/N (% over total patients); [b] only includes second-line treatments.

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B.2.9.3. Network and methodology

The NMA has been conducted for PFS by BICR, PFS by INV, OS and IC-TTP. Table 26 and Figure 14 presents the availability of PFS, OS and IC-TTP in the trials considered in the network.

Furthermore, to address an imbalance in the percentage of patients with brain metastases at baseline between the four trials used, matching-adjusted indirect comparisons (MAICs) were conducted to compare lorlatinib (CROWN) versus alectinib (ALEX and ALESIA) and versus brigatinib (ALTA-1L).[99] These were conducted on the most recent CROWN data cuts available at the time (3 year data cut-off, September 2021) and gave very similar results to previously presented NMA results.[100]

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Table 26: PFS, OS and IC-TTP data reported in included studies

Trial and study name	Treatment 1	Treatment 2	PFS available ITT (BICR)	PFS available (INV)	PFS in strictly treatment naïve population	OS available ITT	OS in strictly treatment naïve population	IC-TTP available (INV)	IC-TTP in strictly treatment naïve population
CROWN - Solomon et al. 2024[7, 73]; Solomon et al 2023[6]; Shaw et al 2020[10]	Lorlatinib	Crizotinib	Yes	Yes	Same as ITT	Yes	Same as ITT	Yes	Same as ITT
ALEX - Mok 2020[81];Mok 2019[82]; Camidge 2019[83]; Peters 2017[84]	Alectinib	Crizotinib	Yes	Yes	Same as ITT	Yes	Same as ITT	Yes	Same as ITT
ALESIA - Zhou 2022[85]; Zhou 2019[86]; Zhou 2018[87]	Alectinib	Crizotinib	Yes	Yes	Same as ITT	Yes	Same as ITT	Yes	Same as ITT
ALTA-1L- Camidge 2021[89]; Popat 2018[90]	Brigatinib	Crizotinib	Yes	Yes	Yes*	Yes	No*	Yes	Yes

Key: BICR, blinded independent review; INV, investigator assessment; IC-TTP, intracranial time to progression; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.
Notes: *ATLA-1 enrolled patients who had received prior chemotherapy (73/275), subgroup analysis stratified for receipt of prior chemotherapy was performed for PFS but not OS.

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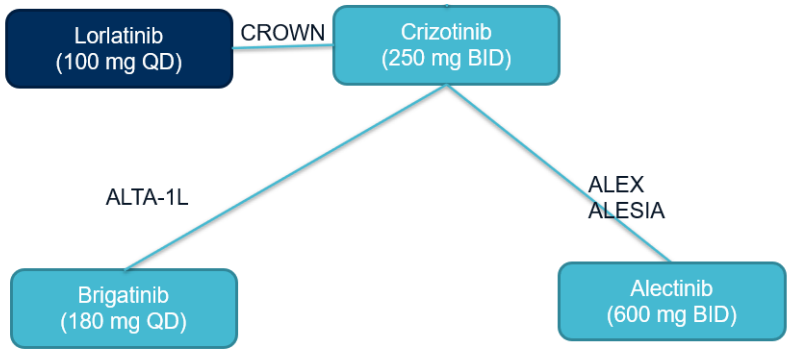
Figure 14: PFS, OS and IC-TTP network diagram



Key: BID, twice daily; PFS, progression-free survival; QD, once daily.

Where available, the reported PFS, OS and IC-TTP HRs, and an associated variance estimate such as the standard error or 95% CI was used to derive the input data for the analysis. Where Kaplan–Meier curves were available, these were digitised using the method of Guyot et al. 2012 to generate pseudo patient-level data to allow the assessment of proportional hazards.[101]

A fixed effects model was used for all analyses, which was deemed appropriate due to the small network size and lack of multiple studies per treatment comparison, and a lack of loops in the network that are made up of more than one multi-armed study.

The proportional hazards assessment (see Appendix N1) suggests that broadly, the proportional hazards assumption does hold between crizotinib, alectinib and brigatinib, but it is unlikely to hold between lorlatinib and crizotinib, as accepted in TA909. This is also illustrated by the shape of the lorlatinib PFS Kaplan–Meier curve in contrast to the shape of the crizotinib, alectinib and brigatinib Kaplan–Meier curves when shown side by side (Figure 15) which suggests that lorlatinib has a distinct hazard profile. Therefore, standard Bayesian NMA was conducted to demonstrate the relative efficacy of all treatments, but only the relative efficacy (OS, PFS and IC-TTP) of alectinib and brigatinib versus crizotinib has been used to inform the economic model (see Section B.3.3 for more details). Furthermore, if some non-proportionality of the hazards is present, the HR obtained is expected to be a type of average over the event times (Royston and Parmar) and notwithstanding the survival estimates generated from the application of the NMA HRs to crizotinib in the cost-effectiveness model were also validated (Section B.3.3.2).[102]

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Further details on the methodology of the NMA are presented in Appendix N2–N4.

B.2.9.4. NMA results

B.2.9.4.1. Progression-free survival

Data for lorlatinib from the September 2021, 3-year data cut-off have been used in the NMA for PFS by BICR, and from October 2023, 5-year data cut-off for PFS by INV. The relative effects of all treatments versus crizotinib (common comparator arm in all studies) and of lorlatinib compared with alectinib and brigatinib are presented in Table 27.[80] For all comparisons, lorlatinib showed a statistically significant improvement in PFS. For the PFS by BICR, the HRs were 0.59 (95% CrI: 0.37, 0.95) versus alectinib and 0.56 (95% CrI: 0.34, 0.93) versus brigatinib, demonstrating lorlatinib to be associated with a 41% and 44% reduction in the risk of progression or death versus alectinib and brigatinib, respectively. For the PFS by INV, the HRs were 0.49 (95% CrI: 0.32, 0.75) versus alectinib and 0.44 (95% CrI: 0.27, 0.72) versus brigatinib, demonstrating lorlatinib to be associated with a 51% and 56% reduction in the risk of progression or death versus alectinib and brigatinib, respectively.[80]

Table 27: PFS relative effect of lorlatinib compared with all treatments (fixed effects)

Treatment	PFS by BICR, HR (95% CrI)	PFS by INV, HR (95% CrI)
Hazard ratios for all treatments vs crizotinib		
Lorlatinib	0.27 (0.18, 0.40)	0.19 (0.13, 0.27)
Alectinib (600 mg BID)	0.46 (0.35, 0.60)	0.39 (0.31, 0.49)
Brigatinib	0.48 (0.35, 0.66)	0.43 (0.31, 0.59)
Hazard ratios for lorlatinib vs relevant comparators		
Alectinib (600 mg BID)	0.59 (0.37, 0.95)	0.49 (0.32, 0.75)
Brigatinib	0.56 (0.34, 0.93)	0.44 (0.27, 0.72)

Key: BID, twice daily; CrI, credible interval; HR, hazard ratio; INV, investigator assessment; PFS, progression-free survival.
Source: Ou et al. 2023; Pfizer Inc., Data on File, 2024.[80, 100]

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B.2.9.4.2. Overall survival

Data for lorlatinib from the March 2020, 18-month data cut-off have been used in the NMA for OS, as OS was not available at later data cut-offs. The relative effects of all treatments versus crizotinib and of lorlatinib compared with alectinib and brigatinib in terms of OS are presented in Table 28.[80] OS data for alectinib and brigatinib are from multiple data cuts from the associated studies and the data is therefore more mature.[81, 85, 89] The resulting HRs were 1.12 (95% CrI: 0.59, 2.11) for lorlatinib versus alectinib and 0.89 (95% CrI: 0.44, 1.78) for lorlatinib versus brigatinib, demonstrating no statistical difference between lorlatinib and alectinib and brigatinib.[80] Given the OS data from the CROWN trial are still very immature, no conclusions could be drawn from this analysis. A further data cut for OS from the CROWN trial is planned. The impact of this immaturity is demonstrated in the 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.[103] In the 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).[85] Importantly, the 5-year OS probability with alectinib was 62.5% in ALEX (at a median follow-up of 48.2 months)[103] and 66.4% in ALESIA trial (at a median follow-up of 61 months)[85]; while the 4-year OS probability with brigatinib in ALTA-1L was 66% (at a median follow-up of 40.4 months).[89] These rates are similar to lorlatinib's PFS rates of 63% at 4 years and 60% at 5 years in CROWN, at a median follow-up of 60.2 months.[7]

Therefore, OS benefit with lorlatinib has the potential to be of higher magnitude than with second generation ALK inhibitors.

Table 28: OS relative effect of lorlatinib compared with all treatments (fixed effects)

Treatment	HR (95% CrI)
Hazard ratios for all treatments vs crizotinib	
Lorlatinib	0.72 (0.41, 1.25)
Alectinib (600 mg BID)	0.64 (0.48, 0.87)
Brigatinib	0.81 (0.53, 1.23)
Hazard ratios for lorlatinib vs relevant comparators	
Alectinib (600 mg BID)	1.12 (0.59, 2.11)
Brigatinib	0.89 (0.44, 1.78)
Key: BID, twice daily; CrI, credible interval; HR, hazard ratio; OS, overall survival.	

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Source: Pfizer Inc., Data on File, 2024.[80]

B.2.9.4.3. Intracranial time to progression

Data for lorlatinib from the October 2023 data cut-off have been used for time to intracranial progression by INV. The relative effects of lorlatinib compared with alectinib and brigatinib in terms of time to intracranial progression are presented in Table 29.[80] Definitions of IC-TTP between trials differ slightly, but in practice give similar results; with competing risk HRs used for the brigatinib and alectinib trials, competing risks analysis calculates HR by treating systemic (i.e. 'PFS') progression as a competing event, whereas the lorlatinib CROWN HR censors patients who receive systemic therapy that is not lorlatinib. For all comparisons, lorlatinib showed a statistically significant improvement in time to intracranial progression. The HRs for IC-TTP were 0.39 (95% CrI: 0.17, 0.89) versus alectinib and 0.20 (95% CrI: 0.07, 0.54) versus brigatinib, demonstrating lorlatinib to be associated with a 61% and 80% reduction in the risk of intracranial progression versus alectinib and brigatinib, respectively.[80]

Table 29: Intracranial time to progression relative effect of lorlatinib compared with all treatments (fixed effects)

Treatment	IC-TTP by INV, HR (95% CrI)
Hazard ratios for all treatments vs crizotinib	
Lorlatinib	0.06 (0.03, 0.12)
Alectinib (600 mg BID)	0.15 (0.10, 0.24)
Brigatinib	0.30 (0.15, 0.60)
Hazard ratios for lorlatinib vs relevant comparators	
Alectinib (600 mg BID)	0.39 (0.17, 0.89)
Brigatinib	0.20 (0.07, 0.54)
Key: BID, twice daily; CrI, credible interval; HR, hazard ratio; IC-TTP, intracranial time to progression; INV, investigator assessment. **Source:** Pfizer Inc., Data on File, 2024.[80]	

B.2.9.5. Uncertainties in the indirect and mixed treatment comparisons

A fixed effects model was used in all analyses. Fixed effects models estimate the same treatment effect for each study, whereas random effects models estimate different treatment effects distributed around a typical value. Therefore, in general, it

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is possible that a fixed effects analysis may underestimate uncertainty, whereas a random effects analysis is likely to overestimate uncertainty. In these analyses, however, it was appropriate to use a fixed effects analysis due to the small network size and lack of multiple studies per treatment comparison, and a lack of loops in the network that are made up of more than one multi-armed study.

The main uncertainty in the NMAs relates to the immaturity of OS data from the CROWN trial. At the March 2020 data cut-off, a total of only 51 (26%) of the total 198 deaths required for the final OS analysis of CROWN had occurred. Therefore, no robust conclusions can yet be drawn from the OS data. Clinical advice suggests that given the lack of OS and progression events we can potentially expect the median OS to be at least 10 years or more.[4] Therefore, it is expected that HR for lorlatinib versus alectinib and brigatinib will improve once longer-term follow-up data becomes available.

Additionally, the high level of crossover (99%) from the crizotinib arm to the brigatinib arm in the ALTA-1L study following disease progression introduces further uncertainty into the OS NMA.[89] As discussed previously, there is a high proportion of subsequent therapies after crizotinib in each of the respective trials that are used in the NMA which are not adjusted for.

Furthermore, there was an imbalance in the percentage of patients with brain metastases at baseline between the trials used as CROWN had fewer patients with baseline brain metastases compared with ALEX, ALESIA and ALTA-1L.[7, 81, 86, 89] To address this, MAICs were conducted to compare lorlatinib (CROWN) versus alectinib (ALEX and ALESIA) and versus brigatinib (ALTA-1L).[99] These were conducted on the most recent CROWN data cuts available at the time (3 year data cut-off, September 2021) and gave very similar results to previously presented NMA results.[100] Matching was based on pre-specified effect modifiers, which were identified based on consultation with clinical experts, a targeted literature review, and a quantitative evidence assessment. The following two sets of effect modifiers were selected to balance precision with potential bias: 1) including most clinically important effect modifiers: Asian race, ECOG PS, and brain/CNS metastases at baseline, and 2) an expanded set comprising the variables included in the first matching set with the addition of prior chemotherapy and brain radiotherapy. Efficacy

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outcomes included PFS (by BICR and INV), objective response (OR), and time to progression in the central nervous system (TTP-CNS). Full methods are presented in Appendix N.

The MAICs showed that lorlatinib demonstrated superior PFS compared to alectinib (ALEX, PFS by INV: HR: 0.54 [95% CI: 0.33, 0.88]) and brigatinib (ALTA-1L, PFS BICR: HR, 0.60 [95% CI: 0.37; PFS by INV: HR: 0.51 [95% CI: 0.31, 0.82]).[99] Lorlatinib improved IC-TTP compared with brigatinib (HR: 0.20 [95% CI: 0.06, 0.69) and alectinib (ALEX: HR: 0.38 [95% CI: 0.10, 0.37]). These results are aligned with the NMA results presented in Section B.2.9.4 and Appendix N as well as those previously published, demonstrating that imbalances in percentage of brain metastases between trials did not greatly impact the results of the NMA.[100] These data also support lorlatinib use as a first-line treatment in ALK-positive advanced NSCLC.[99]

NMAs were deemed unfeasible due to limited data for intracranial time to progression (for the subgroups with and without brain metastasis) and endpoints related to EORTC QLQ C30.[100] Besides the evidence presented in this submission, 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.[100, 104-112] A review of all 10 NMAs found consistent results, demonstrating that the totality of evidence supports lorlatinib's benefit when compared with other ALK inhibitors.[100]

B.2.10. Adverse reactions

- Safety data from the safety analysis set of CROWN are presented from the October 2023 data cut-off[7]
- No new safety signals were detected after additional treatment exposure and longer follow-up[7]
- Median duration of treatment in the lorlatinib arm was 57.0 months (interquartile range [IQR]: 13.9–63.3) versus 9.6 months (IQR: 4.7–17.1) in the crizotinib arm[7]
- At least one dose reduction occurred in 49/149 (33%) lorlatinib patients and 36/142 (25%) patients treated with crizotinib[7]

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- Median relative dose intensity was 99% (IQR: 80–100) with lorlatinib and 99% (IQR: 91–100) with crizotinib[7]
- All-causality any grade AEs occurred in 100% lorlatinib patients and 99% crizotinib patients and all-causality Grade 3/4 AEs occurred in 77% of lorlatinib patients and 57% of crizotinib patients[7]
- Lorlatinib had a higher incidence of Grade 3 or 4 AEs, driven by higher rates of hypertriglyceridemia, hypercholesterolemia, weight gain and hypertension
- Dose reductions, temporary treatment discontinuation and permanent treatment discontinuations were similar between lorlatinib and crizotinib[7]
- Hyperlipidaemia at baseline or during treatment was higher in lorlatinib compared with crizotinib patients (134 versus 32 patients); however, frequency of cardiovascular AEs was higher in the crizotinib arm (38% versus 47%)[7]
- Patients treated with lorlatinib experienced a higher rate of CNS-related AEs (42%) compared with crizotinib, but 86% of them were of Grade 1 or 2 severity[7]
- Patients who experienced dose reductions in the first 16 weeks of treatment saw maintained efficacy of lorlatinib treatment[7]

Safety data from the safety analysis set of CROWN are presented from the October 2023 data cut-off.[7] A summary of adverse events (AEs) is presented in Table 30 and records of specific events are provided in Appendix M3. The safety profile of lorlatinib remains similar to that reported in previous analyses of the CROWN study, with no new safety signals detected after additional treatment exposure and longer follow-up.[7]

The median duration of treatment in the lorlatinib arm was 57.0 months (IQR: 13.9–63.3) compared with 9.6 months (IQR: 4.7–17.1) in the crizotinib arm.[7] At least one dose reduction occurred in 49/149 patients (33%) treated with lorlatinib and 36/142 (25%) treated with crizotinib. The median relative dose intensity was 99% (IQR: 80–100) with lorlatinib and 99% (IQR: 91–100) with crizotinib.[7]

All-causality any grade AEs occurred in all lorlatinib treated patients and 99% crizotinib treated patients and all-causality Grade 3 or 4 AEs in 77% of lorlatinib patients and 57% of crizotinib patients.[7] While lorlatinib had a higher incidence of Grade 3 or 4 AEs, driven by higher rates of hypertriglyceridemia (25% versus 0%),

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hypercholesterolemia (21% versus 0%), weight gain (23% versus 2%) and hypertension (12% versus 1%). Dose reductions (23% versus 15%), temporary treatment discontinuation (62% versus 48%) and permanent treatment discontinuations (11% versus 11%) were similar between lorlatinib and crizotinib patients showing that lorlatinib is generally tolerable with correct management techniques.[7]

At baseline or during treatment, 134 lorlatinib patients developed hyperlipidaemia compared to 32 in the crizotinib arm.[7] However, among those people with hyperlipidaemia, the frequency of cardiovascular AEs was lower with lorlatinib (37 of 134; 28%) than with crizotinib (15 of 32 patients; 47%). This was largely due to fewer occurrences of ischaemic heart disease and embolic and thrombotic events. Hyperlipidaemia is treatable with statins in normal clinical practice.[7]

Patients treated with lorlatinib experienced a higher rate of CNS-related AEs (42%) compared with crizotinib but 86% of them were of Grade 1 or 2 severity.[7] Of patients with CNS-related AEs, only three discontinued treatment permanently. A pragmatic guide for management of AEs with lorlatinib is now published which will also help to manage CNS-related AEs.[4, 113] UK clinicians have indicated that although for some patients lorlatinib may not be appropriate given this increased risk, for many the progression benefits (PFS and intracranial) of lorlatinib will outweigh the additional risks of CNS-related AEs and so there is a need for lorlatinib as an option in the first-line setting.[4]

Patients who experienced dose reductions in the first 16-weeks of treatment saw maintained efficacy of lorlatinib treatment (median PFS and median IC-TTP were not reached in patients given lorlatinib dose reductions, n = 18, Kaplan–Meier curves are presented in Appendix M3).[7] UK clinicians have commented that this is reassuring for clinicians and patients that opt for treatment with lorlatinib in first-line.[4]

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Table 30: Summary of adverse events in the CROWN safety analysis set, October 2023 data cut-off

Events	Lorlatinib (n = 149)	Crizotinib (n = 142)
All-causality AEs, No. (%)		
Any grade	149 (100)	140 (99)
Grade 3/4	115 (77)	81 (57)
Grade 5	14 (9)	7 (5)
Serious	65 (44)	45 (32)
Leading to temporary drug discontinuation	92 (62)	68 (48)
Leading to dose reduction	34 (23)	21 (15)
Leading to permanent drug discontinuation	16 (11)	15 (11)
Treatment-related AEs, No. (%)		
Any grade	145 (97)	133 (94)
Grade 3/4	99 (66)	55 (39)
Grade 5	2 (1)	0
Serious	14 (9)	9 (6)
Leading to temporary drug discontinuation	58 (39)	51 (36)
Leading to dose reduction	31 (21)	19 (13)
Leading to permanent drug discontinuation	8 (5)	8 (6)
Key: AE, adverse events. **Source:** Solomon et al. 2024.[7]		

B.2.11. Ongoing studies

The CROWN trial is still ongoing; the final study completion date is estimated to be in December 2028. Further OS analyses are planned when 70% and 100% of the OS events have occurred. No further trials for lorlatinib in this indication are ongoing.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Interpretation of clinical effectiveness and safety findings

Clinical efficacy of lorlatinib in first-line ALK-positive advanced NSCLC was demonstrated in the Phase III RCT CROWN study.[6, 7, 10]

Lorlatinib provides the longest-ever PFS reported in NSCLC and other solid tumours, with the median PFS not yet reached at 5 years.

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The CROWN trial has not only met its primary endpoint, showing a statistically and clinically significant improvement in PFS by BICR at 18 months compared with crizotinib[10], but has also shown the durability of the PFS benefit at 3 years[6] and 5 years.[7] PFS by INV at 5 years (BICR was stopped after 3 years) showed an 81% reduction in the risk of progression or death compared with crizotinib, and 5-year PFS rate of 60% (95% CI: 51 to 68) for lorlatinib versus 8% (95% CI: 3 to 14) for crizotinib.[7] With the median PFS not reached after 5 years of follow-up, lorlatinib has demonstrated the longest PFS ever reported for a single-agent targeted treatment in advanced NSCLC and across all metastatic solid tumours.[7]

In comparison, the median PFS for alectinib and brigatinib was between 31–35 months as shown in Kaplan–Meier curves in Figure 15.[81, 89] The 3-year rate of PFS for lorlatinib was 65%, compared with 46% and 43% for alectinib and brigatinib pivotal trials, respectively.[6, 7, 81, 89] Clinicians have also highlighted how the 5-year PFS per INV in the CROWN trial continues to demonstrate the superior PFS of lorlatinib versus second generation ALK inhibitors (alectinib and brigatinib).[4] This benefit is further supported by the results of the NMA in which lorlatinib demonstrated a 51% reduction in risk of progression or death (by INV) versus alectinib and a 56% reduction versus brigatinib (Section B.2.9.4); and previously conducted MAICs (Section B.2.9.5).[80, 99] Figure 15 also illustrates that the second generation ALK inhibitors have a similar survival and hazard profile to crizotinib, whereas the shape of the lorlatinib PFS Kaplan–Meier curve suggests a higher proportion of long or durable responders, which has been reinforced by the 5-year data.

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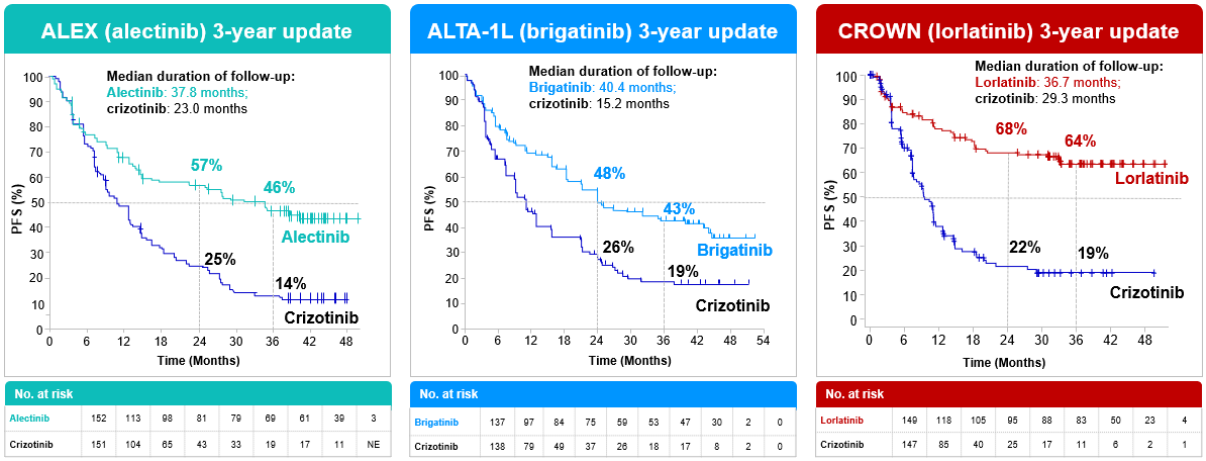
Figure 15: 3-year PFS by BICR Kaplan–Meier curves for pivotal trials of second and third generation ALK inhibitors in ALK-positive advanced NSCLC



Key: PFS, progression-free survival.
Source: Camidge et al. 2020; Camidge et al. 2021; Mok et al. 2020; Solomon et al. 2023.[6, 81, 89, 114]

Clinicians consider lorlatinib a highly efficacious alternative to the current sequence of a second generation ALK inhibitor followed by lorlatinib.

The most recent CROWN data suggest that many patients who start with first-line lorlatinib remain on treatment with an ALK inhibitor for longer than those receiving the current established treatment sequence of alectinib followed by lorlatinib in second-line, particularly given the attrition following treatment with a first-line ALK inhibitor either due to progression, discontinuation or death before receipt of a second-line treatment.[26, 51, 67] This is illustrated visually in Figure 16.[73, 81, 89, 114] The majority of consulted clinicians supported the view that if recommended by NICE, lorlatinib would be prescribed by significant numbers of clinicians because they would favour using the most effective ALK inhibitor upfront, in a position when time on treatment (ToT) for lorlatinib is maximised.[4]

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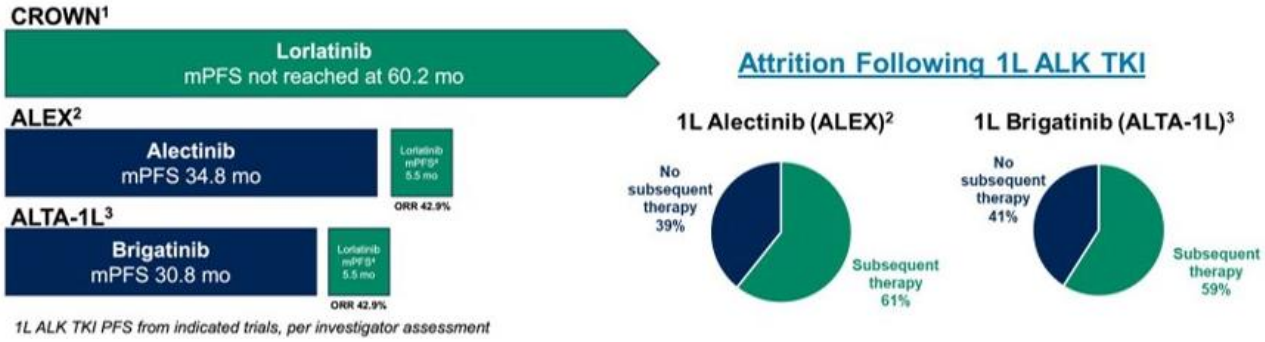
Figure 16: Length of mPFS for lorlatinib in CROWN compared to mPFS in key trials for alectinib and brigatinib including lorlatinib second-line treatment



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; [2.] Mok et al. 2020; [3.] Camidge et al. 2021; [4.] Felip et al. 2021; Solomon et al. 2024 ASCO presentation.[7, 73, 81, 89, 115]

The PFS benefit with lorlatinib is expected to translate into durable OS.

The OS data from CROWN remain immature as the number of deaths required for the final OS analysis has not yet been reached.[7] However, advice from UK clinicians suggests the lack of OS and progression events will potentially translate into a durable OS benefit, with a median OS expected to be longer than 10 years.[4] This is further supported by data from the 30 patients who did not receive prior ALK inhibitors, the EXP1 arm, in Study 1001 (showing 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%), and a pooled analysis of OS from CROWN and Study 1001 (Section B.2.8.1).[77] For context, in the Phase III ALEX study, at a median follow-up of 48.2 months, median OS was NR, with 5-year OS probability of 62.5% with alectinib.[81] In the final analysis of the Phase III ALTA-1L study, with a median follow-up of 40.4 months, median OS was also NR with 4-year OS probability of 66% with brigatinib (Figure 17).[89] In the ALESIA trial, where with median follow-up of 61 months, the median OS was NR and the 5 year OS rate was 66.4%.[85] These clinical trials reported either no OS improvement or an OS benefit as part of a descriptive post-hoc analysis not powered to show statistical significance compared with crizotinib. Also, the 4- and 5- year OS rates in these trials were similar to 4- and 5- year PFS rates reported at 5 years in CROWN for lorlatinib.[7]

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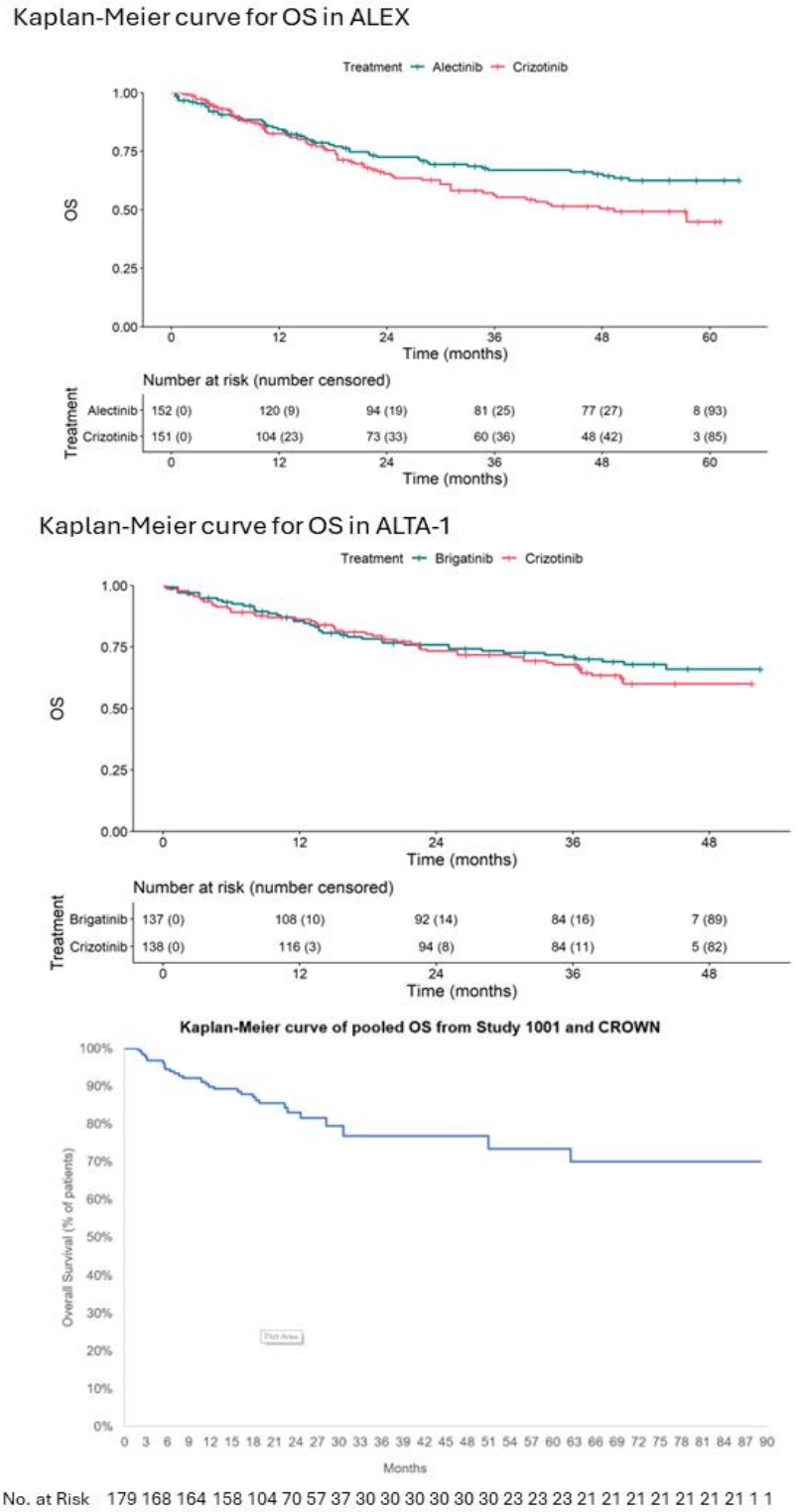
Figure 17: Kaplan–Meier OS curves for ALEX (top), ALTA-1 (middle) and pooled analysis of Study 1001 and CROWN (bottom)



Key: OS, overall survival.
Source: Camidge et al. 2021; Mok et al. 2020; Pfizer Inc., Data on File, 2024.[79, 81, 89]

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Lorlatinib shows durable responses in a high proportion of patients.

At 5 years in CROWN, objective response rate (ORR) by INV was 81% for lorlatinib compared with 63% for crizotinib, with the median DOR NR in the lorlatinib arm and 9.2 months in the crizotinib arm.[7] The percentage of patients with a response of ≥ 2 years was 74% for lorlatinib and 15% for crizotinib, and of ≥ 5 years, 26% for lorlatinib and 2% for crizotinib. These data show the long durability of responses to lorlatinib compared with crizotinib. Naïve comparison with the ALTA-1L trial for brigatinib shows lorlatinib has an improved probability of maintaining response at 2 years (74% versus 55%) and 4 years (60% versus 40%), and longer median DOR compared with brigatinib (NR with a median follow-up of 60 months versus 33.2 months with a median follow-up of 40 months).[7, 89] Long-term follow-up of ORR and DOR for the ALEX trial of alectinib versus crizotinib is not available.

Lorlatinib's high CNS efficacy was maintained, showing effective targeting of existing brain metastases and prevention of new brain metastases.

Lorlatinib was specifically designed to cross the blood–brain barrier and target brain metastases. Data from CROWN show that lorlatinib can both effectively target pre-existing brain metastases and prevent development of new metastases.[6, 7, 10] At the 5-year follow-up, 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.[7] 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. 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 (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. The NMA further

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supported lorlatinib, showing a 61% and 80% reduction in the risk of intracranial progression compared with alectinib and brigatinib, respectively.[80]

Lorlatinib has a manageable safety profile.

Safety analysis in CROWN showed that lorlatinib had a higher rate of all-causality Grade 3 or 4 AEs compared with crizotinib (77% versus 57%); however, rates of dose reductions and temporary or permanent discontinuation were similar between the two arms of the trial, and dose reductions in the first 16 weeks of lorlatinib treatment had no impact on efficacy (see Section B.2.10).[7] UK clinicians advised that many AEs associated with lorlatinib are manageable in clinical practice and that a pragmatic guide for management of AEs associated with lorlatinib has already been published and will further aid clinical management of lorlatinib's AEs.[4, 113]

Lorlatinib would be the only third generation ALK inhibitor available in first-line, offering better CNS penetration and greater coverage of ALK resistance mutations than second generation ALK inhibitors.

Lorlatinib is a brain-penetrant, third generation ALK inhibitor that has greater coverage of ALK resistance mutations than second generation ALK inhibitors such as alectinib.[8-10] Acquired resistance to ALK TKIs limits the durability of responses in patients with ALK-positive advanced NSCLC.[27-29] Data from CROWN's 5-year analysis show that of the 31 patients who had their DNA sequenced at the end of treatment, none had developed new ALK resistance mutations compared with 10/82 crizotinib treated patients, supporting data from the earlier 3-year analysis that indicated that no emerging new ALK resistance mutations were detected in circulating tumour DNA.[7, 116]

With long-term follow-up, the median PFS with lorlatinib was 60.0 months in EML4::ALK variant 3a/b subgroup and 51.6 months in TP53 mutation-positive subgroup. In the ALEX trial, the median PFS with alectinib was 17.7 months for patients with *EML4::ALK* variant 3.[83] In the ALTA-1L trial, the median PFS with brigatinib was 16.0 months in patients with *EML4::ALK* variant 3 and 18.0 months in those with TP53 mutation.[89] The results from this study emphasise that lorlatinib treatment can benefit patients with poor prognostic biomarkers or difficult to treat

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alterations such as *EML4::ALK* variant 3 or TP53 co-mutation relatively more than the second generation ALK TKIs.

B.2.12.2. Overall assessment of the clinical evidence base

B.2.12.2.1. Internal validity of CROWN

As discussed in Section B.2.5, the CROWN trial was methodologically robust, well-reported and considered to be at low risk of bias[75, 78]:

- Participants were appropriately randomised and treatment allocations were concealed
- The sample size was sufficient to detect a difference in the primary outcome of BICR-assessed PFS
- Treatment groups were similar at the outset of the study in terms of prognostic factors
- Patient flow through the study was well-reported and there were no unexpected imbalances in drop-outs between treatment groups. In the lorlatinib arm, there was a 7.4% discontinuation rate due to AEs compared with 9.2% in the crizotinib arm. A further 4.7% and 7.0% of patients withdrew from the study in the lorlatinib and crizotinib treatment arms, respectively[7]
- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis and preserving randomisation
- UK clinicians confirmed that CROWN was generally well-designed[4]

B.2.12.2.2. External validity of CROWN

UK clinicians stated that despite some slight imbalances in ethnicity, demographics were generally similar to that expected of patients with ALK-positive NSCLC in the UK.[4] Subgroup analysis of the primary endpoint and PFS by INV of CROWN shows that lorlatinib provides an efficacy advantage at the 18-month, 3-year and 5-year data cut-offs, regardless of race (Asian/non-Asian) or other patient characteristics (see Appendix E).[6] Therefore, the CROWN study population is generalisable to the population of England and Wales.

Broadly, subsequent treatments in the lorlatinib arm of the CROWN trial are reflective of clinical practice in England and Wales. However, of patients who had

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progressive disease, 6.5% of patients in lorlatinib arm received subsequent treatment with lorlatinib, 26.1% with alectinib and 2.2% with brigatinib, which is not aligned with UK clinical practice (Table 25). This 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 consultations with experts suggested that this would have a limited bias on OS given that the second generation ALK inhibitors were not designed to be used after lorlatinib, given its status as a third generation inhibitor and greater coverage of ALK resistance mutations.[4, 117]

The NMA findings presented in this submission are supported by the results of 10 published NMAs, nine of which were independently published, in which lorlatinib demonstrated either significantly or numerically better PFS compared with second generation ALK inhibitors in the ITT population and across pre-specified subgroups (all using 18-month or 36-month CROWN data).[100, 104-112]

B.2.12.3. Conclusion

Overall, lorlatinib is a highly effective and tolerable treatment for first-line ALK-positive advanced NSCLC.

Findings from CROWN and the NMA show that lorlatinib provides impressive improvements in PFS for patients with ALK-positive advanced NSCLC compared with the current options for first-line treatment.[6, 7, 10] In fact, at the 5-year follow-up of CROWN, lorlatinib provides the longest PFS ever observed for a single targeted agent in any solid tumour trial. 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.[6, 7, 10]

Taken together, this submission demonstrates that lorlatinib provides considerable benefits over second generation ALK inhibitors and should be available as a first-line treatment option for people with ALK-positive advanced NSCLC.

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B.3. Cost-effectiveness

- A three-state partitioned survival model was developed to evaluate the cost-effectiveness of lorlatinib versus brigatinib and alectinib in untreated ALK-positive NSCLC
- The effect of CNS progression was modelled as an intercurrent event that accrues a one-off cost and utility effects
- Parametric curves were fitted to lorlatinib and crizotinib PFS data independently. Additionally, piecewise models were implemented for lorlatinib to better capture its unique PFS features (36-month piecewise Weibull curve was selected for the base case) with 10-year waning to take account of long-term uncertainty
- To overcome the immaturity of CROWN OS data, the Kaplan–Meier data were pooled with study 1001 EXP1, which is unlikely to introduce biases based on comparable baseline characteristics and subsequent therapies
- A standard partitioned survival model (PSM) approach was used to extrapolate lorlatinib OS. A pseudo state transition approach was applied to the model comparators to account for the confounding effect introduced by subsequent therapies in the trials
- Treatment specific PFS utilities were applied in the model. Utility values for brigatinib and alectinib were sourced from their NICE appraisals.[20, 50] Common progressed disease utilities across arms were used based on the brigatinib NICE appraisal (TA670).[20] Utility adjustments were applied to account for the deterioration in HRQL as a patient gets older, and the impact of adverse events (AEs) and CNS progression on HRQL
- Due to the non-linear nature of the model, a probabilistic incremental cost-effectiveness ratio (ICER) is preferred for decision making, and per the NICE methods guide
- In the base case analysis, lorlatinib was associated with a probabilistic ICER of £15,558 per quality-adjusted life year (QALY) gained vs alectinib and £20,421 per QALY gained vs brigatinib

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B.3.1. Published cost-effectiveness studies

An SLR was conducted in August 2018 and updated in November 2019 to identify any published literature on relevant economic analyses of treatments for patients with untreated ALK-positive advanced NSCLC. Full details of the methods and results of published economic evaluations included in the previous SLR are presented in Appendix G. Although the clinical SLR was fully updated on 27 February 2024, the cost-effectiveness SLR was not updated due to the very low probability that an alternative cost-effectiveness analysis related to lorlatinib had been published since that time.

A de novo cost-utility analysis has been conducted for the purpose of this appraisal and is described below.

B.3.2. Economic analysis

B.3.2.1. Patient population

The model evaluates the use of lorlatinib in patients with untreated ALK-positive advanced NSCLC; that is, as a first-line treatment. The licence for lorlatinib relevant to this appraisal is for patients who have not received a prior ALK inhibitor and is consistent with the eligibility criteria for the CROWN trial (i.e. the CROWN trial allowed no previous systemic treatment).

B.3.2.2. Model structure and features

A three-health state partitioned survival model (PSM) was developed to assess the cost-effectiveness of lorlatinib versus relevant comparators in untreated ALK-positive NSCLC, as presented in Figure 18. All patients enter the model in the progression-free state, receiving lorlatinib or comparator treatment. Patients may remain progression-free, their disease may progress or they may die. Patients whose disease has progressed can remain alive with progressed disease or die. Death is an absorbing state.

In the model, the alive health states are further divided into on and off treatment periods, to capture treatment acquisition and administration costs more accurately. The model can allow patients to discontinue treatment before progression (i.e.

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progression-free off treatment), while some patients may receive treatment beyond progression (i.e. progressed on treatment).

Lorlatinib was designed to cross the blood–brain barrier to achieve high exposures in the CNS, and given the most recent cut-off data, it is considered to be the most effective ALK inhibitor for CNS disease control by clinicians.[4] A four-state structure has recently been used in the NICE technology appraisals in first-line ALK-positive NSCLC for brigatinib (TA670) and alectinib (TA536), as these second generation ALK inhibitors are considered to have intracranial activity and an impact on intracranial progression.[20, 50] However, as discussed in the previous lorlatinib appraisal (TA909), the four-health state model can have limitations.[1] In short, the reported CNS endpoint used for modelling – IC-TTP – could not capture CNS progressions in relation to the systemic/clinical progression status of patients in a way consistent with the intended model transitions, often leading to spurious results.

Clinicians at the advisory board strongly endorsed a simple way to model the additional costs and QoL implications of brain metastases, given their importance to clinical practice and patient experience.[4] In line with this, intracranial progressions are modelled within the three-health state structure as intercurrent events that incur utility decrements and one-off costs, not in a dissimilar way to AEs. This is informed by the IC-TTP NMA (Section B.2.9.4.3) and is applied in modelling in a way consistent with the definition of this endpoint. This approach and any limitations are discussed in Section B.3.3.6.

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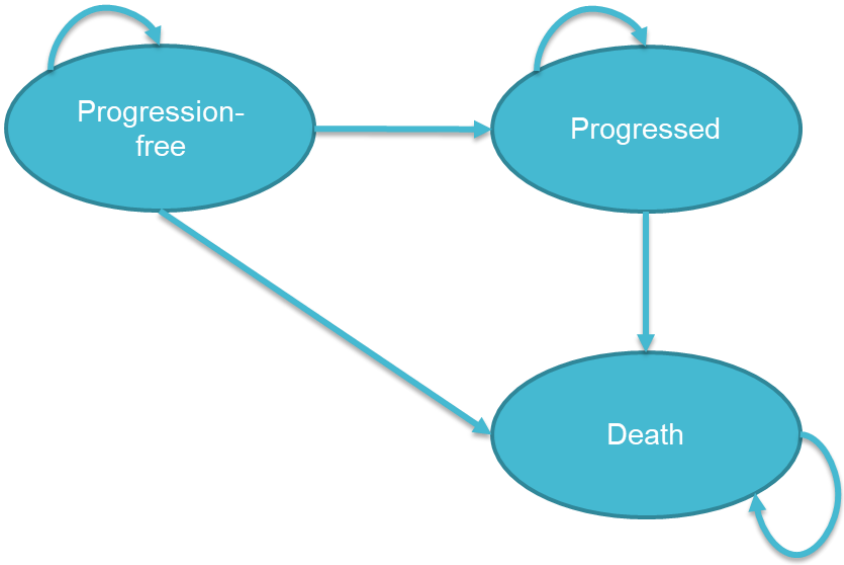
Figure 18: Three-state model structure



Health state membership is determined using a PSM. The alternative approach of a pseudo state transition approach to model post-progression survival (PPS) is retained from the previous appraisal as an option. In the base case, the lorlatinib arm employs the partitioned survival approach in full, whereas the comparator arms employ the state transition approach to model PPS, given the mismatch between subsequent treatments in the comparator trials and lorlatinib second-line use in real-world practice (see B.2.9.2.4 and Table 25).

To inform the PSM, parametric curves were fitted to OS, PFS, and ToT data, for lorlatinib and crizotinib. Parametric survival models are used to extrapolate outcomes beyond the observed data for a lifetime horizon. The ‘standard’ selection of parametric models were fitted, in line with NICE Decision Support Unit guidance.[118] Additionally, advanced survival analysis approaches to model lorlatinib PFS were considered in line with TSD21 (see Section B.3.3.2.1).[119]

Table 31 defines the clinical endpoints used in parametric survival modelling to inform the cost-effectiveness analysis, while Table 32 describes the area-under-the-curve approach used to determine health state occupancy at any given time point, T.

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Table 31: Clinical endpoint definitions

Endpoint	Definition
OS	Defined as the time from date of randomisation to the date of death due to any cause.
PFS	• PFS was defined as the time from randomisation to the date of the first documentation of progressive disease per RECIST v1.1, as assessed by either investigator or an independent radiologist (BICR), or death due to any cause, whichever occurred first • PFS based on INV (5-year data) was considered in the model as the base case • PFS based on BICR was not available at the October 2023 data cut-off. An estimate of the PFS BICR based on the hazard ratio of PFS by BICR versus the PFS by investigator assessment at the September 2021 data cut-off was explored in the scenario analyses
ToT	ToT was defined as the time from first treatment exposure to last treatment exposure. Events occurred when patients finish treatment, and patients were censored if they were still on treatment at data cut-off

Key: CNS, central nervous system; INV, investigator assessment; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours; ToT, time on treatment.

Table 32: Health state occupancy

Health state	Occupancy at time *T*
Progression-free on treatment	Min (PFS^T, ToT^T)
Progression-free off treatment	Max (0, PFS^T minus ToT^T)
Progressed on treatment	Max (0, ToT^T) minus PFS^T)
Progressed off treatment	OS^T minus Max (PFS^T, ToT^T))
Death	1 minus OS^T

Key: Max, maximum; Min, minimum; OS, overall survival; PFS, progression-free survival; T, time; ToT, time on treatment.
Notes: The PFS, and ToT curves in the model are capped to be less than OS at any given time.

B.3.2.2.1. Perspective

The economic model was developed from the perspective of the National Health Service (NHS) and Personal Social Services in England and Wales, with only direct health costs considered in the base case analysis.

B.3.2.2.2. Time horizon and cycle length

A lifetime time horizon of 30 years was considered in the base case analysis. Based on the mean baseline age of 57.4 years observed in the CROWN study, which was used as the starting age in the model, the maximum modelled cohort age is 87 years and after 30 years, less than 5% of patients remained alive across all treatment

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arms. All recent NICE appraisals in first-line ALK-positive NSCLC have used lifetime horizons (ranging from 10 to 30 years).[20, 50]

A cycle length of 30 days was used, as this was deemed to adequately capture transitions and reflect changes in health, whilst also aligning with the 30-day pack size for lorlatinib. A half-cycle correction is applied to all costs and outcomes other than first-line drug and administration costs (which are assumed to be incurred at the start of each cycle). Pill 'wastage' is accounted for the alectinib and brigatinib as lorlatinib treatment cycle matches the model cycle length.

B.3.2.2.3. Discounting

A discount rate of 3.5% per annum is applied to costs and quality-adjusted life years (QALYs) (using a per cycle discount factor) as per NICE requirements.[120]

B.3.2.2.4. Features

The features of the economic model are described in Table 33, which includes a comparison between the economic model in this submission and the models used to inform previous appraisals in untreated ALK-positive advanced NSCLC.

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Table 33: Features of the economic analysis

	Previous evaluations					Current evaluation	
	Crizotinib (TA406)	**Ceritinib (TA500)**	**Alectinib (TA536)**	**Brigatinib (TA670)**	**Lorlatinib (TA909)**	**Chosen values**	**Justification**
Model structure	Standard PSM	Standard PSM	Standard PSM	Standard PSM	Standard PSM	Standard PSM for lorlatinib and pseudo state-transition for comparators	To address the mismatch between subsequent treatments in comparator trials and clinical practice
Time horizon	15 years	20 years	30 years	30 years	30 years	30 years	To ensure the analysis captures all relevant differences in costs and outcomes between the medicines being compared, as per the NICE reference case
Treatment waning effect?	None applied	Scenario analyses explored the same progressive disease survival for ceritinib as crizotinib	Scenario analyses capped OS and PFS treatment effect duration at 3, 5, 7 and 10 years	Scenario analyses assume same mortality rate after 7, 10 and 20 years.	Treatment effect waning at 10 years	PFS and OS treatment effect waning at 10 years	In line with previous appraisal and committee preference and uncertain long-term survival outcomes

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Source of utilities	The company estimated health state utilities from PROFILE 1014 for progression-free disease with crizotinib or with chemotherapy. The company estimated utility values for the progressed disease state in the second-line (treatment with docetaxel) and for third-line treatment (with best supportive care) from PROFILE 1007 and Nafees et al. 2008, respectively.[121]	Utility values for the progression-free health state was estimated using data from ASCEND-464 for ceritinib and for crizotinib, PROFILE 1014 (Solomon et al. 2014).[55] Values for the progressed disease health states were derived from Chouaid et al. (2013).[122]	ALEX for progression-free disease and non-CNS progression. Peters et al. (2017)[84] and Roughley et al. (2014) for CNS progression.[42]	Health state utilities for the pre-progression health state and progressed disease on treatment with an ALK inhibitor are derived from the ALTA-1L mapped utility values (mapped from EORTC QLQ-C30 to EQ-5D-3L). Multipliers from the literature are applied to these utility values to estimate HRQL for CNS progression, progressed disease receiving chemotherapy and progressed disease receiving BSC. The literature includes: Peters et al. (2017)[84] and Roughley et al. (2014)[42]	Submitted with CROWN-trial-derived utilities. Committee preferred health state utilities derived from brigatinib (TA670). Age-adjusted utility values have been incorporated into the model.	Treatment specific utilities for progression-free from respective treatments pivotal trials (as in TA536 and TA670).[6, 20, 50] Progressed utility values treatment independent and derived from brigatinib (TA670).[20] Age adjustment of utility values has been incorporated into the model.	Agree that progressed utilities from CROWN are uncertain. However, treatment specific PFS utilities are the norm in NSCLC appraisals and help capture different treatment characteristics during progression-free health state. Progression-free utilities based on CROWN and previous appraisals. Progressed utilities based on brigatinib submission (TA670). One-off CNS progression disutility based on Roughley et al. (2014).[38,42]

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	Previous evaluations					Current evaluation	
	Crizotinib (TA406)	**Ceritinib (TA500)**	**Alectinib (TA536)**	**Brigatinib (TA670)**	**Lorlatinib (TA909)**	**Chosen values**	**Justification**
				(for CNS progression), PROFILE 1007 (for chemotherapy in progressed disease) and Nafees et al. (2008)[121] (for BSC in progressed disease).			

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	Previous evaluations					Current evaluation	
	Crizotinib (TA406)	**Ceritinib (TA500)**	**Alectinib (TA536)**	**Brigatinib (TA670)**	**Lorlatinib (TA909)**	**Chosen values**	**Justification**
Source of costs	Drugs costs from MIMs and eMIT. Resource use and adverse events were based on TA296,[123] TA162,[124] TA188,[125] TA181[126] and TA258[127] and costed using NHS Reference Costs and PSSRU. Cost year: 2014/2015.[128]	Resource use and adverse events were based on TA406,[53] TA296,[123] TA162,[124] TA181[126] and TA258[127] and costed using NHS Reference Costs, PSSRU. Cost year: 2015/2016.[128]	Drugs costs from BNF. Resource use derived from TA406 and updated and/or validated by clinical experts. Resource use and AEs costed using NHS Reference Costs and PSSRU. Cost year: 2014/2015/2016.[128]	Drug costs from BNF. Resource use derived from TA536 and updated and/or validated by clinical experts. Resource use and AEs costed using the NHS Reference Costs and PSSRU. Cost year: 2018/2019.[128]	Drug costs from MIMS and eMIT. Resource use derived from TA536[50] and TA670[20] and updated and/or validated by clinical experts. Resource use and AEs costed using the NHS Reference Costs and PSSRU. Cost year: 2019/2020.[128,129]	Drug costs from MIMS and eMIT. Resource use derived from TA536[50] and TA670[20] and updated and/or validated by clinical experts. Resource use and AEs costed using the NHS Reference Costs 2021/2022 cost year and PSSRU. 2023.[128,129] CNS progression costs sourced from Le et al. (2024) which is endorsed by clinical opinion and co-authored by a UK clinician.[47]	To ensure the analysis captures all relevant costs for these treatments in this indication, as per the NICE reference case.

Key: AE, adverse event; ALK, anaplastic lymphoma kinase; BNF, British National Formulary; BSC, best supportive care; CNS, central nervous system; eMIT, electronic market information tool; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol Five Dimensions 3 Levels; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; MIMS, Monthly Index of Medical Specialities; HRQL, health-

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	Previous evaluations					Current evaluation	
	Crizotinib (TA406)	**Ceritinib (TA500)**	**Alectinib (TA536)**	**Brigatinib (TA670)**	**Lorlatinib (TA909)**	**Chosen values**	**Justification**
related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.							

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B.3.2.3. Intervention

As previously discussed, the intervention is the third generation ALK small molecule inhibitor, lorlatinib. Clinical data for lorlatinib used in the model (safety, efficacy, and HRQL) were primarily sourced from the Phase III randomised trial, CROWN.[6, 7, 10]

The recommended dose of lorlatinib is 100 mg administered orally once daily. Treatment is recommended for as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity, including beyond progression.[2]

B.3.2.4. Comparators

As discussed in Section B.1.3.5.1, ceritinib and crizotinib are rarely used in untreated ALK-positive patients in UK clinical practice, with most patients in this setting anticipated to receive either alectinib or brigatinib. Therefore, alectinib (600 mg BID) and brigatinib (180 mg once daily) represent the primary comparators of interest in this evaluation and as such were both considered in the cost-effectiveness analysis. However, alectinib is considered the main comparator due to majority market share (around 80%) in the UK, as verified by UK clinical experts, and brigatinib is considered a minor comparator and presented for completeness.[4, 5] Clinical evidence for both alectinib and brigatinib were informed by the NMA described in Section B.2.9.

B.3.3. Clinical parameters and variables

B.3.3.1. Baseline characteristics

Baseline characteristics are presented in Section B.2.3.3. Table 34 describes how the baseline characteristics are used on the economic modelling.

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Table 34. Impact of baseline characteristics on the model

Baseline characteristic	Impact on the model
Age	• Background mortality • Age-adjusted utility values
Baseline utility	Utility regression
Weight	BSA calculation for pemetrexed and cisplatin dose
Height	BSA calculation for pemetrexed and cisplatin dose
% male	• Background mortality • Age-adjusted utility values
% with baseline brain metastases	Utility regression

Key: BSA, body surface area.

B.3.3.2. Approach to extrapolation and NMA

B.3.3.2.1. Extrapolation

The primary source of efficacy data for lorlatinib and comparators in the patient population relevant to this submission was the CROWN trial and the NMA. OS, PFS and ToT Kaplan–Meier curves and NMA results are presented in Section B.2.6 and B.2.9.4, respectively.[6, 7, 10]

To allow for the potential violation of the proportional hazard assumption within the CROWN trial (see Section B.2.9.3), independent parametric survival curves were fitted to time to event endpoints to inform efficacy in the lorlatinib and crizotinib arms of the model.

For alectinib and brigatinib, given that there was no clear evidence that the proportional hazards assumption was violated in the ALEX, ALESIA and ALTA-1L trials (see Section B.2.9.3), a hazard ratio from the NMA (see Section B.2.9.4) was applied to parametric survival curves fitted to the crizotinib treatment arm from the CROWN trial.

In the model base case, curve selection has largely been driven by the clinical plausibility of long-term extrapolations in contrast to the relatively higher certainty of extrapolated proportions closer to observed CROWN Kaplan–Meier data. In addition, consistency with clinical validations from previous NICE appraisals in first-line ALK-positive NSCLC were also captured. Consistency of extrapolations across correlated modelled endpoints (e.g. OS versus PFS), between treatment arms and statistical

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goodness-of-fit to the observed data were also considered (although, as previously discussed, OS data from CROWN were considered immature).

Impact of additional 5-year PFS data

The additional October 2023 PFS data cut reinforced the view among clinicians that lorlatinib is undoubtedly the best ALK inhibitor at preventing clinical progression in patients.[4, 5] Lorlatinib represents a step change in progression expectations in the treatment of ALK-positive NSCLC. Most of the censoring (70/94 patients) occurred at the end of the observed 5-year Kaplan–Meier curve and was due to no progression/death events having occurred, so the unusually long tail may persist for some time. As in TA909, standard parametric models fit the mature crizotinib PFS data well.[1]

As expected, the impact of the additional two years of investigator assessed lorlatinib PFS data has the impact of shifting the standard parametric fittings upwards in comparison to the fittings at the September 2021 data cut (presented in TA909[1]). For example, the exponential curve was selected as the least implausible of the parametric fittings in TA909 and gave a 60-month PFS proportion of 46.5% (with a slightly lower implied median). This is unlikely to be plausible given the new five-year data cut that suggests a 60% PFS proportion at 60-months (and implied higher median). In contrast, the updated exponential curve gives a 60-month PFS proportion of 57% and median just above 71 months (i.e. around 6 years) which is more plausible but may still underfit the observed tail. As discussed below, clinicians suggested this may well be a short-term underestimate and so alternative functions and survival methods are explored below. As in TA909, longer-term extrapolations (i.e. more than 10 years) remain highly uncertain and so treatment effect waning is applied in line with previous appraisals (including TA536 and TA670) in ALK-positive advanced NSCLC. [20, 50] However, given that median PFS has not been reached after a median follow-up of 60 months, earlier waning scenario of 3 and 5 years were not considered plausible for lorlatinib. Therefore, 10-year waning is retained in the base case based on the previous (TA909) appraisal committee preferences[1] and other timepoints are tested in scenario analyses.

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Alternative survival extrapolation approaches

A number of alternative and advanced survival analysis approaches to model lorlatinib PFS were considered in line with TSD21.[119]

- A mixture cure model was discussed with clinicians at the advisory board organised by the company.[1] Clinicians believed this model was unlikely to be appropriate for metastatic NSCLC given that none or very few patients (including durable responders) are likely to have survival consistent with the general population
  - A variant of this approach with a more realistic relative survival applied for durable responders was considered, but it would not be possible to find long-term external data on lorlatinib progression and survival
- More flexible spline models were explored and fit to 5-year PFS data: proportional hazards, proportional odds and inverse normal distribution of survival models. Fifteen spline models with variable knots (1 to 5) produced relatively tight extrapolations that overestimated lorlatinib PFS in a similar way to the standard generalised gamma function and so was not deemed useful for modelling
- Response conditional survival models for PFS were explored, but these posed a challenge given that by the 5-year landmark point there are very few non-responders in the lorlatinib arm and so the weighted model is driven by the large number of responders giving not dissimilar results to more unrealistic standard parametric models
  - A more flexible approach that uses latent trial observations to determine responder/non-responder status over time was tested, however this did not resolve the issue of weighting
- Finally, piecewise models were implemented in which the PFS Kaplan–Meier curve is modelled until a timepoint at which standard parametric curves are fitted. The two timepoints explored produced several extrapolations to consider in line with standard parametric models
  - A 23 month cut point was considered given that hazards of PFS are almost linearly decreasing up to around 24 months and then the rate of decrease slows, which aligns with the flattening in the Kaplan–Meier curve around 24 months (Appendix J.3.1 Figure 1). Only two non-responders remain in pre-

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progression at 24 months, and they are censored after 50 months; before this the last non-responder to have a PFS event experiences it at around 22 months, which again supports a shift in hazard

- A 36-month cut is also considered, given another slowdown in hazards which again reflects the PFS Kaplan–Meier

In summary, in addition to the standard parametric functions, the piecewise functions were also explored (Appendix J). The crizotinib PFS Kaplan–Meier is very mature and so standard parametric functions suffice.

The company also explored fitting piecewise models to OS but this did not add any value over standard approaches (Appendix J). This is because the challenge with OS is immaturity rather than with a unique observed hazard profile that limits the applicability of standard parametric survival approaches (i.e. trade-off between fitting the observed data and long-term plausibility). Instead, to overcome the immaturity of the OS data, the CROWN Kaplan–Meier data was pooled with the Study 1001 cohort EXP1 (Section B.2.8.1). The EXP1 cohort (N=30) includes ALK-positive patients with first-line lorlatinib. CROWN and EXP1 include lorlatinib patients with similar baseline characteristics and subsequent therapies.[77] Pooling both populations provides a longer follow-up (90 months). The impact of pooling moderately increases the survival predictions of the standard parametric fittings versus the CROWN only fittings.

B.3.3.2.2. ***NMA***

HRs for comparators versus baseline (crizotinib) produced by the NMA (Section B.2.9.4) were applied to baseline crizotinib to predict outcomes for each comparator.

Crossover was permitted after progression from crizotinib to brigatinib in ALTA-1L. However, the crossover adjusted NMA HRs for overall survival were not considered in the cost-effectiveness model given that they were considered highly uncertain during the brigatinib appraisal (TA670). The crizotinib arm of all the trials that inform the OS NMA presented in Section B.2.9.4.2 have high proportions of subsequent systemic anti-cancer therapy and, in particular, ALK inhibitor use, so adjustment in one node would bias the NMA results (Table 25).

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This approach of utilising an independent model (for lorlatinib) and HRs applied to crizotinib (for alectinib and brigatinib) allowed the incorporation of both proportional and non-proportional hazards across studies, whilst maintaining CROWN as the reference study. This approach also respects the relatively unique hazard profile of lorlatinib compared to the 2nd generation ALK inhibitors and crizotinib, which is reflected in the unique shape of the PFS curve (Section B.2.9.3 and Figure 17).

B.3.3.3. Progression-free survival

Parametric curves were fitted to lorlatinib and crizotinib PFS data independently. Jointly fitted curves are included in the model as retained settings. Additionally, a 23 and 36 month piecewise approach is presented for lorlatinib.

The model includes the functionality to model either PFS assessed by BICR or PFS assessed by an investigator (INV). However, the October 2023 data cut does not include PFS BICR. Therefore, PFS based on INV was selected as the base case analysis. An alternative analysis is provided using the hazard ratios of PFS INV vs PFS BICR from the September 2021 data cut to derive proxy 5-year PFS BICR fittings (see Section B.3.3.3.1).

The resulting PFS extrapolations based on INV assessment of PFS are presented for lorlatinib standard parametric curves, and lorlatinib 23-month piecewise, lorlatinib 36-month piecewise and crizotinib standard parametric curves in Figure 19, Figure 20, Figure 21 and Figure 22, respectively. The fit statistics are presented in Table 35, Table 36, Table 37 and Table 38.

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Figure 19: INV assessed PFS for lorlatinib – standard parametric curves

Key: BICR, blinded independent central review; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.

Figure 20: INV assessed PFS for lorlatinib – 23 months piecewise

Key: BICR, blinded independent central review; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.

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Figure 21: INV assessed PFS for lorlatinib – 36 months piecewise

Key: BICR, blinded independent central review; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.

Figure 22: INV assessed PFS for crizotinib

Key: BICR, blinded independent central review; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.

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Table 35: Fit statistics of INV assessed PFS extrapolation – lorlatinib standard parametric curves

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	623.98	7	626.98	7
Generalised gamma	600.00	1	609.02	2
Gompertz	602.60	2	608.61	1
Log-logistic	607.92	4	613.93	4
Log-normal	603.58	3	609.59	3
Weibull	610.96	5	616.97	5
Gamma	612.75	6	618.76	6
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BICR, blinded independent central review; INV, investigator; PFS, progression-free survival.				

Table 36: Fit statistics of INV assessed PFS extrapolation – lorlatinib 23 months piecewise

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	170.93	1	173.46	1
Generalised gamma	172.92	7	177.98	6
Gompertz	172.78	4	180.38	7
Log-logistic	172.90	6	177.97	5
Log-normal	172.76	3	177.82	3
Weibull	171.88	2	176.95	2
Gamma	172.80	5	177.87	4
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BICR, blinded independent central review; INV, investigator; PFS, progression-free survival.				

Table 37: Fit statistics of INV assessed PFS extrapolation – lorlatinib 36 months piecewise

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	83.86	1	86.26	1
Generalised gamma	84.78	5	89.57	5
Gompertz	85.61	7	92.79	7
Log-logistic	84.72	3	89.51	3
Log-normal	84.74	4	89.53	4
Weibull	84.42	2	89.21	2
Gamma	85.31	6	90.10	6
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BICR, blinded independent central review; INV, investigator; PFS, progression-free survival.				

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Table 38: Fit statistics of INV assessed PFS extrapolation – crizotinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	862.19	6	865.18	5
Generalised gamma	829.27	2	838.24	3
Gompertz	855.00	4	860.98	4
Log-logistic	825.80	1	831.78	1
Log-normal	830.74	3	836.72	2
Weibull	863.98	7	869.96	7
Gamma	860.96	5	866.94	6

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BICR, blinded independent central review; PFS, progression-free survival.

An overview of the modelled PFS at key time points for lorlatinib and crizotinib is presented in Table 39, Table 40, Table 41 and Table 42. Three one-to-one survival validation sessions with clinicians indicated a broad consensus that selected curves should be consistent with the observed 60% PFS at 60 months (5 years) and that based on this, a median PFS of around 8 years is entirely plausible which should be considered in curve selection.[117]

Clinicians considered the long-term projections of the 23-month piecewise fittings to be more plausible than standard parametric, however even the most conservative of these gave projections of >15% at 30 years and so were deemed implausible. Of the 36-month piecewise only the gamma and Weibull were considered to be clinically plausible, with a slight preference for the Weibull. However, even considering these clinicians suggested there was great uncertainty about lorlatinib PFS over the very long-term given the unprecedented progression data, which is why waning has been retained in the base case.

Therefore the 36-month piecewise Weibull curve was selected for the lorlatinib base case as this curve represents the second-best statistical fit to observed data combined with plausible long-term extrapolation for lorlatinib compared with the other curves, which are likely to be clinically implausible (> 13% alive and progression-free after 30 years). This selection also gives a median PFS of just under 8 years which is consistent with clinical opinion. The 36-month piecewise gamma curve is also considered plausible, but it leads to extrapolations above the equivalent parametric

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OS during most of the time horizon. The standard exponential curve was not considered because clinicians suggested it is too conservative during the early months, especially at the median (6.1 years) and 5-year points with an overall poor fit to observed data: overestimating PFS and then crossing the CROWN PFS curve around 50 months.

For consistency, the Weibull curve was also selected for crizotinib. Although the Akaike information criterion (AIC)/Bayesian information criterion (BIC) suggested the log-logistic curve was the best fit to the observed data, the choice of survival extrapolation does not have a large impact on the survival estimate as Kaplan–Meier PFS data were more complete (≤ 1% of patients alive and progression-free at 10 years across all curves except for generalised gamma and Gompertz which were not considered plausible by clinicians). The log-logistic is tested in scenario analyses.

In general, PFS long-term projections are considered highly uncertain especially after 10 years and so treatment waning is applied, in line with the preference from the previous committee meeting (TA909).[1] All treatment hazards are waned down to the base crizotinib hazards after year 10 in the model.

Table 39: Proportion of patients alive and progression-free INV assessed at key time points – lorlatinib standard parametric curves

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
	12 months	60 months	120 months	180 months	240 months	360 months
Exponential	89.4%	56.9%	32.1%	18.1%	10.2%	3.3%
Generalised gamma	79.2%	60.1%	52.6%	48.6%	45.9%	42.4%
Gompertz	80.6%	59.7%	56.9%	56.7%	56.6%	56.6%
Log-logistic	82.3%	58.4%	45.5%	38.1%	33.2%	26.9%
Log-normal	82.0%	58.8%	46.8%	39.9%	35.2%	28.9%
Weibull	83.1%	59.2%	43.8%	34.1%	27.4%	18.5%
Gamma	83.8%	59.4%	42.4%	31.3%	23.5%	13.7%

Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned.

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Table 40: Proportion of patients alive and progression-free INV assessed at key time points – lorlatinib 23 months piecewise

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
	12 months	60 months	120 months	180 months	240 months	360 months
Exponential	80.2%	60.3%	47.1%	36.8%	28.8%	17.6%
Generalised gamma	80.2%	60.0%	54.3%	51.5%	49.7%	47.4%
Gompertz	80.2%	60.2%	50.9%	46.0%	43.2%	40.6%
Log-logistic	80.2%	60.2%	47.8%	39.3%	33.2%	25.2%
Log-normal	80.2%	60.1%	49.7%	43.2%	38.4%	31.9%
Weibull	80.2%	60.3%	46.6%	35.8%	27.5%	16.0%
Gamma	80.2%	60.3%	46.4%	35.6%	27.2%	15.8%
Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned.						

Table 41: Proportion of patients alive and progression-free INV assessed at key time points – lorlatinib 36 months piecewise

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
	12 months	60 months	120 months	180 months	240 months	360 months
Exponential	80.2%	60.2%	50.4%	42.2%	35.3%	24.7%
Generalised gamma	80.2%	59.3%	54.8%	53.0%	51.9%	50.5%
Gompertz	80.2%	60.5%	27.9%	0.1%	0.0%	0.0%
Log-logistic	80.2%	60.5%	43.0%	29.6%	21.2%	12.3%
Log-normal	80.2%	60.4%	47.1%	38.0%	31.6%	23.3%
Weibull	**80.2%**	**60.5%**	**40.9%**	**22.5%**	**10.6%**	**1.6%**
Gamma	80.2%	60.5%	42.2%	26.4%	15.7%	5.1%
Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned.						

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Table 42: Proportion of patients alive and progression-free INV assessed at key time points – crizotinib

Distribution	Modelled landmarks					
	1 year	**5 years**	**10 years**	**15 years**	**20 years**	**30 years**
	12 months	**60 months**	**120 months**	**180 months**	**240 months**	**360 months**
Exponential	46.6%	2.2%	0.0%	0.0%	0.0%	0.0%
Generalised gamma	40.1%	4.7%	1.3%	0.6%	0.3%	0.1%
Gompertz	41.6%	6.2%	2.9%	2.4%	2.2%	2.2%
Log-logistic	38.9%	3.1%	0.9%	0.4%	0.2%	0.1%
Log-normal	41.9%	3.1%	0.5%	0.1%	0.0%	0.0%
Weibull	**47.2%**	**1.9%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**
Gamma	48.2%	1.3%	0.0%	0.0%	0.0%	0.0%
Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned.						

Figure 23 shows the PFS extrapolations for each comparator using the Weibull curve for crizotinib, with the NMA-derived HRs versus crizotinib for treatments applied (see Section B.2.9.4.1). The figure is inclusive of 10-year waning. Broadly the lorlatinib PFS curve fits the observed Kaplan–Meier data well which is unsurprising given the use of a piecewise survival approach.

Comparison of comparator extrapolations with observed trial data can be beneficial but should be seen in the context of them being derived via anchored network comparisons, which will be influenced by factors such as variations in anchor treatment (crizotinib) efficacy across trials and the chosen fitting to crizotinib PFS from CROWN. The extrapolated brigatinib PFS overshoots the ALTA-1L Kaplan–Meier curve, but underfits the tail and this is in line with the direct fittings presented in TA670 and not an uncommon problem in NSCLC appraisals. The alectinib PFS is centred between the Kaplan–Meier curves from the ALEX and ALESIA trials which is to be expected given that they are nodes in the NMA; the PFS extrapolation again underfits the ALEX tail as with the brigatinib extrapolation.

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Figure 23: Progression-free survival INV assessed for all treatments

Key: INV, investigator; KM, Kaplan–Meier curve; PFS, progression-free survival.

B.3.3.3.1. Scenario analysis: progression-free survival based on blinded independent committee review

As described previously, PFS BICR is not available in the October 2023 data cut, therefore, PFS INV is used as the base case. Despite lorlatinib PFS INV and PFS

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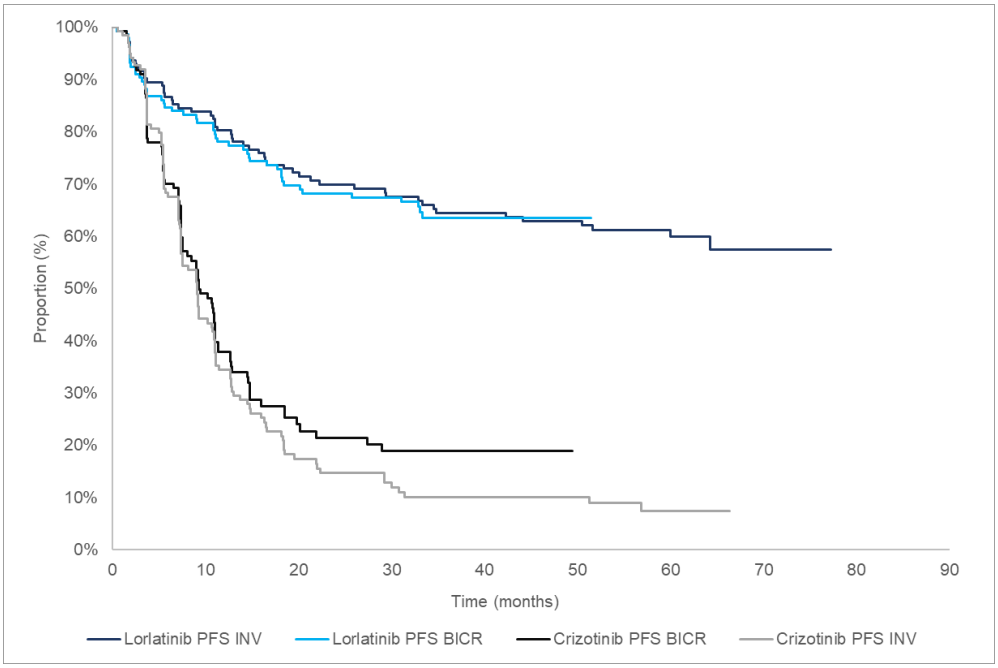
BICR Kaplan–Meier curves being very similar, the crizotinib Kaplan–Meier curve displays differences starting in Month 16 (Figure 24).

Figure 24: Progression-free survival of lorlatinib and crizotinib – INV vs BICR



Key: BICR, blinded independent committee review; INV, investigator; PFS, progression-free survival.

The model includes the functionality to estimate a proxy crizotinib PFS BICR for the 5-year data by applying the hazard ratios of PFS INV vs PFS BICR observed during the September 2021 data cut, the latest data cut for which both endpoints were available. Two options are included: use the hazard ratios observed during the full CROWN follow-up (~36 months), or use the hazard ratio observed after Month 16, when the curves start to diverge (Table 43). These are tested in scenario analyses.

Table 43: Hazard ratios applied to adjust crizotinib PFS BICR – PFS results

Comparison	Median HR (95% CrI)
Using full CROWN follow-up*	0.86 (0.65, 1.13)
Using follow-up after 16 months	0.48 (0.21, 1.12)
Key: 1L, first-line; HR, hazard ratio; PFS, progression-free survival; CrI, credible interval; ITT, intention-to-treat; PFS, progression-free survival. **Notes**: * Of the September 2021 data cut using a Cox regression analysis.	

B.3.3.4. Overall survival

A key challenge of the CROWN survival analyses was the immaturity of the OS data. OS curves were independently fitted to each arm of the CROWN study as described

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in Section B.3.3.3. Additionally, OS curves were independently fitted to lorlatinib using pooled CROWN + Study 1001 Kaplan–Meier data, which was selected for base case as the curves are fit to more mature OS data, as described in B.3.3.2.1.Figure 26 and Figure 27 present OS extrapolations for lorlatinib using CROWN, lorlatinib using pooled CROWN and Study 1001, and crizotinib using CROWN.

Figure 25: Overall survival extrapolations for lorlatinib – CROWN

Key: KM, Kaplan–Meier; OS, overall survival.

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Figure 26: Overall survival extrapolations for lorlatinib – Pooled CROWN + Study 1001

Key: KM, Kaplan–Meier; OS, overall survival.

Figure 27: Overall survival extrapolations for crizotinib – CROWN

Key: KM, Kaplan–Meier; OS, overall survival.

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The AIC and BIC, which provide an indication of the statistical goodness-of-fit of the parametric models to the observed portion of the data, may not be considered as informative as is typical in curve selection given the immaturity of the CROWN survival data. Furthermore, as shown in Table 44,

Table 45 and Table 46 the AIC/BIC across parametric models are within 5 points of each other. This suggests there is not a large difference in the goodness-of-fit to the observed data.

Table 44: Fit statistics of OS extrapolation – lorlatinib using CROWN

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	269.29	1	272.30	1
Generalised gamma	270.32	3	279.33	7
Gompertz	271.27	6	277.27	5
Log-logistic	271.12	4	277.12	3
Log-normal	269.85	2	275.86	2
Weibull	271.27	7	277.28	6
Gamma	271.25	5	277.26	4
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.				

Table 45: Fit statistics of OS extrapolation – lorlatinib using pooled CROWN + Study 1001

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	373.95	3	380.32	1
Generalised gamma	372.33	1	385.08	5
Gompertz	374.74	4	384.30	3
Log-logistic	375.32	5	384.89	4
Log-normal	373.08	2	382.62	2
Weibull	375.92	6	385.48	6
Gamma	375.94	7	385.50	7
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.				

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Table 46: Fit statistics of OS extrapolation – crizotinib using CROWN

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	308.95	3	311.94	1
Generalised gamma	307.14	1	316.11	4
Gompertz	310.76	7	316.74	7
Log-logistic	309.50	4	315.48	3
Log-normal	307.29	2	313.27	2
Weibull	310.45	6	316.43	6
Gamma	310.21	5	316.19	5

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

An overview of the modelled OS at key time points by survival extrapolations, while applying background mortality, for lorlatinib using CROWN, lorlatinib using CROWN and Study 1001 pooled, and crizotinib using CROWN is presented in Table 47, Table 48 and Table 49. The background mortality adjustment applied in modelling allows for better reflection of the model inputted OS extrapolations.

Considering the CROWN and Study 1001 pooled extrapolations, the results indicate that Gompertz, generalised gamma, log-logistic and log-normal curves were likely to produce clinically implausible outcomes (more than 20% and 10% of patients remain alive after 30 years in the lorlatinib and crizotinib arms, respectively). Clinical opinion suggested that the Weibull, gamma and exponential curves would be the most appropriate to use, while all other extrapolations are unrealistic.[117] However, the gamma OS curve (CROWN or pooled) struggles to stay above the Weibull 36-month piecewise PFS curve, so is not a coherent selection. The Weibull OS curve (pooled CROWN + Study 1001) is selected as a compromise, as it is more consistent with the selected PFS curve, although it is also imperfect in that it meets the selected PFS curve between around 6 and 10 years, even when waning is applied. Therefore, Weibull can be considered a conservative selection.

A scenario analysis is explored with a log-logistic OS extrapolation (stays above the base case PFS extrapolation), which makes little difference to cost-effectiveness results when treatment effect waning is applied. Another scenario analysis is presented with standard parametric exponential selections for both lorlatinib PFS and OS (where again there is no meeting of curves).

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Again given the uncertainty in OS extrapolations, treatment effect waning is applied at 10 years in line with TA909.[1] As with PFS, hazards are waned down to the crizotinib hazards for all treatments.

Table 47: Proportion of patients alive at key time points – lorlatinib using CROWN (adjusted for background mortality)

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
	12 months	60 months	120 months	180 months	240 months	360 months
Exponential	90.5%	61.5%	37.7%	19.1%	9.7%	2.5%
Generalised gamma	88.4%	76.2%	71.2%	36.2%	18.3%	4.7%
Gompertz	90.3%	64.1%	45.8%	23.3%	11.8%	3.0%
Log-logistic	90.4%	63.3%	44.9%	22.8%	11.5%	3.0%
Log-normal	90.1%	66.8%	52.4%	26.6%	13.5%	3.5%
Weibull	90.6%	60.5%	35.7%	18.1%	9.2%	2.3%
Gamma	90.6%	60.4%	35.6%	18.0%	9.1%	2.3%
Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned.						

Table 48: Proportion of patients alive at key time points – lorlatinib using Pooled CROWN + Study 1001 (adjusted for background mortality)

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
	12 months	60 months	120 months	180 months	240 months	360 months
Exponential	90.4%	61.5%	37.7%	23.1%	14.1%	5.3%
Generalised gamma	87.8%	74.2%	68.6%	63.5%	56.0%	29.5%
Gompertz	90.1%	71.7%	64.7%	59.9%	52.8%	27.8%
Log-logistic	90.2%	64.6%	47.0%	36.9%	30.3%	15.9%
Log-normal	90.0%	67.1%	52.9%	44.2%	38.1%	20.0%
Weibull	90.3%	62.3%	39.4%	25.1%	16.1%	6.5%
Gamma	90.5%	61.9%	38.4%	23.8%	14.8%	5.6%
Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned.						

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Table 49: Proportion of patients alive at key time points – crizotinib (adjusted for background mortality)

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
	12 months	60 months	120 months	180 months	240 months	360 months
Exponential	87.0%	50.9%	25.8%	13.1%	6.6%	1.7%
Generalised gamma	85.7%	64.1%	55.3%	50.5%	44.5%	23.4%
Gompertz	86.4%	58.0%	44.3%	38.9%	34.3%	18.0%
Log-logistic	87.4%	50.1%	29.9%	20.6%	15.4%	7.9%
Log-normal	87.0%	54.1%	36.4%	27.0%	21.2%	11.0%
Weibull	87.7%	45.7%	17.8%	6.5%	2.3%	0.2%
Gamma	87.8%	45.4%	18.2%	7.1%	2.7%	0.4%

Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned.

As discussed, in the base case, a pseudo state transition approach using external data is used to model PPS for the comparator arms (see Section B.3.3.4.1). Figure 28 shows the OS extrapolations for all treatments using the Weibull curve for lorlatinib and the pseudo state transition approach for the comparators. In the alectinib appraisal (TA536), the exponential curve led to 5.11 life years gained in the company base case,[50] compared to 6.32 life years gained for alectinib using the pseudo state transition approach here. In the brigatinib appraisal (TA670), the exponential curve led to 5.87 life years gained[20] versus 6.05 life years gained using the pseudo state transition approach. Therefore, using the pseudo state transition approach for the comparators in the base case can be considered a more optimistic extrapolation compared to the previous appraisals. Not out of line with the PSM approach below, this approach overestimates OS at first and then underfits the tails of the ALEX and ALTA-1L trials, with the latter in theory not fully reflecting the efficacy of subsequent lorlatinib treatment. It should be noted again that the OS curve selection for lorlatinib is a compromise between long-term plausibility and fit to observed (pooled) data and it is likely that the fitting is conservative (as seen in Figure 45) and more of an underestimate than the respective alectinib and brigatinib extrapolations.

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Figure 28: Overall survival extrapolations for all treatments based on the pseudo state transition approach for comparators

Key: OS, overall survival.
Notes: The per cycle probability of death is capped at the age- and sex-matched general population.

Alternatively, scenario analyses explored using NMA-derived HRs applied to an extrapolated OS curve for crizotinib. The Weibull curve for crizotinib is selected as it gives the most reasonable projections without waning. Figure 30 shows the OS extrapolations for all treatments using the Weibull curve for lorlatinib and the NMA-derived HRs for the comparators. The exponential curve leaves around 2% of patients alive at 30 years which is probably unlikely for crizotinib. The alectinib and brigatinib extrapolations are more optimistic versus their respective trial Kaplan–Meier curves, compared with the PFS extrapolations presented previously. The brigatinib and alectinib extrapolations overestimate OS compared with the Kaplan–Meier curves but do not underfit the observed tails as much (i.e. versus ALEX and ALTA-1L trial Kaplan–Meier curves); the alectinib extrapolation is again centred between the ALEX and ALESSIA Kaplan–Meier curves as expected. It should be emphasised again that the lorlatinib extrapolation is the most conservative in relation to the observed data.

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Figure 29: Overall survival extrapolations for all treatments based on NMA-derived HRs and Weibull curve for crizotinib

Key: KM, Kaplan–Meier curve; OS, overall survival.
Notes: The per cycle probability of death is capped at the age- and sex-matched general population.

B.3.3.4.1. Post-progression survival based on state transition approach for the comparators

During the previous submission (TA909), the External Assessment Group (EAG) had concerns related to the confounding effects introduced by subsequent TKIs in the pivotal trials informing the relative efficacy of comparators in the model.[1] In ALEX, only 13.1% progressed patients received second-line lorlatinib, while 2.4% received alectinib and 9.5% brigatinib. In ALTA-1L, 29.7% received second-line lorlatinib, compared to 21.6% receiving alectinib and 2.7% brigatinib (see Table 25). However, most patients following treatment with alectinib (the main first-line treatment in the UK) and brigatinib in UK clinical practice will receive second-line lorlatinib.[81, 89]

Given the EAG's concerns, the base case analysis uses a pseudo state transition approach with post-progression survival, in which the OS for alectinib and brigatinib is defined as the sum of progression-free survival and post-progression survival. This approach accounts for second-line use of lorlatinib after second generation ALK

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inhibitors by applying second-line OS data from Study 1001 to capture PPS following first-line treatment with an ALK inhibitor. It is the same approach developed during TA909.[1] A summary of the approach used for each treatment base case is presented in Table 50.

Table 50. Summary of the approaches to extrapolate OS

Treatment	Approach	Source
Lorlatinib	Fitted curves to OS	CROWN
Alectinib	Pseudo state transition: PFS + PPS	CROWN (PFS) and Study 1001 (PPS)[77]
Brigatinib	Pseudo state transition: PFS + PPS	CROWN (PFS) and Study 1001 (PPS)[77]

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

For alectinib and brigatinib PPS (base case) 'the expansion cohort EXP3B-5' from Study 1001 is used, which includes 139 patients with disease progression following one or more second generation ALK inhibitors.[77, 78]

The incorporation of time-varying PPS would have required multiple tunnel states. Therefore, exponential curves using data from Study 1001 were used to model PPS, which was considered a minor limitation and alternatives did not make much difference when explored in TA909. The resulting post-progression mortality rate was 2.47%.

However, only 86.8% of patients receive lorlatinib after first-line alectinib or brigatinib (Table 71). The remaining patients receive chemotherapy as second-line treatment.

To account for the efficacy of second-line chemotherapy, a weighted average is used to estimate the post-progression mortality rate in the alectinib and brigatinib arm using the post-progression survival from Ou et al. 2014 (PROFILE 1001/1005). This approach is aligned with what was accepted in the second-line lorlatinib appraisal (TA628).[15]

Ou et al. 2014 (PROFILE 1001/1005) includes two single-arm studies of crizotinib in advanced ALK-positive NSCLC: the molecularly enriched expansion cohort of a Phase I trial (PROFILE 1001) and a Phase II trial (PROFILE 1005) that allowed the continuation of crizotinib beyond RECIST-defined progressive disease in patients

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who continued to derive clinical benefit from crizotinib.[130] The study was identified as the best source of OS for chemotherapy as it was the only study that reported the OS of patients who received 'systemic therapy' following progression and discontinuation of crizotinib. The study reported the overall survival from the time of progressive disease of patients who discontinued crizotinib beyond progressive disease and received subsequent systemic therapy.

Alectinib and brigatinib weighted post-progression mortality rate (3.25%) is presented in Table 51.

Table 51: Post-progression mortality rates by treatment sequence

Sequence	Source	Rate
1L alectinib or brigatinib → 2L lorlatinib	Based on lorlatinib following another ALK inhibitor (Study 1001; EXP3B-5)	2.47%
1L alectinib or brigatinib → 2L chemotherapy	Based on 1L crizotinib and 2L chemotherapy (PROFILE 1001/1005)	9.86%
1L alectinib or brigatinib → 2L lorlatinib/chemotherapy	Weighted average: Based on 1L crizotinib and 2L chemotherapy (PROFILE 1001/1005) and lorlatinib following another ALK inhibitor (Study 1001; EXP3B-5)	3.25%

Key: 1, first-line; 2L, second-line; ALK, anaplastic lymphoma kinase.
Source: Ou et al., 2014 and manuscript in preparation.[77, 130]

B.3.3.4.2. Alternative analysis: post-progression survival based on state transition approach for lorlatinib

A scenario analysis explores the use of post-progression survival for lorlatinib based on the pseudo state transition approach (similar to the PPS approach used for the comparators in the base case). Following treatment with first-line lorlatinib, 21.8% received alectinib and 1.8% received brigatinib after progression in CROWN (see Section B.2.9.2.4). None of the licenses (or NICE recommendations) of the ALK inhibitors allow their use after first-line lorlatinib, so the subsequent treatments in CROWN are not aligned with UK clinical practice. However, in most international pivotal trials that support oncology appraisals there are subsequent treatments that may potentially bias OS (or PPS) that are not reflected in UK clinical practice. In these cases, standard methods (parametric models with exploratory waning) are

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employed to explore uncertainty instead of pseudo state transition models using external data.

Consulted clinicians agreed that subsequent ALK inhibitors were used in a small proportion of patients and the impact of this is uncertain but likely low, considering there is no evidence or expectation that second generation ALK inhibitors will be effective following lorlatinib, which has the greatest coverage of ALK resistance mutations.[117] In Study 1001, among 30 patients who were treatment-naive, only three (10%) patients received either alectinib or brigatinib after first-line lorlatinib[77], which is aligned with the percentage observed in the March 2020 data cut from CROWN. Therefore, pooling the data from Study 1001 and CROWN does not impact the possible confounding effect of the use of TKIs after disease progression.

The pseudo state transition in the lorlatinib arm applies second-line OS data from Ou et al. 2014 (PROFILE 1001/1005) to capture PPS following first-line treatment with an ALK inhibitor.[130] The mortality rates applied in the model (9.86%) are the same as for alectinib and brigatinib first-line and second-line chemotherapy (Table 51).

The PSM approach leads to a mean of 22 months in the progressed health state for lorlatinib, while the semi-PSM approach results in 10 months. The PSM approach leads to a higher post-progression survival than the semi-PSM approach, which is expected as semi-PSM is based on the post-progression survival from PROFILE 1001/1005, which includes patients receiving chemotherapy after first-line crizotinib. The clinical experts consulted expected a higher post-progression survival for lorlatinib than the one observed for crizotinib and therefore this approach reflects a conservative scenario analysis. All three clinicians emphasised that this scenario reflects a conservative floor in post-progression survival expectations for lorlatinib given the historical nature of the PROFILE studies and because the prognosis for a patient after lorlatinib (third generation inhibitor) is much better than after crizotinib (first generation inhibitor).[117]

B.3.3.5. Time on treatment

Figure 30 presents the PFS and ToT Kaplan–Meier curves side by side and shows that the ToT curve is consistently below the PFS curve in CROWN. This is likely due to the unusually long duration of treatment for lorlatinib compared with second

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generation ALK inhibitors; the greater the duration of treatment with an ALK inhibitor, the greater the likelihood of stopping treatment. Lorlatinib is the most effective ALK inhibitor, so patients may stay on the treatment (median 62 months) twice or longer compared with alectinib (median 28.1 months) or brigatinib (median 24.3 months), despite the higher rate of AEs, as discussed in Section B.2.10.[20,81]

In Study 1001 and the related appraisal for lorlatinib in second-line (TA628), the mean ToT was around 16 months, which included ToT beyond progression.[15, 77] However, the treatment beyond progression is explained by the relatively short duration of treatment compared with first-line lorlatinib treatment duration and is not generalisable to treatment with lorlatinib in first-line. The company believes that CROWN data is the most robust source informing the relationship between PFS and ToT and this relationship should be reflected in cost-effectiveness modelling. Two of three consulted clinicians strongly endorsed this rationale for the observed relationship between ToT and PFS in CROWN. The third clinician consulted suggested that in practice lorlatinib would be given to a patient approximately until the time of disease progression but this is uncertain.[117] The CROWN ToT for crizotinib also overlays the PFS almost perfectly – aligned with alectinib and brigatinib as explained below – and this supports the idea that this relationship for lorlatinib is not driven by the CROWN design or protocol.

Importantly, the CROWN protocol allowed treatment beyond progression if patients were ‘continuing to derive clinical benefit from study treatment’ which is also consistent with the Study 1001 protocol (and lorlatinib license).[75] This implies treating clinicians were allowed to treat post-progression in CROWN but chose not to do so, which should be accounted for in cost-effectiveness modelling. Therefore, treatment beyond progression was not included in the model. If treatment beyond progression is expected in clinical practice because clinical benefit is expected, then the additional QALY benefit should be incorporated in the model. However, any attempt to model the additional benefit is uncertain. An alternative would also be to add additional cycles beyond progression for the comparators.

Retaining the pivotal trial observed relationship between ToT and PFS has long been a mainstay of modelling solid tumour cancers across NICE appraisals and this approach is applied here for consistency. Therefore, an HR was estimated for

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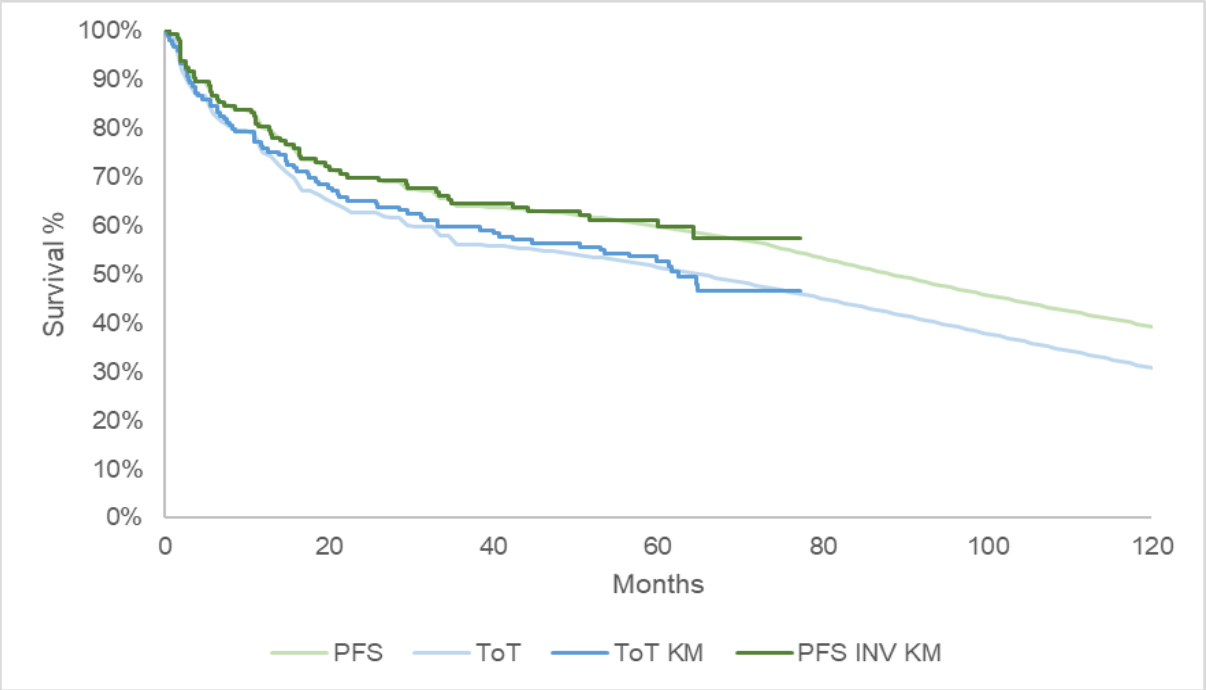
CROWN observed ToT versus PFS using a Cox model with a variable for outcome type and is applied in modelling. In the lorlatinib arm, subsequent treatment costs are applied for those patients who have not progressed but stop lorlatinib use, to be consistent with clinical practice.

For alectinib and brigatinib, as shown in their respective appraisals, observed PFS from a pivotal trial overlayed with ToT almost perfectly and so in line with appraisals TA536 and TA670, ToT is assumed to equal PFS (i.e. HR of 1 is applied).[20, 50]

Figure 30: Extrapolated PFS INV and ToT vs Kaplan–Meier curves from CROWN



Key: INV, investigator assessed; KM, Kaplan–Meier; PFS, progression-free survival; ToT, time on treatment.

B.3.3.6. CNS progression as intercurrent events

Clinicians at the advisory board strongly endorsed a simple way to model the additional costs and QoL implications of brain metastases, given the importance of this to clinical practice and patient experience.[4]

IC-TTP captures the time from randomisation to the development of new brain metastases for patients without brain metastases at baseline; and captures intracranial progression for those with brain metastases already at baseline. Patients

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are censored at death and at the start of subsequent anti-cancer therapy. This means that patients who start a new therapy before clinical/systemic progression were censored.

Analogous with PFS methods, parametric curves were fitted to lorlatinib and crizotinib IC-TTP and NMA-derived HRs (see Section B.2.9.4.3) were applied to the latter to derive IC-TTP for alectinib and brigatinib. To extrapolate the IC-TTP, the exponential function is selected as it provides the most conservative curve for lorlatinib and, at the same time, allows the application of the simplifying assumption of a constant rate of CNS progression. The model uses these curves to calculate a per cycle rate of CNS progression (Table 52). This rate is applied to patients in the model who are alive and on treatment – including patients who stop treatment before progression – in each cycle to calculate the incidence of CNS progression. These then accrue one-off costs and utility decrements associated with the development of brain metastases, not in a dissimilar way to AEs. Thus, this rate of IC-TTP is applied in a way highly consistent with the clinical definition of IC-TTP and reflects the censoring of patients at death and start of subsequent treatments. The modelling of CNS progression as intercurrent events while on treatment is consistent with the clinical view that CNS protection occurs on treatment with an ALK inhibitor and not after systemic progression, which leads to treatment discontinuation.

Table 52: IC-TTP rates by treatment

Treatment	Rate
Lorlatinib	0.15%
Crizotinib	3.35%
Alectinib	0.52%
Brigatinib	1.02%
Key: IC-TTP, intracranial time to progression.	

A duration of 24 months is assumed for the one-off cost, and the same duration is assumed to calculate the utility decrement (see Sections B.3.4.2.3 and B.3.5.2). This is supported by a recent systematic review and meta-analysis, which estimated the post-progression survival of NSCLC patients who develop brain metastases at around 27.5 months.[38] All three consulted clinicians also agreed that this duration is reasonable.[117]

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As discussed in Section B.2.9.4.3, the endpoints in the trials informing the IC-TTP NMA did not perfectly conform with the CROWN definition of IC-TTP. The HRs (treatment versus crizotinib) that feed into the NMA for alectinib from ALEX and ALESIA (0.15) and for brigatinib from ALTA-1L (0.30) look to be from a competing risk analysis, which accounts for death and systemic progression as competing risks.[103,86,98] This sort of analysis is arguably more appropriate for the purpose of this appraisal given that censoring in the context of the Kaplan–Meier estimator is not the same as adjusting for competing risks. However, in practice there is no meaningful difference in these outcomes. The published competing risk analysis HRs from CROWN were 0.06 at 18 months and 0.07 at 36 months, which aligns with the IC-TTP HR from the 5-year data cut of 0.07.[10, 131]

CNS intercurrent events accrued over time are aligned with reported CROWN events at 5 years: nine patients (6%) are reported to have had intracranial progression and this is identical to model predictions. Comparator trials do not consistently report cumulative intracranial progressions, but the ALEX trial reported 9.4% at 12 months (model prediction 5.9%) and the ALTA-1L trial 12% at 12 months (model prediction 11.3%).[10, 131]

B.3.3.7. Adverse reactions

The model includes Grade 3 or higher all-cause AEs observed in at least 5% of patients in the lorlatinib or crizotinib arms of CROWN, in the alectinib arm of ALEX, or in the brigatinib arm of ALTA-1L as reported in TA670. Grade 1/2 AEs are expected to have a negligible impact on costs and HRQL, except all AEs of special interest regardless of grading, following the committee's preferred assumption in TA909. Therefore, all Grade 1/2 AEs are excluded from the model in line with prior appraisals, except for hypertriglyceridemia, hypercholesterolemia, peripheral neuropathy, cognitive effects and mood effects. Furthermore this is a conservative assumption against lorlatinib as we have not included relevant AEs of special interest for alectinib and brigatinib.

Table 53 includes the reported AE proportions. AE management costs and disutilities are applied as a one-off.

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Table 53: Grade 3-4 adverse events proportions

Adverse Event	Lorlatinib (CROWN)[a]	Crizotinib (CROWN)	Alectinib (ALEX)	Brigatinib (NICE TA670)
Hypertriglyceridemia	66.44%	5.63%	0.00%	0.00%
Weight increased	22.82%	2.11%	0.00%	0.00%
Increased lipase level	6.04%	3.52%	0.00%	12.50%
Hypercholesterolemia	72.48%	3.52%	0.00%	0.00%
Aspartate aminotransferase increased	2.01%	3.52%	5.26%	2.21%
Gamma-glutamyltransferase increased	6.04%	4.23%	0.00%	0.74%
Hypertension	12.08%	0.70%	0.00%	7.35%
Anaemia	4.03%	2.82%	5.92%	1.47%
Amylase increased	0.00%	0.70%	0.00%	5.88%
Neutropenia	0.67%	9.15%	0.00%	0.00%
Blood creatine phosphokinase increased	2.68%	4.23%	3.29%	23.53%
Neutrophil count decreased	0.00%	8.45%	0.00%	0.00%
Peripheral neuropathy	43.62%	16.20%	0.00%	0.00%
Cognitive effects	27.52%	7.04%	0.00%	0.00%
Mood effects	20.81%	6.34%	0.00%	0.00%

Notes: [a,] includes all AEs of special interest regardless of grading.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality of life data from clinical trials

HRQL is discussed in Section B.2.6.5. and Appendix M. PROs were assessed on Day 1 of each cycle, at the end of treatment, and at post-treatment follow-up using the EORTC QLQ-C30, the European Organisation for Research and Treatment of Lung Cancer Quality of Life Questionnaire (EORTC QLQ-LC13), and the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L).

Using the mixed effects utility model, the cost-effectiveness model includes the functionality to model CROWN utility values by following stratification factors:

- Health state, treatment status, and treatment arm
- Health state and treatment status

Patient responses from the EQ-5D-5L questionnaire were mapped to the EQ-5D-3L using the mapping function developed by the Decision Support Unit using the

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dataset from the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU).[132] After the application of the mapping algorithm, the UK EQ-5D-3L value set was applied to the data to produce utility values. Analysis datasets were derived using R software version 4.0.4, using the following assumptions:

- Only patients from the CROWN study who were randomised to receive study treatment were included in the analysis (ITT population)
- All observations were considered except for incomplete observations
- Baseline flags were used to define the baseline observation for each patient. Any observations before this baseline flag were removed. Where there was no flag for a patient, and if it was appropriate to do so, their first observation was used as the baseline utility value
- Two health states were defined to align with the structure of the economic model and the survival analysis outcomes: pre- and post-progression
  - Pre-progression includes all observations before the date of objective progression of disease
  - Post-progression includes observations on and after the date of objective progression of disease
  - Health state was defined based on PFS assessed by BICR

The resulting utility values by stratification factors are shown in Table 54 and Table 55.

Table 54: CROWN utility (by health state, treatment status, and treatment arm)

Utility value	Progression-free (on treatment)	Progression-free (off treatment)	Progressed (on treatment)	Progressed (off treatment)
Lorlatinib	0.845	0.768	0.843	0.766
Crizotinib	0.837	0.761	0.814	0.737
Source: Solomon et al. 2023.[6]				

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Table 55: CROWN utility (by health state and treatment status)

Utility value	Progression-free (on treatment)	Progression-free (off treatment)	Progressed (on treatment)	Progressed (off treatment)
Lorlatinib/crizotinib	0.841	0.764	0.828	0.752
Source: Solomon et al. 2023.[6]				

Patients have a slight decrease in utility after progression, with the greatest difference between pre- and post-progression seen in the crizotinib arm. As discussed in TA909, post-progression utilities from CROWN (especially in the lorlatinib arm) do not have face validity. A substantial proportion of records in CROWN occur pre-progression (based on BICR), while post-progression HRQL data for patients from the lorlatinib arm were collected on a small number of patients (n=36). Of the post-progression utilities, most were close to the date of progression, indicating that the post-progression utility in the trial is unlikely to be reflective of the true value of post-progression utility over time after the progression event as they could not capture deterioration in HRQL. Therefore, alternative utility sources for lorlatinib progressed patients were considered, in line with TA909. Utilities for alectinib and brigatinib were also obtained from alternative sources.

B.3.4.2. Health-related quality of life studies

B.3.4.2.1. Systematic literature review of utility values

In October 2019, a SLR was conducted to identify relevant utility evidence for patients with ALK-positive advanced NSCLC. The SLR was then updated in April 2021. The October 2019 SLR identified 28 records reporting on 17 unique studies, 13 of which were economic modelling studies reporting utility data and were extracted in the utility review. In the April 2019 update, only one study of the 41 included studies reported data on QoL outcomes. Full details of the SLRs' search strategies, study selection processes and results can be found in Appendix H.

Due to the limitations of the CROWN-derived utilities described in Section B.3.4.1 the base case utility values for post-progression survival for lorlatinib, alectinib and brigatinib were derived from the NICE appraisal of brigatinib (TA670), shown in Table 56 as per committee preference in TA909.[1, 20] Progression-free utility values for alectinib and brigatinib were sourced from their NICE appraisals (Table 56 and

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Table 57). Applying treatment specific progression-free utilities in addition to AE disutility's informed by respective pivotal trials capture the specific experience of patients on each treatment. Common progressive disease utilities across arms are the norm in solid tumour NICE appraisals (especially in NSCLC) but so are treatment specific PFS utilities including in the ALK space as evidenced in TA536 and TA670.[20, 50]

Table 56: Utility values from NICE TA536 (alectinib)[50]

Health state	Value
PFS	0.814
PD (no CNS progression)	0.725
PD (with CNS progression)	0.520
Key: PFS, progression-free survival; PD, progressive disease. **Notes:** Derived using mixed-model from ALEX EQ-5D data.	

Table 57: Utility values from NICE TA670 (brigatinib)[20]

Health state	Value
PFS	0.793
PD	0.624
Key: PFS, progression-free survival; PD, progressive disease. **Notes:** The manufacturer presented treatment specific progressed utilities, but reporting was not sufficient to derive these values from first principles.	

B.3.4.2.2. Age-related disutility

An age-related utility adjustment was applied to account for the deterioration in HRQL as a patient gets older. These utility values were calculated using the following equation and were informed by UK general population values reported by Ara and Brazier 2010 (Table 58):[133] General population utility = β0 + β1male + β2age + β3age.[2]

Table 58: General population utility

Coefficient	Value	Standard error
Constant (β0)	0.950857	0.095086
Male (β1)	0.021213	0.002121
Age (β2)	-0.000259	0.000026
Age2 (β3)	-0.000033	0.000003
Source: Ara and Brazier 2010.[133]		

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B.3.4.2.3. CNS intercurrent events disutility

In line with the brigatinib appraisal (TA670), multipliers are used to account for the impact of CNS intercurrent events (see Section B.3.3.6) and are applied to PFS on-treatment utilities in the model.[20] These utility values were informed by Roughley et al. 2014, a study that evaluated the impact of brain metastases compared with other metastatic sites in patients with Stage IV NSCLC.[42] Roughley et al. 2014 reported that the utility value associated with brain metastases was 0.52 compared with 0.69 for contralateral lung metastases.[42] Therefore, the multiplier of 75.36% (0.52/0.69) was applied to the progressive disease utility value to estimate the impact of brain metastases. The scenario analyses explore using the absolute decrement value reported in Roughley et al. (2014), which has a negligible impact on the incremental QALYs.

An analysis of the health-related quality of life in patients with ALK+ non-small-cell lung cancer in the Phase 3 CROWN study presented utility values aligned with the decrement from Roughley et al. (2014).[134] Applying a mixed effect (longitudinal model), the study shows a 0.10 difference in the EQ-5D baseline utility values of those patients with brain metastases in comparison to those without brain metastases (versus 0.69-0.52=0.17 with Roughley et al. 2014). All of these alternatives are tested in scenario analyses and make a small difference to results.

The main limitation from Roughley et al. (2014) is the small number of people with brain metastases (n = 29) and the fact that treatment-related AEs, comorbidities or age were not reported. During the brigatinib assessment (TA670), Roughley et al. was the only available source, and therefore, it is used in the base case.[20, 42] However, when presented all three clinicians deemed that a 25% reduction in HRQL because of brain metastases is entirely reasonable.[117]

B.3.4.3. Adverse reactions

The loss of QALYs per AE was calculated as the product of the utility decrement and the duration of the AE. Utility decrements are presented in Table 59. The disutility for neutropenia is -0.090, sourced from Nafees et al. 2017.[135] The disutility for peripheral neuropathy, cognitive and mood effects have been assumed to be the same as neutropenia to reflect the relative severity of these events in the absence of identified literature. AE utilities have also been sourced from TA670.[20]

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Table 59: Adverse event utility decrements

Adverse event	Utility decrement	Source
Hypertriglyceridemia	-0.037	TA670 (ALTA-1L HRQL analysis)
Weight increased	-0.037	TA670 (ALTA-1L HRQL analysis)
Increased lipase level	-0.037	TA670 (ALTA-1L HRQL analysis)
Hypercholesterolemia	-0.037	TA670 (ALTA-1L HRQL analysis)
Aspartate aminotransferase increased	-0.037	TA670 (ALTA-1L HRQL analysis)
Gamma-glutamyltransferase increased	-0.037	TA670 (ALTA-1L HRQL analysis)
Hypertension	-0.037	TA670 (ALTA-1L HRQL analysis)
Anaemia	-0.037	TA670 (ALTA-1L HRQL analysis)
Amylase increased	-0.037	TA670 (ALTA-1L HRQL analysis)
Neutropenia	-0.090	Nafees et al.
Blood creatine phosphokinase increased	-0.037	TA670 (ALTA-1L HRQL analysis)
Neutrophil count decreased	-0.037	TA670 (ALTA-1L HRQL analysis)
Peripheral neuropathy	-0.090	Assumption (equal to neutropenia)
Cognitive effects	-0.090	Assumption (equal to neutropenia)
Mood effects	-0.090	Assumption (equal to neutropenia)
Source: NICE, TA670, 2021.[20]		

Table 60 shows the duration of AEs. Where possible, the duration of AEs is informed by evidence from CROWN. Neutropenia AE duration is informed by Nafees et al. 2017.[135] For the rest of the AEs, it is assumed that the duration is equal to neutropenia duration.

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Table 60: Adverse event durations

Adverse event	Duration (days)	Source
Hypertriglyceridemia	714	CROWN
Weight increased	778	CROWN
Increased lipase level	30	Assumption (equal to neutropenia)
Hypercholesterolemia	770.5	CROWN
Aspartate aminotransferase increased	30	Assumption (equal to neutropenia)
Gamma-glutamyl transferase increased	30	Assumption (equal to neutropenia)
Hypertension	30	Assumption (equal to neutropenia)
Anaemia	30	Assumption (equal to neutropenia)
Amylase increased	30	Assumption (equal to neutropenia)
Neutropenia	30	Nafees et al.
Blood creatine phosphokinase increased	30	Assumption (equal to neutropenia)
Neutrophil count decreased	30	Assumption (equal to neutropenia)
Peripheral neuropathy	380	CROWN
Cognitive effects	221	CROWN
Mood effects	218	CROWN
Source: Nafees et al. 2017; Solomon et al. 2024.[7, 135]		

B.3.4.4. Health-related quality of life data used in the cost-effectiveness analysis

The final utility model values applied in the model are presented in Table 61.

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Table 61: Summary of utility values for cost-effectiveness analysis

	State	Utility value: mean	Reference in submission (Section)
Utility values	**Progression-free (on treatment)**		
	Lorlatinib	0.845	B.3.4.1
	Brigatinib	0.793	B.3.4.2.1
	Alectinib	0.814	
	Progression-free (off treatment)		
	Lorlatinib	0.768	B.3.4.1
	Brigatinib	0.793	B.3.4.2.1
	Alectinib	0.814	
	Progressed (on and off treatment)		
	Lorlatinib	0.624	B.3.4.2.1
	Brigatinib	0.624	
	Alectinib	0.624	
One-off utility for CNS progression (based on 24 months duration)	Lorlatinib	0.416	B.3.4.2.3
	Brigatinib	0.401	
	Alectinib	0.391	
Utility decrement	Age	NA	B.3.4.2.2
Key: CNS, central nervous system.			

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B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify relevant cost and HCRU evidence for patients with ALK-positive advanced NSCLC. The SLR was initially conducted for all lines of therapy in August 2018 and was updated to focus on therapies in the first-line setting in November 2019. Full details of the SLR search strategy, study selection process and results can be found in Appendix I.

Although the clinical SLR was fully updated in February 2024, the HCRU SLR was not updated because of the very low probability that an alternative set of health state costs (or similar) would have been published since that time that could be useful. Indeed, these costs are well established in NSCLC appraisals.

B.3.5.1. Intervention and comparators' costs and resource use

Drug acquisition costs

Drug costs for comparator treatments were sourced from the Monthly Index of Medical Specialities (MIMS) online database and are presented in Table 62 alongside the costs for lorlatinib.[136] The base case results use the proposed patient access scheme (PAS) discount for lorlatinib and assumed discounts for alectinib and brigatinib but the presentation here uses list prices.

Table 62: Drug unit costs – list prices

Treatment	Form	Unit	Pack size	Pack price (list price)
Lorlatinib	Tablets	25 mg	120	£7,044.00
	Tablets	25 mg	90	£5,283.00
	Tablets	100 mg	30	£5,283.00
Alectinib	Capsules	150 mg	224	£5,032.00
Brigatinib	Tablets	Starter pack	28	£4,900.00
	Tablets	30 mg	28	£1,225.00
	Tablets	30 mg	56	£2,450.00
	Tablets	90 mg	7	£918.75
	Tablets	90 mg	28	£3,675.00
	Tablets	180 mg	28	£4,900.00
Source: MIMS.[136]				

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The pack size with the lowest cost per mg was selected. Dosing schedules were informed by the SmPCs for each product, as shown in Table 63. Treatment cycles and subsequent treatment cycle costs were calculated in the model based on how long the pack size would last at the required dose. The treatment cycle cost was then adjusted within the model to account for the 30-day model cycle length.

Table 63: Dosing schedules

Treatment	Dose	Frequency	Administration
Lorlatinib	100 mg	Once daily	Oral
Alectinib	600 mg	Twice daily	Oral
Brigatinib (Cycle 1)	Starter pack	Once daily	Oral
Brigatinib (Cycle 2+)	180 mg	Once daily	Oral
Source: Lorlatinib, Summary of Product Characteristics; Alectinib, Summary of Product Characteristics Brigatinib, Summary of Product Characteristics.[18, 60, 61]			

Administration costs for oral therapies in the model were captured as pharmacist dispensing time. An administration cost of £10.40 was applied per pack, sourced from the Personal Social Services Research Unit (PSSRU) 2023 as the cost for 12 minutes of work for a Band 6 community-based scientific and professional staff member (£52 per hour).[128] Drug and administration costs are incurred at the beginning of each cycle and so differences between pack size (drug cycle) and model cycle length produce drug 'wastage' which is included in modelling. For lorlatinib the pack size aligns with cycle length but for alectinib and brigatinib the pack size is equivalent to 28 days and so any pill wastage is costed.

For lorlatinib and the comparator treatments, the relative dose intensity (RDI) was applied in the model to reflect treatment costs more accurately, by adjusting per cycle costs to account for dose interruptions, reductions or non-compliance (Table 64).

Table 64: Relative dose intensity

Treatment	Mean RDI	SD	Source
Lorlatinib	92.3%	0.14	CROWN CSR[75]
Alectinib	95.6%	0.10	NICE TA536[50]
Brigatinib	85.5%	0.19	NICE TA670[20]
Key: CSR, Clinical Study Report; NICE, National Institute for Health and Care Excellence; NR, not reported; RDI, relative dose intensity; SD, standard deviation.			

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The overall drug and administration costs applied in the base case are presented in Table 65 (assuming list prices).

Table 65: Treatment cycle and model cycle costs

Treatment	Selected pack	Selected pack size	Treatment cycle (days)	Treatment cycle cost	Model cycle cost (after RDI)	Admin cost per model cycle
Lorlatinib	100 mg	30	30	£5,283.00	£4,876.21	£10.40
Alectinib	150 mg	224	28	£5,032.00	£5,154.21	£11.14
Brigatinib (cycle 1)	Starter pack	28	28	£4,900.00	£4,869.64	£11.14
Brigatinib (cycle 2+)	180 mg (28 pack)	28	28	£4,900.00	£4,869.64	£11.14

B.3.5.2. Health state unit costs and resource use

Resource use and costs for each of the health states were based on NHS Reference costs. A micro-costing approach was used in line with the brigatinib (TA670) and alectinib (TA536) appraisals, whereby the frequencies of individual resources were broken down depending on the health state.[20, 50] Medical resources for monitoring patients with NSCLC based on the progression-free and post-progression health states are presented in Table 66 and Table 67, respectively. Frequencies are based on NICE TA670 and TA536.[20, 50] All monitoring costs are derived from the latest NHS Reference costs (2021/22) and from the PSSRU 2023.[128, 129] Unit costs are presented in Table 68.

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Table 66: Medical resources for monitoring patients based on progression-free/on treatment[20, 50]

Resource use - progression-free/on treatment - first cycle				Cost per month	Cost per cycle
Category	**Item**	**Frequency per month**	**Proportion of patient requiring resource**		
Physician visits	Oncology outpatient (f)	1	100%	£363.83	£358.60
Tests and procedures	Full blood test	1	100%	£2.96	£2.92
	Biochemistry	1	100%	£1.55	£1.52
Total cost per cycle					£363.04
Resource use - progression-free/on treatment - ongoing cycles				**Cost per month**	**Cost per cycle**
Category	**Item**	**Frequency per month**	**Proportion of patient requiring resource**		
Physician visits	Oncology outpatient (s)	0.75	100%	£166.11	£163.72
	GP visit	1	10%	£5.50	£5.42
	Cancer nurse	1	50%	£59.50	£58.65
Tests and procedures	Full blood test	1	100%	£2.96	£2.92
	Biochemistry	1	100%	£1.55	£1.52
	CT scan	0.5	100%	£61.74	£60.86
	MRI	0.2	50%	£34.64	£34.14
	X-ray	0.3	50%	£5.74	£5.66
	ECG	1	100%	£134.35	£132.42
Total cost per cycle					£465.31

Key: CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; MRI, magnetic resonance imaging.

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Table 67: Medical resources for monitoring patients based on progression/off treatment[20, 50]

Resource use - progressed/off treatment					
Category	**Item**	**Frequency per month**	**Proportion of patients requiring resource**	**Cost per month**	**Cost per cycle**
Physician visits	Oncology outpatient(s)	1.25	100%	£276.84	£272.87
	GP visit	1	50%	£27.50	£27.10
	Cancer nurse	1.5	80%	£142.80	£140.75
Tests and procedures	Full blood test	1.5	100%	£4.44	£4.38
	Biochemistry	1.5	100%	£2.32	£2.29
	CT scan	0.75	100%	£92.62	£91.28
	MRI	0.5	80%	£138.57	£136.58
	X-ray	0.5	60%	£11.49	£11.32
Total cost per cycle					£686.57
Key: CT, computerised tomography; GP, general practitioner; MRI, magnetic resonance imaging.					

Table 68: Resource use unit costs

Resource	Cost	Source	Description
Oncology outpatient (first)	£363.83	NHS Reference Costs (2021/22)	OP, CL, 370, WF01B, 'Medical Oncology Non-Admitted F2F Attendance, First'
Oncology (subsequent)	£221.48	NHS Reference Costs (2021/22)	OP, CL, 370, WF01A, 'Medical Oncology Non-Admitted F2F Attendance, Follow-up'
GP visit	£55.00	PSSRU (2023)	Per surgery consultation lasting 10 minutes, including direct care staff costs with qualification costs
Cancer nurse	£119.00	NHS Reference Costs (2021/22)	CHS, NURS, N10AF, 'Specialist nursing, cancer related, adult face to face'
Biochemistry	£1.55	NHS Reference Costs (2021/22)	DAPS, DAPS04, 'Clinical Biochemistry'
Full blood test	£2.96	NHS Reference Costs (2021/22)	DAPS, DAPS05, 'Haematology'
CT scan	£123.49	NHS Reference Costs (2021/22)	Total HRGs, Weighted average: RD20A, RD20b, RD20C, RD21A, RD21B, RD21C and RD22Z
X-ray	£38.28	NHS Reference Costs (2021/22)	DADS, DAPF, 'Direct Access Plain Film'
MRI	£346.43	NHS Reference Costs (2021/22)	IMAG, IMAGOP, Imaging: Outpatient', RD03Z, 'Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast'

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Resource	Cost	Source	Description
ECG	£134.35	NHS Reference Costs (2021/22)	IMAG, IMAGOP, Imaging: Outpatient, RD51A , 'Simple Echocardiogram, 19 years and over'
Cognitive impairment	£282.28	NHS Reference Costs (2021/22)	MHCC, MHCCIA, MHCC18, 'Cluster 18: Cognitive impairment (low need)'
Mental health assessment	£196.11	NHS Reference Costs (2019/20)	MHCC, MHCCIA, MHCC01, 'Cluster 01: Common mental health problems (low severity)'
Statins	£16.83	British National Formulary	Annual cost of generic atorvastatin 10 mg
Key: CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; MRI, magnetic resonance imaging; NHS, National Health Service.			

Following the same approach as for the one-off disutility in Section B.3.4.2.3, a one-off cost is applied for intercurrent CNS progressions (see Section B.3.3.6). The additional costs associated with CNS progression are sourced from Le et al. 2023 and described in Table 69.[137] This is considered superior to the source used in TA670 for the following reasons: it is very recent and soon to be published, UK specific, co-authored by a UK based clinical expert, validated via panel interviews with UK clinicians for the purpose of the study, and finally further validated in three clinical consultations conducted by Pfizer for the purpose of this submission.[117]

The study compares the average costs for patients without CNS metastases with patients with CNS metastases during the first and subsequent years after CNS progression. The cost difference associated with CNS metastases is estimated and applied in the model as one-off costs. As the costs provided in the study are annual costs, the cost difference is adjusted to fit the assumed 24-month duration of CNS intercurrent events. Only the specific procedures for the treatment of CNS metastases are not adjusted, as they are assumed to be incurred at the start of the progression. The 24-month assumption is also supported by CNS metastases specific procedures – i.e. holocranial radiotherapy, radiosurgery (or stereotactic radiotherapy) and surgical resection – which in practice require at least 1 year for these procedures to take place as validated in the one-to-one clinical validations.[117] Therefore, the other resource use categories are assumed to last for only 1 year more beyond this.

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Table 69: HCRU associated with intercurrent CNS events

Resource	Patients without CNS metastases (First and subsequent years)	Patients with CNS metastases (First year)	Patients with CNS metastases (Subsequent years)
Specific procedures for the treatment of metastases	£0.00	£5,715.86	£2,393.70
Hospitalisations	£370.41	£1,062.09	£2,070.73
Medical visits	£2,817.43	£5,068.47	£5,068.47
Laboratory tests	£99.91	£99.91	£99.91
Imaging techniques	£1,039.23	£2,724.23	£2,724.23
Key: CNS, central nervous system; HCRU, healthcare resource utilisation.			

B.3.5.3. Adverse reaction unit costs and resource use

As discussed in Section B.3.3.7, it was assumed that Grade 1/2 AEs had negligible impact on costs and these were excluded from the model in line with prior appraisals except for AEs of special interest: hypertriglyceridemia, hypercholesterolemia, peripheral neuropathy, cognitive effects and mood effects.

Le et al. 2023 conducted interviews with UK clinical experts to assess the HCRU associated with CNS progression.[47] During the interviews, experts agreed that most of the adverse effects would require two blood tests and two medical oncology outpatient visits, aligned with NICE TA628 and TA670.[15, 20] However, experts also flagged that managing the AEs will not require additional resources as it will be considered during the regular visits and tests. These are nevertheless costed in this submission, which is a conservative approach.

AE costs were informed by NHS Reference Costs and the brigatinib appraisal (TA670), as shown in Table 70.[20, 129] AE unit costs were applied to the yearly patient AE rate to calculate annual AE costs, before these were combined with life years in each cycle of the model.

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Table 70: Adverse event costs per event

Adverse event	Cost	Source	Resource assumption
Hypertriglyceridemia	£0.00	NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits, statins
Weight increased	£0.00	NICE TA670, NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits
Increased lipase level	£0.00	NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits
Hypercholesterolemia	£0.00	NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits, statins
AST increased	£0.00	NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits
Gamma-glutamyltransferase increased	£0.00	NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits
Hypertension	£770.10	NICE TA670, NHS Reference Costs (2021/22)	NHS Reference Costs 2021/22; Total HRG; EB04Z Hypertension
Anaemia	£865.53	NHS Reference Costs (2021/22)	Total HRGs, Iron deficiency anaemia with CC score 0-1, 2-5, 6-9, 10-13 and 14+
Amylase increased	£0.00	NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits
Neutropenia	£627.97	NICE TA670, NHS Reference Costs (2021/22)	Agranulocytosis with CC Score 0-1, 2-4, 5-8, 9-12, 13+
Blood creatine phosphokinase increased	£0.00	NHS Reference Costs (2021/22)	Standard clinical practice requires: Blood tests x2, medical oncology outpatient visits x2 (NICE TA628). Managing the adverse event will not require additional resource as it will be considered during the regular visits and tests
Neutrophil count decreased	£0.00	NICE TA713, NHS Reference Costs (2021/22)	2 additional blood tests, 2 outpatient visits
Peripheral neuropathy	£442.95	NHS Reference Costs (2021/22)	2 outpatient visits
Cognitive effects	£725.23	NHS Reference Costs (2021/22)	2 outpatient visits, Cognitive impairment assessment (MHCC18)
Mood effects	£639.06	NHS Reference Costs (2021/22)	2 outpatient visits, mental health assessment (MHCC01)
Key: AST, Aspartate aminotransferase; CC, complications and comorbidities; HRG, healthcare resource group; TA, technology appraisal.			

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B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Subsequent treatment

Subsequent treatments following progression and cessation of initial treatment are included in the model and are applied once at the point of progression as a simplifying assumption.

The proportion of patients incurring the cost of subsequent treatments in each cycle was estimated as the proportion of patients who transitioned out of the on treatment health state in each model cycle without dying. This was estimated using the proportion of INV assessed PFS events that were deaths from the October 2023 data cut-off of the CROWN trial for lorlatinib (16.36%) and crizotinib (4.35%), and assuming the same proportion as crizotinib for alectinib and brigatinib.[7] The proportion of INV assessed PFS events that were deaths was assumed to be constant over time. The inverse of this proportion was applied to the proportion of patients leaving the on treatment health state in each cycle to estimate the proportion of patients whose ToT events were discontinuation. This approach was consistent with that used in the second-line lorlatinib model (TA628) and many other NSCLC appraisals, and was a simplifying assumption to enable an estimation of the proportion of patients in each cycle who are discontinuing treatment and are entering the progressed health state and hence are eligible for subsequent treatment.[15]

Subsequent treatment distributions for lorlatinib were applied based on clinical feedback from the UK advisory board (Table 71).[4] Advisors reported that currently available ALK TKIs are unlikely to be used in second-line following lorlatinib treatment; therefore, most patients receiving lorlatinib in first-line will receive chemotherapy as second-line treatment. Subsequent treatment distributions following first-line treatment with alectinib or brigatinib have been estimated using UK market share data for second- and third-line treatment and were also further validated more recently in one-to-one sessions with clinicians.[117] These proportions, after adjusting by the proportion of PFS events that are death (described above), broadly reflect the share of patients who would receive the next line of treatment in practice, around 83% (86.8%*[1-4.35%]) of all patients starting treatment with the comparators.

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Table 71: Re-weighted subsequent treatment distributions in clinical practice

Subsequent treatments	Lorlatinib	Alectinib	Brigatinib
Alectinib	0.00%	0.00%	0.00%
Crizotinib	0.00%	0.00%	0.00%
Ceritinib	0.00%	0.00%	0.00%
Brigatinib	0.00%	0.00%	0.00%
Lorlatinib	0.00%	86.80%	86.80%
Chemotherapy	86.80%	54.00%	54.00%
Immunotherapy	0.00%	0.00%	0.00%
VEGF-R	0.00%	0.00%	0.00%

Key: VEGF-R, vascular endothelial growth factor-receptor

Subsequent treatment durations were sourced from the literature and are presented in Table 72. Lorlatinib duration is based on a lorlatinib second-line trial Study 1001. Chemotherapy duration is based on the ASCEND-5 trial.[20] [138]

Table 72: Subsequent treatment durations (weeks)

Subsequent treatment	Duration	Source
Lorlatinib	64.36	Study 1001
Chemotherapy	6.30	ASCEND-5
Key: 2L, second-line; N/A, not applicable; TA, technology appraisal.		

Costs (excluding administration costs) of chemotherapy are presented in Table 73.

Table 73: Subsequent treatment unit costs

Treatment	Form	Unit	Pack size	Pack price (list price)
Pemetrexed	Vial	100 mg	1	£160.00
	Vial	500 mg	1	£800.00
Cisplatin	Vial	100 mg	1	£29.27
	Vial	50 mg	1	£27.98
Source: MIMS.[136]				

Table 74 presents subsequent treatment costs per administration for treatments that are not already included in the model at first-line. In line with NICE TA670, pemetrexed plus cisplatin is assumed representative of chemotherapy.[20]

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Table 74: Subsequent treatment costs (other than first-line treatments)

Treatment costs	Treatment cost (per administration)	Administration cost (per administration)	Administrations per month
Pemetrexed	£1,380.97	£221.35	1.45
Cisplatin	£15.62	£0.00	1.45

Table 75 presents the final calculated one-off treatment cost applied upon progression for each treatment, considering the subsequent treatment distributions, drug costs (assuming no PAS), administration costs and subsequent treatment durations.

Table 75: One-off subsequent treatment cost applied upon progression in the model

First-line treatment	Cost (at list price)
Lorlatinib	£3,172
Alectinib	£70,970
Brigatinib	£70,970

B.3.5.4.2. End-of-life care costs

A one-off end-of-life cost is applied in the model on entering the death health state. Round et al. evaluates end-of-life costs for patients with various cancers.[139] Unit costs, resource requirements and survival estimates are together modelled probabilistically to give overall health and social care costs during the end-of-life for each type of cancer included (breast cancer, colorectal cancer, lung cancer and prostate cancer). It is assumed that those costs reported for lung cancer are generalisable for ALK-positive NSCLC. In this approach, each of the costs has been inflated to 2022/23 for application within the model (Table 76).

Table 76: End-of-life costs (Round et al. 2015)[139]

End-of-life costs	Cost	Source
Mean health cost per condition	£3,157	Round et al. 2015[139]
Mean social care cost per condition	£1,358	Round et al. 2015[139]
Total end-of-life cost	£5,123.24	Uplifted using PSSRU (2022/2023)[128]
Key: PSSRU: Personal Social Services Research Unit.		

B.3.5.4.3. Testing costs

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ALK status testing is well established in UK practice and takes place with other diagnostic testing before first-line treatment and so testing costs are not included.[19]

B.3.6. Uncertainty

Given lorlatinib represents a transformational change in treatment for patients with ALK-positive advanced NSCLC, significant uncertainty remains despite 60 months of follow-up, as only a small number of progression events and deaths have occurred in the lorlatinib treatment arm. The OS data from the CROWN study remain very immature, with only 51 (26%) of the total 198 deaths required for the final OS analysis having occurred at the March 2020 data cut-off. Further OS analyses are planned when 70% and 100% of the 198 OS events required for the final OS analysis have occurred.

Various survival extrapolation methods were explored to help capture the unique PFS hazard profile observed for lorlatinib. An additional more mature external source (Study 1001, EXP1 cohort) of OS data was used to supplement immature CROWN data. Nevertheless, although this helps to establish credible short-term predictions, there is great uncertainty in longer-term projections and so 10-year waning is retained in the base case.

In contrast to PFS NMA results, the NMA OS results are highly uncertain given that the PFS benefit has not yet fed through into available observed OS. The separation between lorlatinib and crizotinib is expected to emerge later in the protocol driven OS data cuts and will give more certainty to the relationship between PFS and OS and relative OS versus second generation ALK inhibitors.

Sequencing and subsequent treatments add another layer of uncertainty to this appraisal. As discussed, subsequent ALK inhibitor 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 (see Section B.2.9.2.4 and B.3.3.4.1). Most patients following treatment with alectinib (the majority first-line treatment) and brigatinib will receive second-line lorlatinib in clinical practice and the trial sources of evidence that inform OS underestimate this proportion, particularly for alectinib: 13.1% in ALEX, 15.0% in ALESIA and 29.7% in ALTA-1L

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(see Section Table 25). To account for the confounding effect introduced by subsequent therapies, a pseudo state transition approach was used for alectinib and brigatinib, which is in line with TA909.[1]

Overall, this modelling approach implies the following broad outcomes under base case conditions:

- Progression-free survival is predicted to be greater for lorlatinib versus the second generation ALK inhibitors. This is indisputable and consistent with available clinical evidence and with clinical expert interpretation of the data during the advisory board and one-to-one clinical consultations[4] [117]
- PPS is predicted to be lower for lorlatinib versus second generation ALK inhibitors. This is highly uncertain and broadly unknown, but is also plausible given the subsequent treatments available in each case according to clinicians[4]
- OS is predicted to be greater for lorlatinib versus second generation ALK inhibitors. Due to the immaturity of the trial data, no robust conclusions can yet be drawn from the OS data.[10] However, clinical advice suggests that although long-term OS is uncertain, given the lack of death and progression events it can be expected that the long PFS will translate to a long OS, with potentially a 'decadal' median OS (i.e. at least 10 years).[4] Further OS analyses are event-driven, planned when 70% and 100% of the 198 OS events needed for the final OS analysis have occurred, and therefore their date is unknown
  - Assuming there was no second-line lorlatinib use, clinicians would agree that lorlatinib would provide an OS benefit over alectinib/brigatinib, with only the degree of benefit subject to uncertainty
  - Even with subsequent second-line lorlatinib available, many patients will receive the most effective ALK inhibitor (lorlatinib) for a longer duration of treatment than alectinib/brigatinib plus second-line lorlatinib, even accounting for some stopping lorlatinib treatment before progression under long durations of treatment (evidenced by CROWN)

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B.3.7. Summary of base case analysis inputs and assumptions

B.3.7.1. Summary of base case analysis inputs

A summary of the model parameters in the base case is presented in Appendix O.

B.3.7.2. Assumptions

The model made several key assumptions, which are outlined in Table 77.

Table 77: Summary of key assumptions

Assumption	Justification	Section in submission
Lorlatinib - Partitioned survival analysis	Consulted clinicians agreed that subsequent ALK inhibitors were used in a small proportion of patients, and the impact of this is uncertain but likely low, considering there is no evidence or expectation that second generation ALK inhibitors will be effective following lorlatinib, which has the greatest coverage of ALK resistance mutations.	B.3.3.4.1
Comparators – Pseudo state transition approach	During the previous submission (TA909), the EAG had concerns related to the confounding effects introduced by subsequent TKIs in the pivotal trials informing the relative efficacy of comparators in the model. Given the EAG's concerns, the base case analysis uses a pseudo state transition approach with post-progression survival for the comparators. This model structure for the comparators follows the same approach as in TA909.	B.3.3.4.1
The model time horizon was 30 years	The time horizon of 30 years was based on the base case model settings, at which point less than 5% of patients remained alive (in all treatment arms) and the maximum modelled cohort age was 87 years (based on the mean baseline age of 57.4 years observed in the CROWN study). All recent NICE appraisals in first-line ALK-positive NSCLC used lifetime horizons (ranging from 10 to 30 years).	B.3.2.2.2
PFS	Parametric and non-parametric survival curves were fitted independently to lorlatinib and crizotinib patient-level data from CROWN. NMA HRs, which estimate the relative effect on survival outcomes versus crizotinib, were applied to baseline crizotinib curves to generate efficacy in the alectinib and brigatinib arms of the model. The use of HRs derived from an NMA relied on the assumption of proportional hazards between treatments. The 36-month piecewise Weibull curve was selected for the lorlatinib, and a standard Weibull curve for crizotinib.	B.3.3.3
OS - Lorlatinib	Parametric curves were fitted to the pooled CROWN + Study 1001 data for lorlatinib. A Weibull survival curve was chosen for lorlatinib following clinical feedback on the plausibility of long-term extrapolations.	B.3.3.4

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Assumption	Justification	Section in submission
PPS - Comparators	The pseudo state transition applies second-line OS data from Study 1001 (expansion cohort EXP3B-5', which includes patients with disease progression following one or more second generation ALK inhibitors) to capture post-progression survival following first-line treatment with an ALK inhibitor. The exponential curve was selected. The incorporation of time-varying PPS would have required multiple tunnel states.	B.3.3.4.1
ToT - Lorlatinib	A HR was estimated for ToT versus PFS observed in CROWN. That HR is applied in modelling to retain the pivotal trial observed relationship.	B.3.3.5
ToT - Comparators	For alectinib and brigatinib, as shown in their respective appraisals, observed PFS from pivotal trial overlayed with ToT almost perfectly and so in line with appraisals TA536 and TA670, ToT is assumed to equal PFS.[20, 50]	B.3.3.5
AE criteria	Includes Grade ≥ 3 AEs occurring in at least 5% of patients in either arm of CROWN, the alectinib arm of ALEX, or the brigatinib arm of ALTA-1L; as well as AEs of special interest for lorlatinib, regardless of grading.	B.3.3.7
Subsequent treatments	Subsequent treatments are applied as one-off cost and utility benefit upon entry to the progressed disease states.	B.3.5.4.1
Subsequent treatment options	Subsequent treatment distributions in clinical practice were estimated based on UK market share data and validated by UK clinicians.[4]	B.3.5.4.1
Subsequent treatment duration	Subsequent treatment durations were obtained from available lorlatinib second-line data, the previous brigatinib appraisal and the literature.[20, 138]	B.3.5.4.1
Resource use	In the micro-costing approach, resource use was assumed equal to that reported in the alectinib (TA536) and brigatinib (TA670) NICE submissions[20, 50] Additional resource use was applied for intercurrent CNS events to reflect the resource-intensive nature of brain metastases based on Le et al. 2023.[47]	B.3.5.2
ALK testing	ALK testing is now considered current clinical practice for advanced NSCLC[19], and so no testing costs were included in the model.	B.3.5.4.3

Key: AE, adverse event; ALK, anaplastic lymphoma kinase; CNS, central nervous system; HR, hazard ratio; HRQL, health-related quality of life; KM, Kaplan–Meier; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal; TKI, tyrosine kinase inhibitor; ToT, time on treatment.

B.3.8. Base case results

B.3.8.1. Probabilistic results

As already discussed, alectinib is considered the main comparator given large market share; brigatinib is the minor comparator and has been included for

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completeness. Base case results assume a [redacted] PAS for lorlatinib. Alectinib and brigatinib have confidential discounts; for illustrative purposes, the model assumed [redacted] discount for both alectinib and brigatinib.

The probabilistic sensitivity analysis (PSA) was performed with 2,000 iterations. Pairwise analyses versus alectinib and brigatinib are presented in Table 78 and Table 79. Lorlatinib probabilistic total costs are consistently below the deterministic results and this reduces the probabilistic ICERs. This is due to the non-linear nature of modelling which is reflected in nonsymmetric distribution of model outputs produced by the PSA.

In particular, uncertainty in lorlatinib survival extrapolations leads to a wide range of iterations of the PFS curve (and subsequently ToT) being capped by OS (i.e. consistent with proper modelling practice) leading to a lower mean probabilistic life years in the progression-free health state, ToT, acquisition costs and ICERs. Additionally, iterations with longer overall survival are affected proportionally more by treatment effect waning than the iterations with shorter overall survival, leading to a lower mean probabilistic life years for lorlatinib. The NICE methods guide is clear that committees should use probabilistic ICERs for decision making where there are differences because of nonlinearity in modelling.

Table 78: Probabilistic base case results versus alectinib

Intervent-ion	Total costs	Total LYs	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£ per QALY)
Alectinib	[redacted]	5.64	3.48				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,558
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 79: Probabilistic base case results versus brigatinib

Intervent-ion	Total costs	Total LYs	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£ per QALY)
Brigatinib	[redacted]	5.36	3.19				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,421
Key: ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life years gained; QALY, quality-adjusted life year.							

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The visual results of the PSA are presented in Figure 31 and Figure 32 which plot the incremental cost and QALY results for each PSA iteration.

Figure 31: Cost-effectiveness plane from 2,000 PSA iterations versus alectinib

Figure 32: Cost-effectiveness plane from 2,000 PSA iterations versus brigatinib

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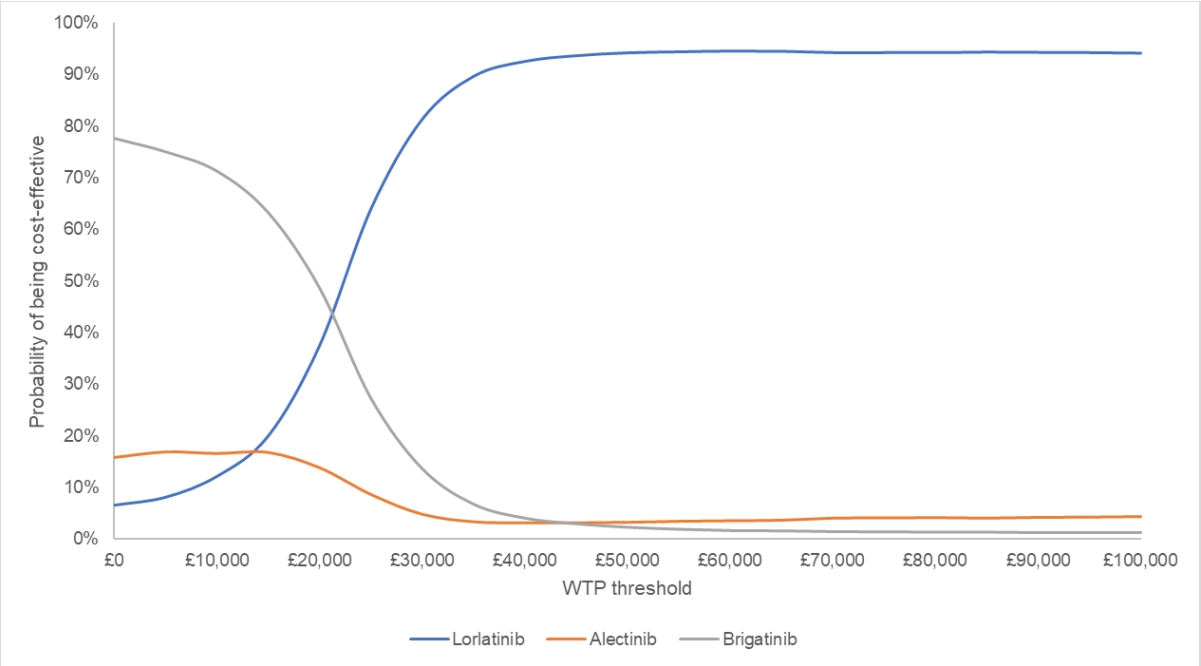
From the PSA, a cost-effectiveness acceptability curve (CEAC) was constructed. The CEAC is presented in Figure 33 and shows the likelihood that lorlatinib is a cost-effective option at different willingness to pay (WTP) thresholds. At a WTP threshold of £30,000 the probability that lorlatinib is the most cost-effective treatment option versus all comparators is 81.4%.

Figure 33: Incremental cost-effectiveness acceptability curve



B.3.8.2. Deterministic results

The model predicts an additional [redacted] QALYs versus alectinib, and [redacted] QALYs version brigatinib, with a pairwise ICERs of £19,138 and £23,042 per QALY gained, respectively. It is important to note that the probabilistic ICER is lower and that this should be used for committee decision making (in line with the methods guide).

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Table 80: Base case results versus alectinib

Intervention	Total costs	Total LYs	Total QALYs	Lorlatinib versus comparators			
				Incr. costs	Incr. LYG	Incr. QALYs	ICER (£ per QALY)
Alectinib	[redacted]	5.55	3.44	[redacted]	[redacted]	[redacted]	£19,138
Brigatinib	[redacted]	5.28	3.17	[redacted]	[redacted]	[redacted]	£23,042
Lorlatinib	[redacted]	[redacted]	[redacted]				

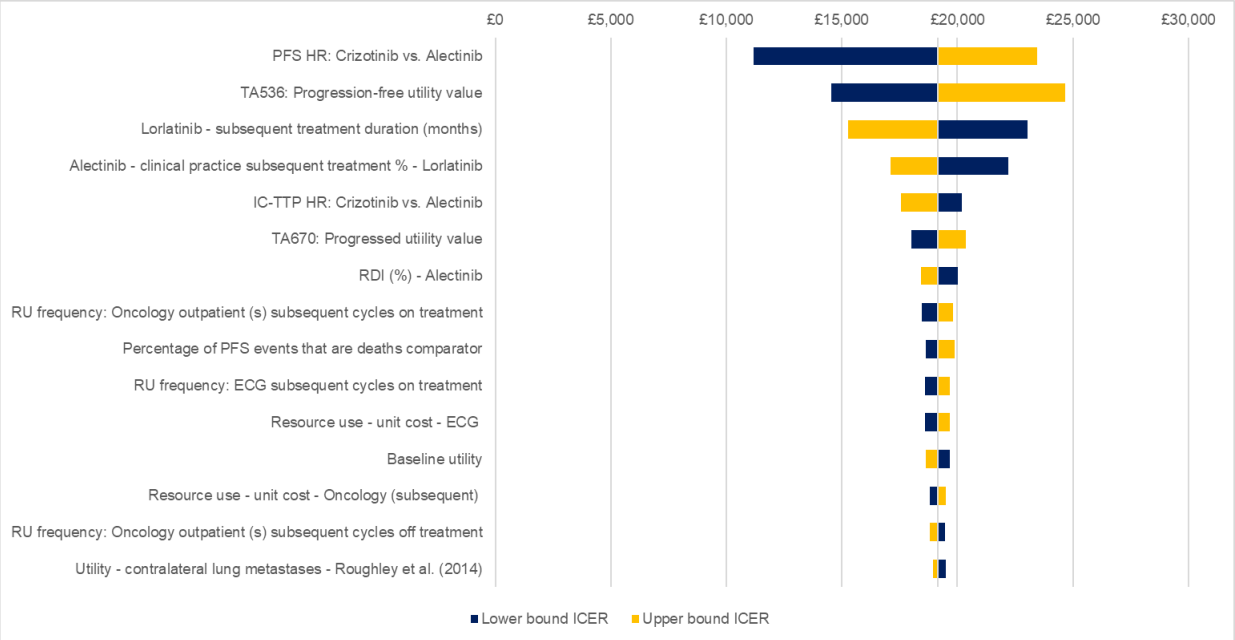
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

B.3.9. Exploring uncertainty

B.3.9.1. Deterministic sensitivity analysis

Figure 34 presents a tornado diagram showing the parameters that have the greatest impact on the ICER in the base case analysis, with descending sensitivity.

Figure 34: Tornado diagram showing the 10 most influential parameters on the base case versus alectinib



Key: ECG, electrocardiogram; HR, hazard ratio; IC-TTP, intracranial time to progression; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; RU, resource use; RDI, relative dose intensity; TA, technology appraisal

As expected, the largest driver of the cost-effectiveness was the alectinib PFS hazards ratio versus crizotinib, followed by the progression-free utility value used for

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alectinib and lorlatinib subsequent treatment duration after first-line alectinib. Similar results were observed for the comparison with brigatinib.

B.3.9.2. Scenario analyses

Several additional scenario analyses were considered to explore the uncertainty around various assumptions. A list of the scenarios and results are presented in Table 81. Note that these are deterministic ICERs and as already discussed probabilistic ICERs should be taken into account in decision making.

Table 81: Results of scenario analyses versus alectinib

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	Base case	[redacted]	[redacted]	£19,138
1	TA670 EOL cost source	[redacted]	[redacted]	£19,292
2	Criztotinib PFS BICR estimates (full follow-up)	[redacted]	[redacted]	£19,681
3	Criztotinib PFS BICR estimates (after month 16)	[redacted]	[redacted]	£11,559
4	Lorlatinib semi-PSM approach for lorlatinib	[redacted]	[redacted]	£28,949
5	OS/PFS waning at 12 years	[redacted]	[redacted]	£21,836
6	OS/PFS waning at 15 years	[redacted]	[redacted]	£23,635
7	Lorlatinib PFS utility from TA536 (ALEX)	[redacted]	[redacted]	£20,559
8	PFS utility from TA670 (ALTA 1L)	[redacted]	[redacted]	£21,369
9	Lorlatinib OS/PFS - Exponential	[redacted]	[redacted]	£18,830
10	Crizotinib PFS (best AIC/BIC) - Log logistic	[redacted]	[redacted]	£19,821
11	Standard PSM approach for comparators - Crizotinib OS/PFS Weibull	[redacted]	[redacted]	£26,632
12	Crizotinib PFS - Exponential	[redacted]	[redacted]	£18,531
13	Roughley et al. (2014) - decrement approach	[redacted]	[redacted]	£19,193
14	CNS progression utility decrement based on Liu et al.(2022)	[redacted]	[redacted]	£19,324

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BICR, Blinded Independent Central Review; CNS, central nervous system; EOL, end-of-life; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival models.

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The scenarios that had the largest impacts were related to lorlatinib model structure (using a semi-PSM approach) and the comparators model structure (using a standard PSM approach).

B.3.10. Benefits not captured in the QALY calculation

CNS progression has a substantial impact on QoL for patients. Patients report lower EQ-5D-3L utility index, EQ-5D visual analogue scale (EQ-VAS) and EORTC QLQ-C30 global health status and greater work and activity impairment with worsening ECOG performance status,[43] therefore the benefit of lorlatinib in delaying CNS disease progression is likely to have a substantial impact on QoL for patients. Therefore, the impact of CNS progression on utilities, as calculated by applying a one-off disutility based on the CNS multiplier from Roughley et al. (2014)[42] and the 24 months of post-CNS progression survival,[38] may not fully capture the QoL impact of CNS metastases.

The QoL impact of advanced lung cancer on caregivers is also substantial which has not been included in the cost-effectiveness model. Caregivers also report greater activity impairment and higher burden of caring for patients (as measured by Zarit-Caregiver-Burden) with worsening ECOG performance status. Caregivers report missing 6.9% of work time.[140] The increased impact of CNS progression on carers is also significant in terms of reduced QoL and ability to work, further amplifying the missed value within the model framework.

B.3.11. Validation

B.3.11.1. Validation of cost-effectiveness analysis

External validation – trial data sources

The PFS extrapolations were derived via anchored network comparisons, which will be influenced by factors such as variations in anchor treatment (crizotinib) efficacy across trials and the chosen fitting to crizotinib PFS from CROWN. Therefore, a direct comparison of the NMA-based extrapolations with observed trial data should be interpreted with caution. The extrapolated brigatinib PFS overshoots the ALTA-1L Kaplan–Meier curve, but underfits the tail and this is in line with the direct fittings presented in TA670 and not an uncommon problem in NSCLC appraisals.[20] The

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alectinib PFS is centred between the Kaplan–Meier curves from the ALEX and ALESIA trials which is to be expected given that they are nodes in the NMA; the PFS extrapolation again underfits the ALEX tail as with the brigatinib extrapolation.

Regarding the OS extrapolations, in the alectinib appraisal (TA536), the exponential curve led to 5.11 life years gained in the company base case,[50] compared to 5.55 life years gained for alectinib using the pseudo state transition approach here. In the brigatinib appraisal (TA670), the exponential curve led to 5.87 life years gained[20] versus 5.28 life years gained using the pseudo state transition approach. Additionally, in line with the PFS extrapolations, this approach overestimates OS at first and then underfits the tails of the ALEX and ALTA-1L trials.

CNS intercurrent events accrued over time are aligned with reported CROWN events at 5 years: nine patients (6%) are reported to have had intracranial progression and this is identical to model predictions. A summary of the validation of the modelled outcomes versus the respective trials is presented in Table 82. For comparison with long-term follow-up landmark survival please see Section B.3.3.

Table 82. Clinical outcomes summary

Treat-ment	Average OS (months)				Average PFS (months)			
	Model result		External data		Model result		External data	
	Mean	Median	Median	Source	Mean	Median	Median	Source
Lorlatinib	100.28	88.71	NR	CROWN (Shaw 2020)[10]	78.11	88.71	NR	CROWN (Solomon 2024)[7]
Alectinib	66.65	57.17	NR	ALEX (Mok 2020)[83]	37.61	27.6	34.8	ALEX (Mok 2020)[83]
Brigatinib	63.41	54.21	NR	ALTA-1L (Camidge 2021)[98]	34.37	25.63	24	ALTA-1L (Camidge 2021)[98]

Key: PFS, progression-free survival; OS, overall survival.

External validation – one-to-one interviews

Model inputs such as CNS progression HCRU (see Section B.3.5.2) and subsequent treatment distributions (see Section B.3.5.4) were validated in one-to-one interviews.[117] Survival extrapolations outputs were also validated in one-to-one interviews (see Section B.3.3.3 and B.3.3.4).[117]

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B.3.12. Interpretation and conclusions of economic evidence

B.3.12.1. Strengths and weaknesses of the economic evaluation

The economic analysis has a number of key strengths:

- Piecewise models were implemented for lorlatinib to better capture its unique PFS curve with waning employed to capture long-term uncertainty (see Section B.3.3.3)
- CROWN OS data were pooled with Study 1001 to overcome the immaturity of the CROWN OS data without introducing biases based on baseline characteristics and subsequent therapies differences (see Section B.3.3.2.1)
- A pseudo state transition approach was applied to the model comparators to account for the confounding effect introduced by subsequent therapies in the trials (see Section B.3.3.2.1)
- The modelling of CNS intercurrent events is consistent with the definition of the IC-TTP endpoint and allows modelling of the impact of brain metastases on costs and QoL with a simple and straightforward approach which can be easily validated (see Section B.3.3.6)
- The additional costs associated with CNS progression are sourced from Le et al. 2023, which is UK specific, co-authored by a UK based clinical expert and validated via panel interviews with UK clinicians for the purpose of the study (see Section B.3.5.2)[137]
- EQ-5D-5L was collected in CROWN. The mapping of this allowed utility to be aligned with the NICE reference case – EQ-5D; measured directly from patients; valued using the UK general population tariff (see Section B.3.4.1)
- CROWN OS data are immature. To overcome the immaturity of the OS data, the CROWN Kaplan–Meier data were pooled with Study 1001 cohort EXP1 (see Section B.3.3.2.1)
- In the trial, the comparators display a mismatch between subsequent treatments and lorlatinib second-line use in real-world practice. To account for the confounding effect introduced by subsequent therapies, a pseudo state transition approach was used for alectinib and brigatinib (see Section B.3.2.2 and B.3.6).

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The approach used to account for the uncertainty caused by subsequent therapies is based on the previous lorlatinib submission TA909[1]

- The CROWN trial lacks direct head-to-head comparison versus alectinib and brigatinib. An NMA was conducted to assess the comparative efficacy between lorlatinib, alectinib and brigatinib (see Section B.2.9). The NMA results were supported by additional published MAICs using data from the September 2021 (Section B.2.9.5)[98]

B.3.12.2. Conclusions from the economic evidence

Lorlatinib demonstrates a clinical benefit over comparators in terms of improved PFS and IC-TTP, which translated into substantial QALY and LY gains. As discussed, probabilistic ICERs are preferred for decision making and these give ICERs of £15,558 per QALY gained versus alectinib and £20,421 per QALY gained versus brigatinib. In conclusion, lorlatinib is undoubtedly the most effective ALK inhibitor available to date at delaying systemic and CNS progression in patients (see Section B.3.6 for a discussion of survival uncertainties). Clinicians strongly endorse it as an additional option for clinicians and patients in first-line. The archetypal patient for which lorlatinib will be most effective in first-line will emerge in clinical practice based on factors such as overall symptom burden and fitness, age, extent of existing brain metastases, likelihood of developing brain metastases and patient preference.

The clinical and economic evidence suggests that even while displacing lorlatinib in second-line, lorlatinib will be transformational for this patient: a duration of treatment on the most effective ALK inhibitor greater than the alternative sequence, lower risks of clinical and CNS progression, and a longer life.

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B.4. Appendices

Appendix A:

Appendix B:

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: CROWN additional information

Appendix N: Indirect treatment comparison – additional information

Appendix O: Summary of base case analysis inputs

B.5. References

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Single technology appraisal

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

Summary of Information for Patients (SIP)

September 2024

File name	Version	Contains confidential information	Date
ID6434_Lorlatinib_SummaryInformationPatients_Sep2024(ACiC)	FINAL	No	12th Sept 2024

Summary of Information for Patients (SIP):

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response:
Lorlatinib / Lorviqua®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
Patients with advanced ALK-positive non-small cell lung cancer (NSCLC) that has not previously been treated with an ALK inhibitor.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
Marketing authorisation was granted on the 23rd September 2021. Lorlatinib can be prescribed for patients if they have not been previously treated with an ALK inhibitor. https://mhraproducts4853.blob.core.windows.net/docs/7723672bc3caa21b31eb89e1b97d4e75b7e9b4f6 Lorlatinib was previously available only for patients who have been previously treated with another first-line ALK inhibitor, and it is still available for these patients as a second line therapy.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response: Pfizer has previously collaborated with ALK+ UK to co-create educational materials for patients and carers and has also provided donations to support their work. This work has now ceased but during the appraisal there may be ongoing collaboration on patient support programs.

SECTION 2: Current landscape

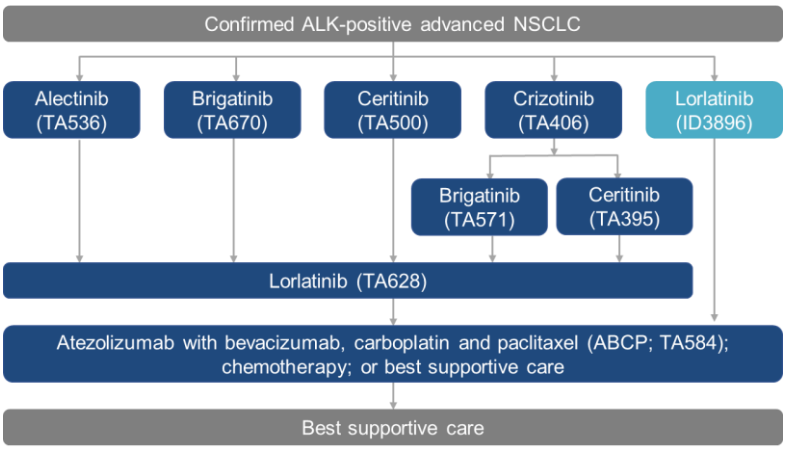
2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Response: There were 36,886 cases of lung cancer diagnosed in England in 2022.[1] About 90% of lung cancers are classified as non-small cell lung cancer. It is estimated that between 3 and 7% of non-small cell lung cancers are ALK-positive, which is when patients have a change in the DNA of their cancer cells which makes their cancer grow more quickly. These patients are eligible for lorlatinib if they have not previously received treatment with an ALK inhibitor for this condition. Patients diagnosed with ALK-positive non-small cell lung cancer are typically younger than patients diagnosed with all cancers. About half of patients with ALK-positive non-small cell lung cancer are diagnosed before the age of 50. There is no known correlation of ALK-positive non-small cell lung cancer with any environmental toxins, including smoking, second-hand smoke, asbestos and air pollution.[2] (https://www.alkpositive.org/what-is-alk) Patients diagnosed with ALK-positive non-small cell lung cancer live for 6.2 years on average.[3] As their cancer progresses, patients report lower quality of life (measured by their ability to: conduct their usual activities, pain, anxiety and depression and self-care abilities). They also report worse physical, emotional and cognitive function, and reduced ability to work. ALK-positive non-small cell lung cancer commonly spreads to the brain (brain metastases) which can cause confusion, drowsiness, weakness and headaches, which impacts on patients' quality of life and survival and requires additional care. Brain metastases is particularly worrying for the patient because it can impact the ability to live independently with significant negative impacts on emotional wellbeing, ability to drive and work which can have financial ramifications. https://www.christie.nhs.uk/patients-and-visitors/your-treatment-and-care/types-of-cancer/secondary-brain-tumours

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Response: Genetic testing is already routinely done for patients diagnosed with non-small cell lung cancer. No additional diagnostic tests are required with this new treatment.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: ○ if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. ○ are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
Response: Currently available treatments for patients who have not previously received an ALK inhibitor are alectinib, brigatinib, ceritinib and crizotinib.[4-7] Of these, alectinib and brigatinib are currently the most effective treatments, which are therefore most commonly used. The dark blue boxes show existing treatment options, and the light blue box shows where lorlatinib is expected to be used.      Lorlatinib has demonstrated that it is able to cross into the brain well, to prevent the spread of tumours into other parts of the body including the brain, or to treat tumours which have already spread.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

There are 2 studies which have been identified reporting on the results of questionnaires to patients living with advanced non-small cell lung cancer and their caregivers.[8,9]

The studies show that as lung cancer progresses, patients report lower quality of life (measured by their ability to: conduct their usual activities, pain, anxiety and depression and self-care abilities). They also report worse physical, emotional and cognitive function, and reduced ability to work. The impact on caregivers on needing to provide additional care is also reported. The impact of lorlatinib on quality of life is discussed further in section 3f of this document.

The humanistic burden associated with caring for patients with advanced non-small cell lung cancer (NSCLC) in three European countries—a real-world survey of caregivers | Supportive Care in Cancer (springer.com)

The humanistic burden of advanced non-small cell lung cancer (NSCLC) in Europe: a real-world survey linking patient clinical factors to patient and caregiver burden - PubMed (nih.gov)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Lorlatinib is an ALK inhibitor which works by turning off the faulty ALK proteins in cancer cells causing the cancer cells to die. In addition, Lorlatinib can help to prevent the spread of cancer into the brain.

Lorlatinib (Lorviqua) | Cancer information | Cancer Research UK

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Response: Lorlatinib is not intended to be used in combination with any other treatments.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Response: The dose is one tablet to be taken by mouth (orally) once a day (100 mg). Lorlatinib may be taken with or without food.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
Response: Lorlatinib is being investigated in the following clinical trial[10]: *"A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC"* (https://clinicaltrials.gov/ct2/show/NCT03052608) This current NICE submission will include updated progression-free survival data of more than 5 years. The most recent data was only presented recently and can be found in the link below. Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study | Journal of Clinical Oncology (ascopubs.org) CROWN is a global clinical trial of two hundred and ninety-six patients. Eligible patients are aged eighteen years and over, have lung cancer with the ALK mutation and must not have previously received treatment with an ALK inhibitor for this condition. The clinical trial has already been underway for approximately sixty months but is ongoing to continue to assess how many patients

remain in a stable disease state and alive over a longer time period.

A publication from this clinical trial at approximately eighteen months is available here[11]: https://www.nejm.org/doi/full/10.1056/NEJMoa2027187

A plain language summary of the clinical trial is available here[12]:

Plain Language Summary of the CROWN Study Comparing Lorlatinib with Crizotinib for People with Untreated Non-Small Cell Lung Cancer: Future Oncology: Vol 17, No 34 (tandfonline.com)

An earlier study, which included previously untreated ALK-positive patients, in addition to previously treated patients and another gene mutation, can be found here[13]:

Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study - ScienceDirect

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

Of the two hundred and ninety-six patients in the clinical trial, one hundred and forty-nine received lorlatinib and one hundred and fifty-seven received crizotinib (a current treatment option for ALK-positive non-small cell lung cancer). Comparing the treatment effect between lorlatinib and crizotinib it was found that:

- More patients responded to lorlatinib than crizotinib and on average these responses lasted longer.
- After sixty months of treatment, more patients receiving lorlatinib than crizotinib in the clinical trial had not seen their condition progress/worsen (progression-free survival).
    - At 5 years 60% of lorlatinib patients had yet to progress compared with 8% of crizotinib patients yet to progress.
    - Lorlatinib patients had an estimated 81% less risk of progressing compared with crizotinib (a statistically significant treatment effect).
- More patients who took lorlatinib had cancer that shrank, including in the brain. This is called intracranial progression and was measured in a similar way to overall progression-free survival.
    - The treatment effect here was even higher than with overall progression-free survival.
- Fewer patients who took lorlatinib died or had tumour progression. Most patients receiving lorlatinib were alive after eighteen months of treatment.
- Patients in the clinical trial are still being monitored to observe how lorlatinib benefits patients over a longer time period.

More information can be found in the NICE evidence submission (Document B (Section 2.6)) and also the link for the five year results: Lorlatinib Versus Crizotinib in Patients With Advanced ALK-

Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study | Journal of Clinical Oncology (ascopubs.org)

This trial-based comparison versus crizotinib also meant we could compare effectiveness with alectinib and brigatinib using indirect treatment methods (network meta-analysis), by combining evidence from all the trials for these medicines. Comparing treatment effectiveness for lorlatinib and alectinib and brigatinib it was found that:

- Lorlatinib patients had an estimated 51% less risk of progressing compared with alectinib (a statistically significant treatment effect).
- Lorlatinib patients had an estimated 56% less risk of progressing compared with brigatinib (a statistically significant treatment effect).
- More patients who took lorlatinib had cancer that shrank, including in the brain. This is called intracranial progression and was measured in a similar way to overall progression-free survival. The risk reductions for this were even higher than for overall progression.

More information on these indirect comparisons can be found in the NICE evidence submission (Document B (Section 2.9))

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Patients who received lorlatinib in the clinical trial had a significantly greater overall improvement in quality of life than those who received crizotinib.
Quality of life was assessed by asking patients to complete the EQ-5Q-5L questionnaire that is required by NICE to give a quantitative structure to how patients feel. The questionnaire assesses self-care, ability to do daily activities, mobility, pain, anxiety and depression. In addition, patients were also asked to complete a questionnaire specific to cancer (EORTC QLQ-C30).

ALK-positive non-small cell lung cancer commonly spreads to the brain (brain metastases) which can cause confusion, drowsiness, weakness and headaches, which impacts on patients' quality of life and survival and requires additional care. Brain metastases is particularly worrying for the patient because it can impact the ability to live independently with significant negative impacts on emotional wellbeing, ability to drive and work which can have financial ramifications.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had

treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Almost all patients receiving both lorlatinib and crizotinib had some side effects, either mild, moderate or serious. These side effects can be well managed by either temporary dose reductions and/or with additional standard medical therapies such, as lipid lowering agents[14].

More detail on the management of these adverse events can be found in the following document: Clinical Management of Adverse Events Associated with Lorlatinib - PMC (nih.gov)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

Lorlatinib is a newer treatment which has been designed to cross into the brain to help prevent the spread of cancer to the brain. This both helps prevent the progression of lung cancer into the brain, and if the cancer has already spread into the brain, helps prevent further progression.

Lorlatinib extends the amount of time in which patients do not experience a worsening in their condition versus all other currently available treatments (progression-free survival). It is expected that this will increase the amount of time patients will live overall too (overall survival). Although the clinical trial has not yet been conducted for a long enough time period to measure how long patients live overall, the clinical trial is ongoing to help assess this.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

Almost all patients receiving both lorlatinib and crizotinib had some side effects, either mild, moderate or serious. These were broadly in line with other ALK inhibitor medicines and management would be similar (see above 3g for more detail).

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

A health economic model has been developed to assess the value of the drug lorlatinib to the NHS. The model is split into three health states which is designed to reflect the condition of patients. The four-health states are:

1) Progression-free; when the patient is responding well to treatment
2) Progressed disease; to capture worsening disease
3) Death

The impact of progression in the brain (brain metastases) on patient quality of life and costs to the NHS were accounted for in modelling.

Eighteen months of overall survival clinical trial data was included in the model because not enough events have occurred for a later data cut to be used. Sixty months of clinical trial data for progression-free survival and prevention of progression in the brain were included in the model.

Lorlatinib treatment is projected to extend life, but it is uncertain by how much, as the clinical trial has not been conducted for a long enough time and many patients are still alive. Therefore, the clinical trial data has had to be extrapolated to estimate how long patients respond to lorlatinib.

Quality of life was assessed by asking patients to complete the EQ-5Q-5L questionnaire, which assesses self-care, ability to do daily activities, mobility, pain, anxiety and depression. Patients were also asked to complete a questionnaire specific to cancer (EORTC QLQ-C30).

Patients who received lorlatinib in the clinical trial had a significantly greater overall improvement in quality of life than those who received another first line treatment (known as crizotinib) for non-small cell lung cancer. The clinical trial did not look at the quality of life against the other first line treatments (known as alectinib and brigatinib) for non-small cell lung cancer, but the outcome is expected to be similar.

If a new medicine has any impact to the NHS that will result in additional costs to them which are over and above the current standard of care, such as additional hospital visits or costs in administering the medicine, these also have to be included in the health economic model. For lorlatinib, there are no cost implications for the health service compared to existing treatments. In addition, there are no differences in the way the medicine is given which need to be taken into consideration compared to existing treatments, as all treatments are in tablet form.

With all these costs and clinical inputs included in the model it is then possible to estimate, through a series of scenarios, how effective lorlatinib might be over a period of thirty years (a timeframe NICE request the analysis to be run over). As we do not have thirty years' worth of clinical trial data available (to date the clinical trial has run for thirty-six months (which is three years)), the data had to be extrapolated. Consequently, there is uncertainty in how the extrapolations will reflect reality. We will continue to collect data to reduce this uncertainty through a clinical trial extension period.

The progression free survival that was used was for alectinib, brigatinib and crizotinib. This was collected over a four- or five-year time period through their clinical trial extension period. The inclusion of these additional comparisons showed us that the extrapolations we had made reasonably reflected what would happen in reality after four to five years. However, there remains some uncertainty in the longer time frames out to thirty years, which NICE will expect to be reflected in the cost effectiveness analysis and also to be reflected in the subsequent price of the medicine.

Having modelled the survival data, the next step is to assess the overall cost effectiveness of the medicine. The cost effectiveness model shows that non-small cell cancer patients gain additional years of life (life years) when receiving treatment with lorlatinib compared to alectinib and brigatinib. When also considering the quality of these additional years of life combined with the additional years (quality-adjusted life years; QALYs), lorlatinib also showed improvements compared to alectinib and brigatinib.

Pfizer has proposed a discount to the list price of lorlatinib (this is known as a patient access scheme). Using the economic modelling, lorlatinib has an ICER below £30,000 per QALY when the patient access scheme is applied.

Finally NICE ask for any additional factors that should be considered when assessing this medicine. At the moment there is not enough evidence to ask NICE to assess lorlatinib above the standard threshold, as the higher threshold is for more severe diseases. However, as lorlatinib has been demonstrated to be effective at reducing progression of cancer in the brain, this treatment is expected to have a substantial impact to patients and reduce their care needs, by reducing the symptoms of headaches, seizures (fits), feeling sick (nausea), being sick (vomiting) and drowsiness, behavioural changes, weakness and vision and speech problems.

The health economic model does not completely capture all of the benefits that lorlatinib is expected to offer patients. For example, the negative impact on quality of life for patients with progression in the brain may be greater in reality than can be captured in the model. A one-off cost of the progression of cancer to the brain is applied in the model, however the ongoing cost of social care and additional care requirements are not captured.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Lorlatinib offers patients improvements compared to existing treatments and therefore has been recognised as innovative by the Regulatory authorities in the UK, where the MHRA granted lorlatinib an Innovation Passport on 1st March, 2020.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

Some socio-economic, ethnic groups and underserved communities have their cancer diagnosed later than the general population and so receive treatment later (this is likely to include ALK+ NSCLC). Therefore, these groups are disproportionately impacted by the negative quality of life and economic impacts of progressing and in particular impact of progressing in the brain. Brain metastases has negative impacts on a patient's ability to live independently and can increase carer burden.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

- ALK Positive https://www.alkpositive.org/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/

- INAHTA: http://www.inahta.org/

4b) Glossary of terms

Response:

ALK-positive (ALK+)	Describes a type of cancer in which cells have a change in structure in the ALK gene or make too much ALK protein
EORTC QLQ-C30	A questionnaire to measure quality of life, specific to cancer
EQ-5D-5L	A questionnaire to measure quality of life
Life years	The number of additional years that patients spend alive.
Progression-free survival	The length of time that a patient lives with a disease without it getting worse.
QALY	Quality-adjusted life year. The number of additional years patients spend alive, however this measure also takes into account the quality of these additional years.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. State of the Nation Report 2024. Available at: REF444_NLCA-SotN-v13.05.24_2.0_FINAL.pdf (hqip.org.uk) (accessed June 2024)

2. ALK Positive. Accessed June 2024, https://www.alkpositive.org/what-is-alk
3. Gomes F, Yip K, Tokaca N, et al. The ALK project: a real-world national network and database. 2019;
4. NICE. Ceritinib for untreated ALK-positive non-small-cell lung cancer [TA500]. Available at: https://www.nice.org.uk/guidance/ta500 (accessed June 2024)
5. NICE. Alectinib for untreated ALK-positive advanced non-small-cell lung cancer [TA536]. Available at: https://www.nice.org.uk/guidance/ta536 (accessed June 2024)
6. NICE. Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor [TA670]. Available at: https://www.nice.org.uk/guidance/ta670 (accessed June 2024)
7. NICE. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [TA406]. Available at: https://www.nice.org.uk/guidance/ta406 (accessed June 2024).
8. Wood R, Taylor-Stokes G, Lees M. The humanistic burden associated with caring for patients with advanced non-small cell lung cancer (NSCLC) in three European countries—a real-world survey of caregivers. *Supportive Care in Cancer*. 2019;27(5):1709-1719.
9. Wood R, Taylor-Stokes G, Smith F, Chaib C. The humanistic burden of advanced non-small cell lung cancer (NSCLC) in Europe: a real-world survey linking patient clinical factors to patient and caregiver burden. *Quality of Life Research*. 2019;28(7):1849-1861.

10. ClinicalTrials.gov (NCT03052608). Available at: https://clinicaltrials.gov/ct2/show/NCT03052608 (accessed June 2024).
11. Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *New England Journal of Medicine*. 2020;383(21):2018-2029.
12. Solomon BJ, Bauer TM, De Marinis F, et al. Plain language summary of the CROWN study comparing lorlatinib with crizotinib for people with untreated non-small cell lung cancer. *Future Oncology*. 2021;17(34):4649-4656.
13. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *The lancet oncology*. 2018;19(12):1654-1667.
14. Bauer TM, Felip E, Solomon BJ, et al. Clinical management of adverse events associated with lorlatinib. *The Oncologist*. 2019;24(8):1103-1110.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

October 2024

File name	Version	Contains confidential information	Date
ID6434 lorlatinib_clarification_response_noCON_15Oct24_FINAL	1.0	No	16/10/2024

Note: an addendum ("Addendum – Flatiron RWE alectinib analysis") has been submitted with this response that summarises an additional validation analysis based on the Flatiron data, with a description of supporting documents (also provided) and impact on cost-effectiveness modelling. As described in that document, this could also form an alternative base case versus alectinib. An updated model has also been provided with this and any additional options requested in the clarification questions. In relation to modelling assumptions:

- *Pfizer accept that that CROWN PFS derived utilities are less valid than the alternatives and the EAG can update base case assumptions (see response to B9)*
- *Pfizer reject the concept of applying treatment beyond progression for lorlatinib, which is inconsistent with observed CROWN data (see response to B10)*
- *Pfizer believe the aforementioned flatiron analysis and using lorlatinib as the base treatment for applying NMA derived PFS HRs (see response to B2 and B5) can inform the plausible range of cost-effectiveness estimates*
- *Pfizer believe that the scenario that uses the pseudo state transition approach for lorlatinib (i.e. that uses post-hoc PROFILE study rates of mortality) can inform the plausible range of cost-effectiveness estimates, but should be seen as a pessimistic floor in PPS expectations following lorlatinib*

Section A: Clarification on effectiveness data

Additional information from CROWN and Study 1001

A1. Priority question: Please provide the latest versions of the statistical analysis plan, protocol (including a complete list of protocol amendments), and protocol deviations for CROWN and Study 1001 at the latest data cut available.

CROWN and Study 1001 SAPs and final or most recent protocol amendments have been submitted with this response (5 PDF files):

- "B7461006 SAP v3.0 final 02NOV2023"
- "B7461006 PA 8_clean_Public"
- "Protocol deviations list CROWN (1006)"
- "4_b7461001-sap"

- “Study 1001 final protocol amendments”

CROWN overall survival data

A2. Priority question: Whilst the EAG acknowledges the pre-specification of OS analyses in the CROWN trial protocol following the occurrence of 70% and 100% of OS events, the immaturity of overall survival (OS) data presented at 18-months follow-up only and lack of updated OS data from the previous appraisal of lorlatinib (TA909) are a considerable limitation of the current company submission (CS). The inclusion of immature OS data introduces substantial uncertainty into the indirect treatment comparisons of lorlatinib with a median of 18 months of follow-up compared to both alectinib (with 48 months follow-up) and brigatinib (with up to 61 months follow-up), as well as to extrapolations of OS for the purposes of economic modelling. Therefore, the inclusion of such immature OS data for lorlatinib has significant limitations for decision making.

To align with the ‘unplanned’ 5-year analysis of other clinical effectiveness (e.g. progression-free survival (PFS) and intracranial outcomes) and safety outcomes which inform the current CS, please provide an updated analysis of OS at the October 2023 data cut (or later if available), for the CROWN trial including Kaplan–Meier curves and a summary table of OS, as per CS Document B, Table 15, and a proportional hazard assessment.

According to the CROWN protocol, overall survival (OS) is a key secondary endpoint. As per the statistical analysis plan a maximum of three analyses were planned for OS. The first OS interim analysis took place at the time of the primary data cut-off at a median follow-up of 18 months, OS data were still maturing. At the time of the 5-year analysis, the required number of OS events for a protocol specified second OS interim analysis (at least 139 deaths) was not met (i.e. 70% information fraction).

Pfizer acknowledges that having only 18 months of overall survival for modelling makes decision making more challenging, however it is impossible for Pfizer UK to provide this data. OS is an alpha protected endpoint and as such any analyses that may occur before the endpoint is met must be pre-specified in the protocol to avoid selective and biased reporting of trial results. The 18-month presented OS is the first

interim analysis and the second interim analysis requires the 70% information fraction to be met as noted in the question (both pre-specified). Regulatory agencies have also requested the second interim analysis and the same standard is applied in that case. In the case of PFS, “unplanned” descriptive analyses have only occurred after protocol specified analyses in which the primary endpoint was met, which does not break trial reporting conventions.

A3. The EAG acknowledges that the CROWN trial OS data is confounded by the use of subsequent therapies following progression, including ALK inhibitors, and that the subsequent therapies patients received do not align with UK clinical practice (CS, Document B, Table 25 and p96). Without access to individual participant data from the CROWN trial, the EAG is unable to assess which methods, if any, outlined in updated NICE Decision Support Unit (DSU) Technical Support Document (TSD) 24 could be suitable for adjusting for the effect of the subsequent therapies used in the CROWN trial and if it is possible to fully adjust for the confounding effect of subsequent therapies on the comparison of lorlatinib and crizotinib for OS in the CROWN trial.

As exploratory analyses, to further investigate the extent and impact of the confounding of treatment effect by subsequent therapies, please consider and apply where appropriate, the following treatment switching adjustment approaches to the latest OS data cut available (preferably October 2023 or later):

a. **Inverse Probability of Censoring Weights method within a Marginal Structural Model as described in Section 4.2.2 of TSD 24);**

b. A ‘two-stage’ method as described in Section 4.2.3 of TSD 24;

c. Other methods as described in Section 4.2.4 of TSD 24.

For each of these suggested exploratory analyses, where feasible, please provide Kaplan–Meier curves and a summary table of OS.

As explained in Document B, large proportions of patients in all the crizotinib arms of the relevant trials (CROWN, ALEX, ALESIA, ALTA-1L) received subsequent ALK inhibitors. Crizotinib is no longer established treatment in first-line in the UK, but a case can be made that many of these subsequent treatments would be received if it

were in use given historic NICE approvals (brigatinib and ceritinib are recommended by NICE post-crizotinib) or the efficacy of some can be equated in a pragmatic fashion (e.g. alectinib is similarly effective to brigatinib after crizotinib). However, the OS in the end was not directly used in the submitted base-case given concerns about subsequent lorlatinib use following second generation ALK inhibitors and so is less relevant here.

In contrast and as acknowledged in Document B, the subsequent ALK inhibitors in the lorlatinib arm of CROWN would not reflect UK clinical practice. Also as discussed, data reported in the most recent data cut suggest relatively small proportions of those that are reported to have progressed have had these treatments (Table 25, Section B.2.12.2 and Section B.3.3.4.2). As explained in Document B, it is unclear how effective a second generation ALK inhibitor would be following lorlatinib, given mechanisms of action and mutation coverage. Also, it is not out of line with most international pivotal trials to have small proportions of subsequent treatments that could potentially have some impact on efficacy.

Please see the response to Question A2, only the March 2020 data cut of OS is available for the submission. However, it is worth considering the viability of using the exploratory analyses suggested to adjust the lorlatinib OS data.

The 2020 data, which corresponds to the OS presented in the submission, shows that in the lorlatinib arm of CROWN there were a total of 23 death events by this snapshot, 40 total progression-free survival (PFS by investigator assessment) events (34 progressions and six deaths in pre-progression), with 17 patients having had a second-line ALK inhibitor following lorlatinib treatment (i.e. in post-progression or just before). In the crizotinib arm 28 total deaths, 104 PFS events (99 progression events and five deaths in pre-progression), with 79 patients having a second-line ALK inhibitor following crizotinib.

At this snapshot in the lorlatinib arm, most patients have not progressed, with 34 recorded as progressed with an implied 17 death events recorded in (investigator assessed) post-progression. This means there is a very small sample of patients (and number of events) for these methods and correspondingly small patient-time in the relevant status groups: those who have switched in general (yes switcher status)

or who have progressed and who have or have not received a subsequent treatment (yes/no switcher status).

Assume that prognostic variables required in many of the switching methods that are assumed to determine switcher status as well as death are consistent with those used in non-small-cell lung cancer (NSCLC) match adjusted analyses, which is a reasonable assumption. This is usually a variable set of more than 5. These methods do not seem feasible with the available OS data cut:

- The inverse-probability-of-censoring weighting (IPCW) requires these prognostic variables over time to fit binary outcome regression models to determine probability of switcher status to derive weights that can be applied to non-switchers after censoring patients who have switched.
    - Given that the first step is to censor confirmed switchers and that this number is a small proportion of total randomized (17/149), this sort of adjustment may make very little difference to OS (as discussed in TSD24 with examples)
    - The number of variables would be close to the number confirmed progressed with a yes/no switcher status (perhaps around half), which would make fitting the regressions a challenge
    - The positivity assumption may not hold (i.e. there could be one prognostic variable that has the same level/value for all switchers)
- Two-stage methods require a similar approach but require prognostic variables only from the “second baseline” (point of progression in this case) to estimate a switching “treatment effect”. This method will have the same if not more of the issues identified for the IPCW method: the prognostic factor model would struggle to fit the small number of progressed with yes/no switcher status
- Alternative and exploratory methods would face similar issues
    - Random forest-based predictions use an algorithm and bootstrapped sampling to produce a counterfactual non-switcher group but would require random sampling from very small groups of relevant patients (i.e. progressed and yes/no switcher status). Models with covariates can also be specified which would have the same covariate/n issues.

- Semi-competing risk models use survival models applied to time from progression to death, again with a specified set of prognostic variables. This is not dissimilar to the two-stage method above and would suffer from the same sample size and covariate/n issues as the above methods.

A4. Priority question: Section 11.1.1.2.2.1 of the CROWN Interim CSR (CS Document B, reference 75) states that an analysis for the discordance between the Blinded independent central review (BICR) and investigator assessment (INV) of disease progression for PFS was reported in Table 14.2.1.3, and showed that the overall discrepancy rate was 22.1% in the Lorlatinib arm and 46.9% in the Crizotinib arm, and the total event discrepancy rate was 14.1% in the Lorlatinib arm and 19.0% in the Crizotinib arm.

a. **Please provide Table 14.2.1.3 and the time point that these analyses were conducted.**

b. **Please conduct and provide the results of statistical tests comparing the discrepancy rates.**

c. **The overall discrepancy rates appear to be high in both arms, and to differ significantly between the Lorlatinib and Crizotinib arms. Please explain why discrepancies may have occurred and provide an assessment of bias in outcome measurement for PFS by investigator assessment as per the Cochrane RoB2 tool (see Cochrane Handbook Version 6.5, 2024, Chapter 8.6).**

Table 14.2.1.3 is provided below and is based on the 20 Mar 2020 data cut.

Table 1 Table 14.2.1.3

Table 14.2.1.3
PF-06463922 Protocol B7461006
Summary of PFS Discordance Between BICR and Derived Investigator Assessments (RECIST v1.1) - Full Analysis Set (Protocol B7461006)

	Treatment Group		
	Lorlatinib (N=149)	Crizotinib (N=147)	Lorlatinib vs Crizotinib Difference (%)
Concordance/Discordance Type, n (%)			
a1 = Agreement by INV and BICR on timing and occurrence of event (within 7 days)	18 (12.1)	40 (27.2)	-15.1
a2 = Agreement on occurrence of event but timing of event by INV later than by BICR	8 (5.4)	31 (21.1)	-15.7
a3 = Agreement on occurrence of event but timing of event by INV earlier than by BICR	4 (2.7)	10 (6.8)	-4.1
b = Event by INV and no event by BICR	10 (6.7)	23 (15.6)	-8.9
c = No event by INV and event by BICR	11 (7.4)	5 (3.4)	4.0
d = Agreement on no event by INV and BICR	98 (65.8)	38 (25.9)	39.9
Discrepancy Rates, (%)			
Total event discrepancy rate: (b+c)/N	14.1	19.0	-4.9
Early discrepancy rate: (a3+b)/(a+b)	35.0	31.7	3.3
Late discrepancy rate: (a2+c)/(a2+a3+b+c)	57.6	52.2	5.4
Overall discrepancy rate: (a2+a3+b+c)/N	22.1	46.9	-24.8

Total event discrepancy represents a disagreement between investigator and BICR with respect to the progression status of a patient; overall discrepancy, besides disagreement in progression status, also considers disagreement in timing at which progression occurs.

Total event discrepancy rates were 14.1% and 19.0% (Chi-squared p value = 0.2516) in the Lorlatinib and Crizotinib arms, respectively. The overall discrepancy rates, that included differences in timing of progression of more than 7 days, were 22.1% and 46.9% (Chi-squared p value <0.0001), respectively.

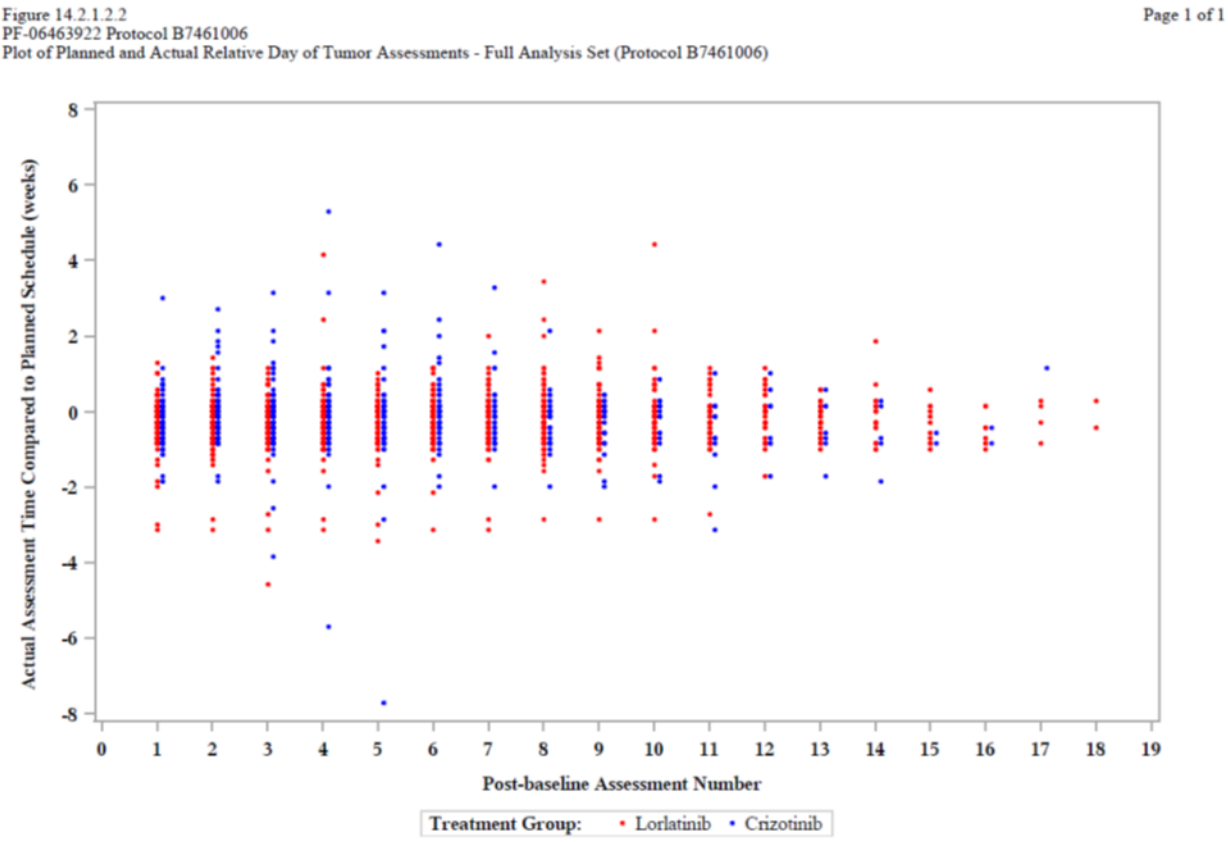
It should be noted that it is expected that there will be higher discrepancy rates with crizotinib versus lorlatinib, especially for the overall discrepancy rate that considers “discrepant” progressions that are assigned by both investigator and BICR, but more than 1 week apart. In fact, even in the absence of evaluation bias, the less efficacious arm will have a greater opportunity to have disagreements by virtue of having more events. In this analysis the number of progressions in the crizotinib arm were 2.5–3 times more than those in the lorlatinib arm for both investigator and BICR.

Notwithstanding these apparent high discrepancy rates, the PFS benefit of lorlatinib over crizotinib is very much consistent in this analysis with a PFS hazard ratio (HR)

of 0.28 for BICR and 0.21 for investigator and an estimate of crizotinib median PFS of 9.3 and 9.1 months for BICR and investigator, respectively.

Finally, a plot comparing planned and actual relative day of tumour assessments by treatment arm was generated to explore possible assessment bias in terms of timing of assessment (see below) and no specific deviation was found. The completed Cochrane RoB2 tool has been provided separately with this response.

Figure 1 Planned and actual relative day of tumour assessments



CROWN subgroup analyses

A5. Please provide results of statistical tests for subgroup differences and interaction for the subgroup analysis by the presence of brain metastases for PFS for the 5-year data cut reported in CS, Appendix E, Figure 2.

As observed in CS, Appendix E, Figure 2, lorlatinib was favoured compared to crizotinib in the subgroup of patients who had brain metastases at baseline, more so than for patients who did not have brain metastases at baseline. The forest plot of PFS by investigator assessment split by baseline brain metastases at the 5-year

data cut-off is presented in in a separate Microsoft Word document ("Response to A5 and A6"). The following is observed:

- Ethnic origin – The hazard ratio and confidence interval for Asian patients with and without brain metastases are similar to the hazard ratio and confidence interval for patients with and without brain metastases in the global population. Therefore the hazard ratio and confidence interval for non-Asian patients with and without brain metastases are also similar to those in the global population. So there does not appear to be an interaction effect between ethnic origin and brain metastases in terms of PFS by investigator assessment

- Eastern Cooperative Oncology Group (ECOG) – Amongst patients who have brain metastases at baseline there were only three patients who had Eastern Cooperative Oncology Group (EGOG) performance status ≥ 2 and all three of these patients were in the crizotinib arm, therefore a hazard ratio could not be calculated for patients with brain metastases at baseline with EGOG performance status ≥ 2. Only nine patients had no brain metastases at baseline and EGOG performance status ≥ 2. For these nine patients crizotinib seems to be favoured compared to lorlatinib, however the sample size is too small to draw any inference. Most patients have EGOG performance status 0 or 1; the hazard ratio and confidence interval for patients with and without brain metastases in the EGOG performance status 0 or 1 subgroup is similar to the hazard ratios within the global population

- Gender – Female and male patients with brain metastases at baseline have similar hazard ratios and confidence similar to each other for PFS by investigator assessment. For patients who did not have brain metastases at baseline, lorlatinib seems to be favoured to a greater extent for females compared to males, while for both genders lorlatinib is preferable to crizotinib

- Age – Patients with brain metastases at baseline in the age group < 65 years and ≥ 65 years have similar hazard ratios and confidence similar to each other for PFS by investigator assessment. For patients who did not have brain metastases at baseline, lorlatinib seems to be favoured to a greater extent for patients aged < 65 years compared to patients aged ≥ 65 years, while for both age groups lorlatinib is preferable to crizotinib

- Smoking status – Patients with brain metastases at baseline in the current/former smoker and never smoker categories have similar hazard ratios and confidence similar to each other for PFS by investigator assessment. For patients who did not have brain metastases at baseline, lorlatinib seems to be favoured to a greater extent for patients who have never smoked compared to patients who are current or former smokers, while for both groups lorlatinib is preferable to crizotinib

- Extent of metastases – It is not possible for a patient to have brain metastases while only having locally advanced disease, so there are three subgroups for extent of metastases (locally advanced/no brain metastases, metastatic/no brain metastases, and metastatic/brain metastases). There were 22 patients with locally advanced disease. For these patients the confidence interval around the hazard ratio for PFS by investigator assessment crossed 1, but the hazard ratio still numerically favours lorlatinib. Most patients have metastatic disease; the hazard ratio and confidence interval for patients with and without brain metastases in the metastatic disease subgroup is similar to the hazard ratios within the global population

- Histology –There were only 16 patients with non-adenocarcinoma; of which, one patient treated with lorlatinib had brain metastases at baseline, one patient treated with crizotinib had brain metastases at baseline, eight patients treated with lorlatinib did not have brain metastases at baseline, and six patients treated with crizotinib did not have brain metastases at baseline. Most patients in CROWN had adenocarcinoma; the hazard ratio and confidence interval for patients with and without brain metastases in the adenocarcinoma subgroup is similar to the hazard ratios within the global population

A6. Please provide results of subgroup analyses for objective response rate by BICR assessment as specified in the CROWN Interim CSR document, Section 9.7.3.1.2 (CS Document B, reference 75).

This has been provided in a separate Microsoft Word document (“Response to A5 and A6”).

Lorlatinib safety

A7. Priority question: Please provide a summary of deaths including causes of death (as per Table 43 of the CROWN Interim CSR [CS Document B, reference 75]) at the October 2023 (or latest available) data cut of the CROWN trial

As explained in response to A2, Table 43 in the 2020 data snapshot CSR is the latest available version of this table.

A8. Please present a summary table of rates of AEs of special interest for all lorlatinib studies regardless of indication at the latest available data cut specifying sources of evidence and cut-off dates, as per the company response to clarification question A7, Table 4, in TA909, Lorlatinib EAG clarification letter to PM, June 2022.

This has been provided as separate files for CROWN ("adae_s063_si_imm") and Study 1001 ("aectc1s1_ct_comp").

Study 1001

A9. Priority question: Please provide a summary of the design, methods, study baseline characteristics, and results of Study 1001, as presented for CROWN in CS, Document B, Section B.2.3 to B.2.6.

This has been provided as a separate document with these responses (including with the 2017 CSR that is referenced within): "ID6434 lorlatinib clarification questions_Appendix 2_Study 1001_7Oct24". Note that the clinicaltrials.gov page has also been updated with the latest results: Study Details | A Study Of PF-06463922 An ALK/ROS1 Inhibitor In Patients With Advanced Non Small Cell Lung Cancer With Specific Molecular Alterations | ClinicalTrials.gov

A10. Please provide the latest available manuscript for CS, Document B, Reference 77 (Ou et al.) where available (whether published, submitted or still in preparation), including superimposed OS KM curves across all study cohorts.

This has been provided as a separate document with these responses ('Lorlatinib_B7461001_Brief_Report_submitted_29Aug24'). Please note that this has been submitted for publication and will be shortly published and publicly

available (and so should be treated as confidential and not presented wholesale in the NICE papers).

Pooled analysis of CROWN and Study 1001

A11. Please present the methods of the pooled analysis of OS from CROWN and Study 1001 presented in CS, Document B, Section 2.8.1. Please provide further details about the rationale for pooling these studies and acknowledge any limitations of this approach.

The methodology of pooling the OS from EXP1 cohort (treatment naïve cohort of n=30 patients) of Study 1001 with CROWN lorlatinib OS involved treating the combined group (n=179) as a trial arm and refitting the Kaplan–Meier estimator (see Section B.2.8.1). For the summary statistics showing Table 21 (Document B), the reverse Kaplan–Meier method was used to estimate median duration and survival probabilities were calculated using the normal approximation to the log transformed cumulative hazard rate.

Despite pooling, parametric fittings are nevertheless “driven” by the larger CROWN sample size; however, the Study 1001 Kaplan-Meier plot is more mature which provides some longer term validation of OS for patients on lorlatinib and arguably improves fittings given the addition of more mature data.

As discussed, more mature CROWN OS data would be preferred for modelling and the main limitation of this analysis is that we are combining data from independently run trials (i.e. the n=30 patients were not randomized to the lorlatinib arm of CROWN). Inevitably there will be discrepancies in trial procedures and OS results for the 30 patients may differ from a hypothetical set of an additional 30 patients that could be randomized to the lorlatinib arm of CROWN.

However, lorlatinib dosing and treatment procedures were identical between studies, with only differences in the cycle of administration/measurement differing between them. This alignment of drug dosing is reflected in the licence and Summary of Product Characteristics (SmPC), see Document B appendices. Trial procedures were broadly aligned, with differences in follow-up (8 weeks +/- 1 week in CROWN versus every 3 weeks in Study 1001 then 6 weeks after 30 months of follow-up).

Such differences are not thought to greatly bias the OS endpoint. The main inclusion and exclusion criteria were broadly aligned:

- Age >=18 or >=20 in CROWN but >=18 in Study 1001
- Patients had to have at least one extracranial measurable target lesion (RECIST version 1.1) in both
- Asymptomatic treated or untreated central nervous system (CNS) metastases were permitted in both
- ECOG performance status score of 0 to 2 in both
- No previous systemic treatment for metastatic disease was allowed in CROWN and no pre-treatment was allowed in the EXP1 cohort of Study 1001 (all 30 had zero previous tyrosine kinase inhibitor (TKI) regimens and 29 had no previous chemotherapy)

The full list of trial methodology for EXP1 (Study 1001) can be found in the response to A9 and for CROWN in Document B. A comparison of key baseline criteria is presented below for EXP1 (Study 1001) and the CROWN lorlatinib arm. There are minor differences in sex, with proportions of female/male roughly reversed and some differences between the white to Asian ethnic mix. However, age, ECOG status, brain metastases at baseline and pre-treatments are virtually identical.

Table 3: Baseline characteristics comparison of EXP1 cohort Study 1001 and CROWN lorlatinib arm

Characteristics	Treatment naïve patients (n = 30)	CROWN Lorlatinib arm (N = 149)
Age, years		
Median (IQR)	59 (48.0–68.0)	61 (51.0-69.0)
Sex (%)		
Female	13 (43)	84 (56)
Male	17 (57)	65 (44)
Race (%)		
White	10 (33)	72 (48)
Black	1 (3)	0
Asian	17 (57)	65 (44)
Other	1 (3)	
Unspecified †	1 (3)	12 (8)
ECOG performance status (%)		

0	13 (43)	67 (45)
1	16 (53)	79 (53)
2	1 (3)	3 (2)
Brain metastases at baseline (%) ‡	8 (27)	38 (26)
Previous anti-cancer therapy (%)	1 (3)	12 (8)
Previous brain-directed radiotherapy (%)	2 (7)	9 (6)

Key: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group.
Notes: †In France, information about race was not allowed to be collected per local regulations. ‡By independent central review; includes measurable and non-measurable CNS lesions at baseline. §One patient in EXP1 received previous adjuvant chemotherapy but no previous treatment for metastatic disease.
Source: Solomon et al. 2018 (provided at submission)

Network meta-analysis

A12. Priority question: Following on from question A2, please update the OS NMAs including updated OS data from the CROWN trial at the October 2023 data cut, or a later data cut if available.

As discussed in A3 this OS data is not available.

A13. Priority question: In TA536 (alectinib) and TA670 (brigatinib) the proportional hazards (PH) assumption was not made. In both appraisals the submitting companies argued that the PH assumption did not hold and the treatment arms for ALEX and ALTA-1L were modelled separately (in the respective appraisals). However, in CS, Document B, Appendix N it is argued that PH does hold for PFS in ALEX and ALTA-1L.

a. **Please compare the arguments against PH and the supporting plots presented in the documentation for TA536 and TA670 with those presented in CS, Document B, Appendix N explaining any reasons for the different conclusions.**

b. **Please explain what is meant by the following statement (CS, Document B, Appendix N, p146): "Since the crossing occurs within the first 6 months of the trial and is likely due to trial protocol rather than treatment effect."**

c. **Please clarify what is meant by the following statement (CS, Document B, Appendix N, p148): "the crossing of Kaplan–Meier curves during the first 4**

months (two assessment visits) due to the assessment schedule for PFS and is likely due to trial protocol rather than treatment effect."

In TA536 (alectinib) it was concluded that fitting curves independently to each arm did not require any specific assumption about treatment to hazard relationship, and parametric models were fitted separately to each treatment arm (there does not seem to be any explicit assessment of proportional hazards). However, an exponential model was also fitted to the data after 18 months as it was concluded that the proportional hazards assumption was valid after the initial 18 months. An indirect treatment comparison was not conducted, as at the time of the submission the only relevant comparator (crizotinib) was included in the ALEX trial. Therefore, the proportional hazards assumption did not need to be considered in the context of indirect treatment comparison.

The proportional hazards for ALEX were assessed in the relevant appendix of the Pfizer submission, Appendix N.1. Figure 2 shows the log-cumulative hazard plot and Schoenfeld residual plot for ALEX. There was crossing of the log-cumulative hazard plot for alectinib and crizotinib for approximately the first 6 months. Progression assessments were conducted every 8 weeks.[1] For the first three cycles there was no separation between the Kaplan–Meier plots for alectinib and crizotinib. The scheduled progression assessments per the protocol could mask the treatment effect early in the trial and if a smooth line was plotted through the step function of the Kaplan–Meier plots during this time differentiation may be observed. This correlates with the change in shape of the time varying log-hazard ratio in the Schoenfeld residual plot. Since the crossing of curves occurs for 6 months out of more than 48 months of observed data, after which the proportional hazards assumption was said to be appropriate in TA536, a hazard ratio based on a Cox proportional hazard ratio can be considered an appropriate approximation of the average treatment effect between alectinib and crizotinib in ALEX.

In TA670 (brigatinib) it was concluded that there could be a "potential violation of proportional hazards" in PFS due to crossing of the log-cumulative hazard lines early in the trial follow-up, although the Schoenfeld test and Schoenfeld residual plot did not suggest that the proportional hazards assumption was unreasonable. The company also citing clinical opinion argued that proportional hazards assumption is not relevant. The EAG questioned whether proportional hazards held, their response

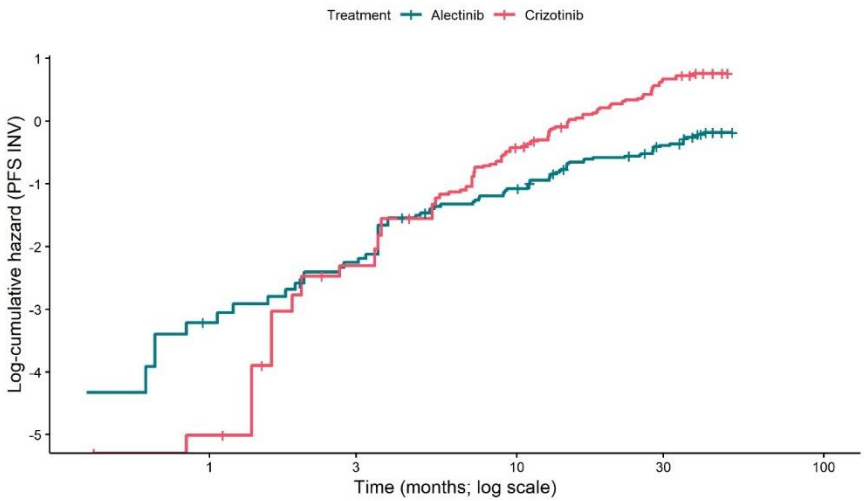
was: “The ERG is satisfied from the testing of Schoenfeld residuals that there is no statistically significant evidence that the PH assumption was violated and that it is appropriate for the Cox PH model to be used and for HRs to be presented for ALTA-1L trial BIRC-assessed PFS”. TA670 included indirect treatment comparison between ALEX and ALTA-1L using anchored and unanchored matching-adjusted indirect comparison (MAIC). When calculating hazard ratios using a weighted Cox proportional hazards model following MAIC the proportional hazards assumption is implicitly assumed between the weighted data from ALTA-1L and the data in ALEX.

The proportional hazards for ALTA-1L were assessed in Appendix N.1. Figure 2 shows the log-cumulative hazard plot and Schoenfeld residual plot for ALTA-1L. There was crossing of the log-cumulative hazard plot for brigatinib and crizotinib for approximately the first 4 months. Progression assessments were conducted every 8 weeks.[2] For the first two cycles there was no separation between the Kaplan–Meier plots for brigatinib and crizotinib. As for ALEX, the scheduled progression assessments per the protocol could mask the treatment effect early in the trial. The Schoenfeld test statistic did not suggest that the proportional hazards assumption was violated. Since the crossing of curves occurs for 4 months out of more than 48 months of observed data, a hazard ratio based on a Cox proportional hazard ratio can be considered an appropriate approximation of the average treatment effect between brigatinib and crizotinib in ALTA-1L.

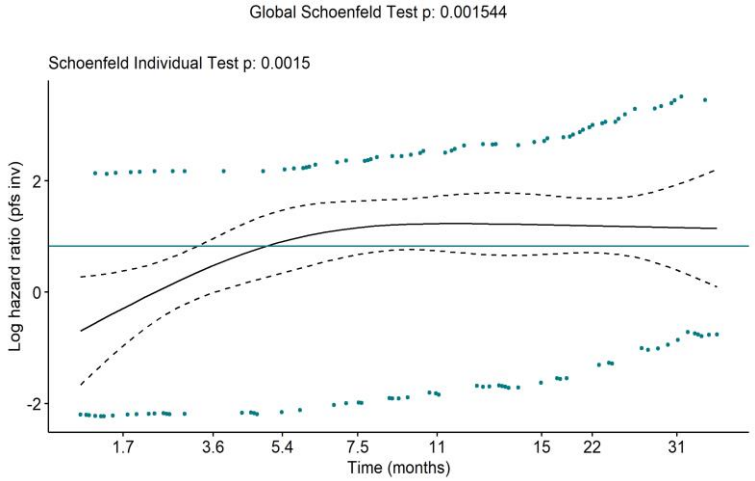
Proportional hazards NMA was considered appropriate for the evidence base since uncertainty in the proportional hazards assumption was only present at the very start of data collection for ALEX and ALTA-1L. Hazard ratios were thought to be an appropriate approximate average for the treatment effect over time within these studies, as well as for CROWN and ALESIA. In addition, an NMA has the advantage that it is a pragmatic and simple way to allow modelling treatment effects accounting for the two efficacy sources for alectinib (i.e. by applying anchored methods).

Figure 2: Log-cumulative hazard plot and Shoenfeld residual plots for ALEX and ALTA-1L – PFS (INV)

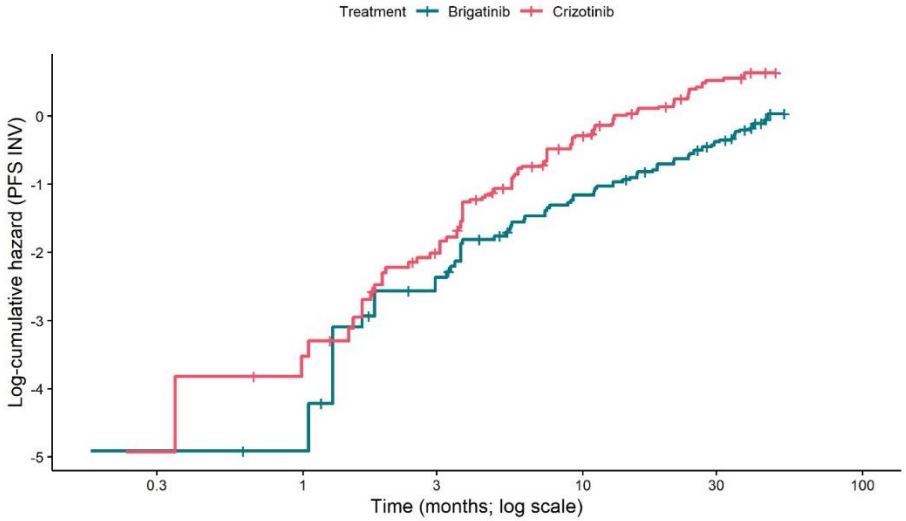
A) ALEX log-cumulative hazard plot



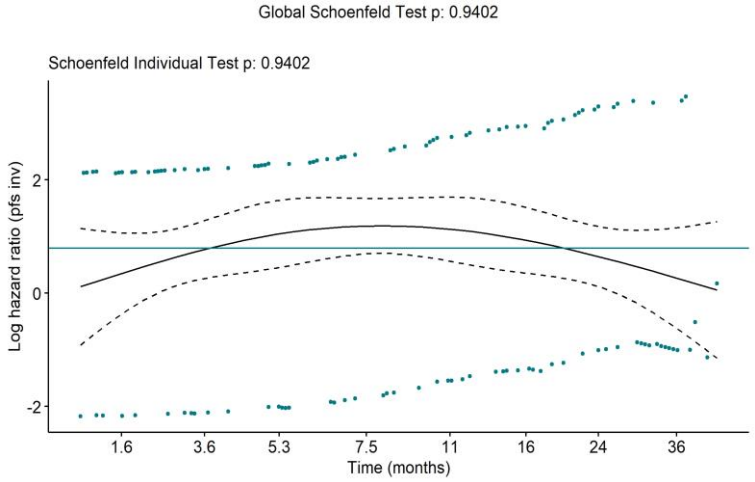
B) ALEX Schoenfeld residual plot



C) ALTA-1L log-cumulative hazard plot



D) ALTA-1L Schoenfeld residual plot



A14. Priority question: Please provide all prior distributions used for the NMA analyses. The EAG is unable to execute the sample JAGS code provided in CS, Document B, Appendix N.5 without this information.

The NMA was conducted using both fixed effects and random effects models, and model comparison methods were used to assess the goodness-of-fit. Fixed effects models were identified as the best-fitting models in original analyses; therefore, only fixed effects models were run in subsequent updates to the NMA such as those presented in the current CS. Table 2 lists the number of iterations, burn-in and thinning interval used in each of the fixed effect analyses. No prior distribution was used for the between-trial SD.

Table 2: Iteration specifications for NMA

Analysis	Number of iterations	Burn-in	Thinning interval
OS	50,000	10,000	1
PFS INV	50,000	10,000	1
PFS BICR	50,000	10,000	1
IC-TTP	50,000	10,000	1
OS – crossover adjusted*	50,000	10,000	1

Key: BICR, blinded independent central review; IC-TTP, intracranial time-to-progression; INV, investigator assessed; OS, overall survival; PFS, progression-free survival.
* See response to A17.

A15. Priority question: As described in CS, Document B, Section B.2.9.2.4, substantial numbers of participants in the CROWN, ALTA-1L, ALEX and ALESIA trials switched to subsequent therapies following disease progression. Please further discuss this issue in relation to the interpretation of the OS NMA results in the presence of confounding due to treatment switching. Please comment specifically on the results provided in Table 28 (CS, Document B, Section 2.9.4.2) which shows that lorlatinib has numerically inferior OS compared to alectinib and had only a small benefit compared to brigatinib.

Table 25 in Document B, Section B.2.9.2.4 shows that all studies (CROWN, ALEX, ALESIA and ALTA-1L) had retreatment with tyrosine kinase inhibitors (TKIs) at

second-line or beyond. For CROWN only second-line treatment is reported in Table 25 based on the 5-year data cut. For the other studies multiple treatment lines are included. It was thought that most treatments after second-line are expected to be best supportive care or palliative care; please also see response to Question A16.

Based on Table 25 in CS, Document B, Section B.2.9.2.4 we can see that on average, the use of subsequent ALKi in the alectinib arm of ALEX was similar to the use of subsequent ALKi in CROWN, while the use of subsequent ALKi in the alectinib arm of ALESIA and the brigatinib arm in ALTA-1L was higher. This could mean that the treatment effect in ALESIA and ALTA-1L studies could be inflated by the use of subsequent TKIs. However, as only aggregate data is available for the comparator trials an analysis adjusted for the use of ALK TKIs as subsequent treatments is not possible.

As acknowledged in Document B, the subsequent ALK inhibitors in the lorlatinib arm of CROWN would not reflect UK clinical practice. Also as discussed, data reported in the most recent data cut suggest relatively small proportions of those that are reported to have progressed have had these treatments (Table 25, Section B.2.12.2 and Section B.3.3.4.2). As explained in Document B, it is unclear how effective a second generation ALK inhibitor would be following lorlatinib, given mechanisms of action and mutation coverage; although it is expected to have little additional effect.[3] Also, it is not out of line with most international pivotal trials to have small proportions of subsequent treatments that could potentially have some impact on efficacy. Please see the response to Question A3 for more information on assessment of exploratory methods to adjust for potential confounding.

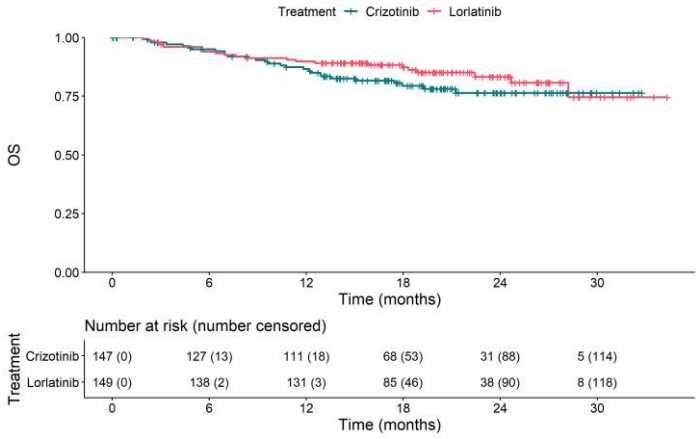
Results presented in Table 28 in Document B, Section 2.9.4.2 use 18-month CROWN data which were very immature. It is also worth noting that although OS data for comparator treatments was more mature than for lorlatinib, only the crizotinib arm in ALEX reached the median overall survival at the end of follow-up, as shown in Figure 3. Based on the data available the most appropriate analyses were conducted. Importantly, with the median PFS not reached after 5 years of follow-up, lorlatinib has demonstrated the longest PFS not only among ALK inhibitors, but also longest PFS ever reported for a single-agent targeted treatment in advanced NSCLC and across all metastatic solid tumours.[4] While the overall survival data from CROWN remain immature, as the number of deaths required for the final OS

analysis has not yet been reached, the advice from UK clinicians suggests the lack of progression events or deaths will likely translate into a durable OS benefit, with a median OS expected to be longer than 10 years.[3] This is further supported by data from the 30 patients who did not receive prior ALK inhibitors, the EXP1 arm, in Study 1001 (showing 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%).[5]

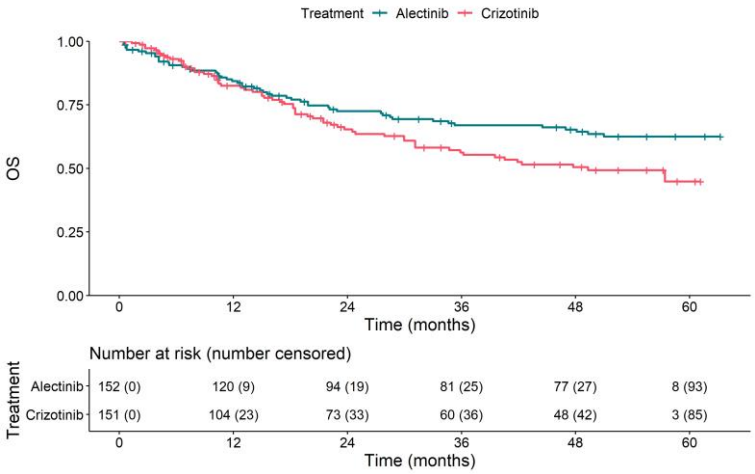
It should also be noted that Pfizer acknowledges the issue of sequencing on comparator efficacy and therefore does not rely on this data in its base case analysis to minimise uncertainty and instead uses the pseudo state transition approach to model OS for the comparators in the submission. In addition, an analysis is provided (see addendum) that explores the efficacy of the sequence using a flatiron RWE approach for the main comparator (alectinib) which reflects the efficacy impact of most patients receiving lorlatinib as a second-line treatment.

Figure 3: Kaplan–Meier figures for CROWN, ALEX, ALESIA and ALTA-1L

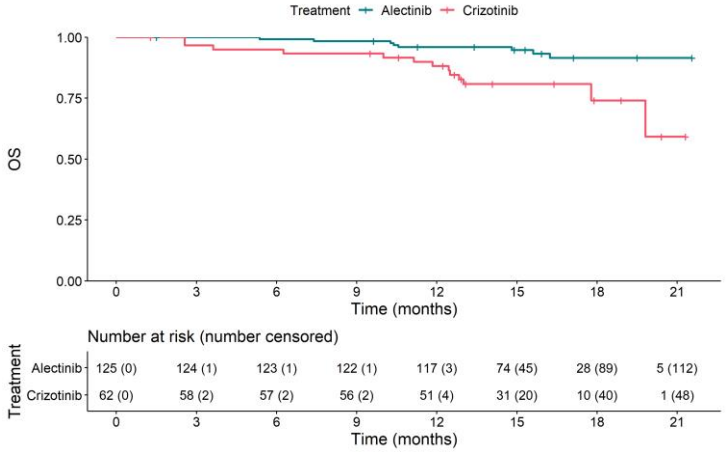
CROWN



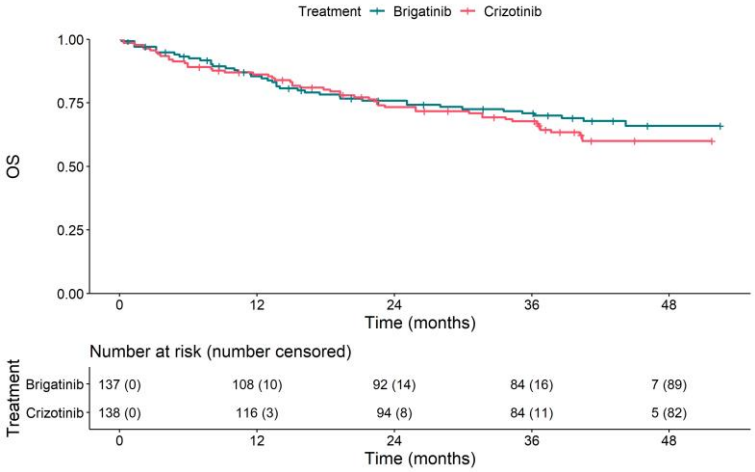
ALEX



ALESIA



ALTA-1L



A16. Please provide further details to the summary table of treatments in studies considered in the NMA (Document B, Table 25), by specifying the line of therapy at which each subsequent treatment was administered (or state where not available) for each of the trial's arms of CROWN, ALEX, ALESIA and ALTA-1L, as well as the EXP1 cohort of Study 1001.

Table 25 in the Company Submission presents the proportion of patients treated with lorlatinib who received second-line ALK inhibitors in CROWN. Table 14.4.3.2 of the CROWN 5-year CSR details lorlatinib and crizotinib subsequent anti-cancer systemic therapies by line of therapy. Regarding EXP1 cohort of Study 1001, a total of nine (30%) patients received at least one subsequent anti-cancer therapy; eight (27%) patients received at least one subsequent systemic anti-cancer therapy; two (7%) patients received at least one subsequent radiotherapy treatment and two (7%) patients received at least one subsequent anti-cancer surgery.[5] Most patients received one subsequent systemic anti-cancer therapy, most commonly, another ALK inhibitor.

Information on the usage of subsequent ALK inhibitors per treatment line was not available for comparator trials, so the proportions provided in Table 25 represent the proportion of patients with 'any subsequent treatment'. The subsequent treatment after second-line therapy will usually be BSC/palliative given that patients are on the third line of treatment. Indeed, in the second-line appraisal of lorlatinib (TA628) there was an agreement that 40–50% of subsequent treatments would be "costed" as BSC (£0) with the remaining as either pemetrexed or platinum doublet chemo (pemetrexed + usually cisplatin); this was uncontroversial throughout the appraisal and accepted. Therefore, the third line would be no treatment or chemotherapy, and this is thought to be the case internationally given the lack of third-line trial or licences for third-line ALK inhibitors.

A17. Where available, as an exploratory analysis, please include OS data with adjustments for treatment switching or treatment crossover in the NMA, including:

a. **Adjusted updated OS data as per question A3;**

b. **final OS data from the ALTA-1L trial adjusted for treatment crossover (MSM model or IPCW model) available in Camidge 2021 (CS, Document B, Reference 89).**

Please further discuss this issue, including any analyses to explore the risk and magnitude of confounding due to crossover in ALTA-1L for the results of the NMA.

As described in the response to Question A3, treatment switching or crossover has not been adjusted for in the CROWN data due to the small number of patients with treatment switching.

Table 3 presents a comparison of unadjusted OS results, alongside results which used the updated crossover adjusted results for ALTA-1L in Camidge 2021. Results were also included for ALESIA (Zhou 2022); these data were unadjusted as ALESIA did not allow crossover. It was not possible to include crossover adjusted results for ALEX as these were not reported. Please note that the analyses presented in Table 3 cannot account for any confounding introduced by the use of subsequent treatment with TKIs discussed in response to Question A15. Also note, as discussed in Document B, all crizotinib trials in reported studies had significant proportions of ALK TKI subsequent treatment (i.e. given post-crizotinib use is approved in most countries) and so it is relatively arbitrary to include only one adjusted node in the NMA.

The crossover adjusted analysis reports higher HRs for lorlatinib versus both alectinib and brigatinib compared with the unadjusted analysis, however results do not show statistical significance for either scenario. This suggests that the unadjusted data for brigatinib in ALTA-1L may underestimate the relative treatment effect of brigatinib versus crizotinib due to treatment switching.

As ALEX did not report crossover adjusted data, results for alectinib in the adjusted analysis are based only on data reported in ALESIA.

Due to the immaturity of the OS data from the CROWN trial, definitive conclusions regarding the magnitude and precision of the relative OS effect of lorlatinib versus alectinib/brigatinib, with or without adjustment for treatment switching, cannot be reached. As the data from the CROWN trial becomes more mature, the uncertainty around the OS benefit of lorlatinib versus alectinib/brigatinib may reduce. As previously discussed, the pseudo state transition approach is used to overcome the issue of confounding in treatment switching/subsequent therapies.

As noted previously, an alternative analysis has been conducted using flatiron data for alectinib (the main comparator) which gives some sense of the real-world impact of lorlatinib following alectinib (please see the addendum).

Table 3: OS relative effect of lorlatinib compared with all treatments (fixed effects)

Treatment	Unadjusted	Crossover adjusted
	HR (95% CrI)	
Hazard ratios for all treatments vs crizotinib		
Lorlatinib	0.72 (0.41, 1.25)	0.72 (0.41, 1.25)
Alectinib (600 mg BID)	0.64 (0.48, 0.87)	0.60 (0.37, 0.98)
Brigatinib	0.81 (0.53, 1.23)	0.50 (0.28, 0.89)
Hazard ratios for lorlatinib vs relevant comparators		
Alectinib (600 mg BID)	1.12 (0.59, 2.11)	1.20 (0.57, 2.52)
Brigatinib	0.89 (0.44, 1.78)	1.44 (0.65, 3.18)

Key: BID, twice daily; CrI, credible interval; HR, hazard ratio; OS, overall survival.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority question: The company's base case economic analysis uses a different modelling approach in the lorlatinib arm (partitioned survival model) and comparator arms (pseudo state transition model).

a. Please justify why it is appropriate to use two different approaches to model each treatment arm.

b. Please clarify the assumptions made within each approach, specifically highlighting the methodological differences between a partitioned survival model and pseudo state transition model (see NICE DSU TSD 19 for

reference. Please complete the summary table below, outlining the relevant attributes of the two approaches used within the company base case.

Please also see Table 31 and Table 32 from Document B for additional information.

Table 4. Assumptions used in the cost-effectiveness model for lorlatinib and comparator arms

	Lorlatinib arm (Partitioned survival analysis)	Alectinib/Brigatinib arm (Pseudo state transition)
How state membership estimated	As with all "partSA" models there is structural independence between the proportions projected as being dead/alive or progression-free/progressed in modelling. Determined by independently fitted parametric models to CROWN trial (time-to-event) data and or pooled CROWN and Study 1001 EXP1 cohort in the case of OS (Document B.3.3). ToT is determined by applying the estimated hazard ratio between PFS and ToT applied to the PFS extrapolations.	Explicitly modelled structural relationship between deaths and proportion progressed in given model cycles. Death state membership will vary with different progression-free survival state membership. Proportions in PFS determined by alectinib/brigatinib PFS projections which are estimated by applying NMA derived HRs to parametric survival models fitted to CROWN crizotinib PFS data.
Data inputs	In the model base case PFS is determined by parametric models fitted to CROWN lorlatinib data (Document B.3.3.3). In the base case OS is determined by parametric models fitted to pooled CROWN and Study 1001 EXP1 cohort (Document B.3.3.4). The model includes options to use models fitted only to CROWN OS data.	In the base case, comparator PFS is determined by applying the NMA derived HRs to the CROWN crizotinib curves (i.e. in line with a partSA approach). OS and death state membership is determined by the sum of PFS and post-progression survival (PPS). More precisely, progressed disease patients are derived using the decrease in PFS

		patients and adjusting for the percentage PFS events that are death. For the remaining patients, the post-progression mortality rates are applied. The latter rate is determined by estimated survival rates (assuming an exponential distribution) from external data (see Document 3.3.4.1 for full details). The external data sources are the Study 1001 EXP3B-5 cohort to reflect 2L lorlatinib efficacy (also used to reflect lorlatinib efficacy in the 2L NICE appraisal). For post ALK inhibitor efficacy a post-hoc follow-up analysis of PROFILE 1001/1005 (post crizotinib on chemotherapy) is used. The weighted average of rates, based on subsequent treatment proportions, is applied. Pfizer also provides an addendum with this response (and relevant documents/results) of a flatiron real-world alectinib cohort that reflects the alectinib to lorlatinib sequence well and provides useful validation.
Methods for reflecting time dependency in event risks	This approach reflects time varying event risks in the same way as other partSA models, by fitting parametric survival models which	For PFS time dependency is explored in a similar way to the lorlatinib arm but are based on applying NMA derived HRs (see above).

	explore the time dependency of PFS and OS event risks. PFS is capped by OS and OS and PFS endpoints are conditioned on general population mortality (standard features).	For OS, PPS event risks are constant, but OS risks will vary given that PFS events are time dependent.
How extrapolation of overall survival performed	As above, beyond the observed OS, extrapolations are determined by parametric models. With curve selection determined in the usual way including three clinical validation sessions.	As above, overall OS extrapolation depends on PFS extrapolations, and a constant PPS rate estimated from external sources. Curve selection for crizotinib PFS was based on the usual methods including three clinical validation sessions. This is to explore concerns related to standard methods that would use trial published survival data, which would not fully reflect the efficacy of 2L lorlatinib.
How extrapolation of treatment effects on overall survival performed	The implied lifetime treatment effects are derived from the above methods. Differences between treatments in PFS over the lifetime are driven by curve selection for lorlatinib (CROWN), the NMA results and curve selection for crizotinib (CROWN). Differences in OS will be determined by curve selection for lorlatinib OS (CROWN), curve selection for crizotinib PFS and subsequent treatment proportions (determines weighting for rates). Treatment waning also impacts implied projected treatment effects. Ad discussed in the submitted flatiron RWE addendum; the analysis provides a reasonable validation of the alectinib base-case approach.	
Risks to validity of extrapolation of OS	Standard methods were employed to validate extrapolated lorlatinib OS, including validation using the more mature (but small sample) of treatment naïve patients	Extrapolated OS derived as above was validated with clinicians, both in terms of predictions but also in terms of methods (i.e. source of rates).

	from Study 1001 (EXP1 cohort) and plausibility checks via clinical validation.	Note again that a flatiron analysis for alectinib has been provided, which will help to validate the base case approach (pseudo state transition) for alectinib.
Consideration for use within decision making process	Immature lorlatinib OS is not ideal for decision making, however uncertainty has been explored, particularly via alternative curve selections and treatment waning.	The original alectinib and brigatinib trials could not fully reflect 2L lorlatinib efficacy, mainly because of timing of these versus lorlatinib 2L approval and uptake. Using a pseudo state transition model to account for sequencing makes a reasonable and pragmatic use of available data. The alectinib flatiron analysis also helps to show that the real-world efficacy of the main sequence that lorlatinib first-line would be displacing (i.e. alectinib followed by most patients receiving lorlatinib) would not be better in terms of OS/PFS than the pseudo state transition approach (i.e. similar or slightly lower efficacy overall). This will help to reduce uncertainty in decision making.

The table above has been populated. In response to Part A, Pfizer retained the pseudo state transition approach for lorlatinib, to align with the approach for comparators, and this was presented as a scenario analysis. Pfizer believe this scenario has some benefit, in that it shows the bottom end of PPS expectations for the lorlatinib arm and should be interpreted this way, but was not used in the base-case given it is likely on the pessimistic side of plausible. As quoted in Document B.3.3.4.2: “The clinical experts consulted expected a higher post-progression

survival for lorlatinib than the one observed for crizotinib and therefore this approach reflects a conservative scenario analysis. All three clinicians emphasized that this scenario reflects a conservative floor in post-progression survival expectations for lorlatinib given the historical nature of the PROFILE studies and because the prognosis for a patient after lorlatinib (third generation inhibitor) is much better than after crizotinib (first generation inhibitor)." Note that the deterministic/probabilistic incremental cost-effectiveness ratio (ICER) remains below £30,000 under this exploratory scenario (keeping other base case settings).

Please see the addendum describing the flatiron RWE analysis, which provides additional validation for the pseudo state transition approach employed for the main comparator alectinib.

Treatment effect

B2. Priority question: The company's economic evaluations assume PH to model the relative PFS and OS treatment effects between alecinib/brigatinib and crizotinib, with the crizotinib arm of the CROWN trial modelled as the reference arm.

a. Given the uncertainty in the PH assumption (see question A13), please justify this approach.

b. Please justify why the lorlatinib arm of the CROWN trial has not been used as a reference arm to model PFS and OS outcomes.

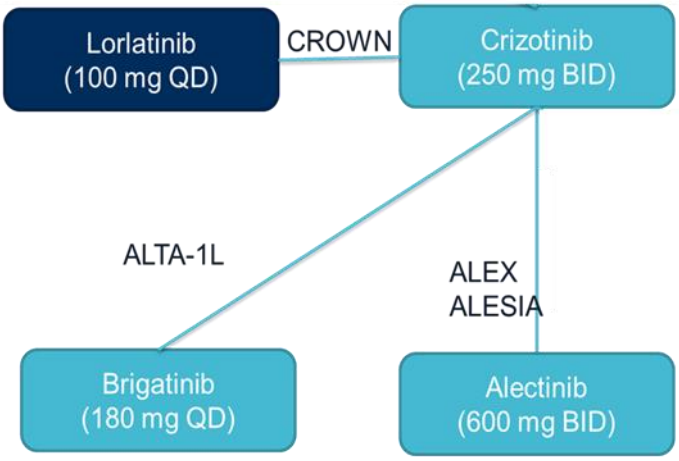
c. Please adapt the executable model to allow the reference arm to be switched to the lorlatinib arm.

A) As described in the response to question A13, proportional hazards NMA was considered appropriate for the evidence base since uncertainty in the proportional hazards assumption was only present at the very start of data collection for ALEX and ALTA-1L. Hazard ratios were thought to be an appropriate approximate average for the treatment effect over time within these studies, as well as for CROWN and ALESIA. In addition, an NMA has the advantage that it is a pragmatic and simple

way to allow modelling treatment effects accounting for the two efficacy sources for alectinib (i.e. by applying anchored methods).

B) The network of evidence in the indirect treatment comparisons consists of four studies as represented in the network diagram, Figure 4. All studies include a crizotinib treatment arm. Since crizotinib was the reference treatment for all studies and there are the most data for crizotinib out of any of the other treatments (i.e. explored in four studies), crizotinib was chosen as the anchor point for the network meta-analyses. Results can be calculated with lorlatinib as the reference treatment, which have been implemented in part c.

Figure 4: Initial network of evidence from the RCTs identified in the SLR



Key: BID, twice daily; QD, once daily; RCT, randomised controlled trial; SLR, systematic literature review.

C) Pfizer has updated the model to allow the use of hazard ratios compared to lorlatinib. Figure 4 displays the base case Markov traces for the main comparator alectinib (where OS uses the pseudo state transition approach). Figure 5 shows the alectinib Markov traces for the scenario using lorlatinib as the reference treatment for the NMA. For illustration, a comparison is made with the ALEX Kaplan–Meier curve, however, as discussed in Document B.3.3 PFS is determined by the NMA results which include both the ALEX and ALESIA trials as alectinib nodes. Until Month 17, PFS extrapolations are close to the ALEX trial Kaplan–Meier curve. After Month 17, a gap is observed, but fluctuations are similar. After the Kaplan–Meier curve follow-up, the scenario PFS curve is above the base case PFS curve. For OS, using lorlatinib as the reference treatment in the NMA generates an extrapolated OS curve that lies above the base case OS curve.

Figure 4. Alectinib base case Markov traces

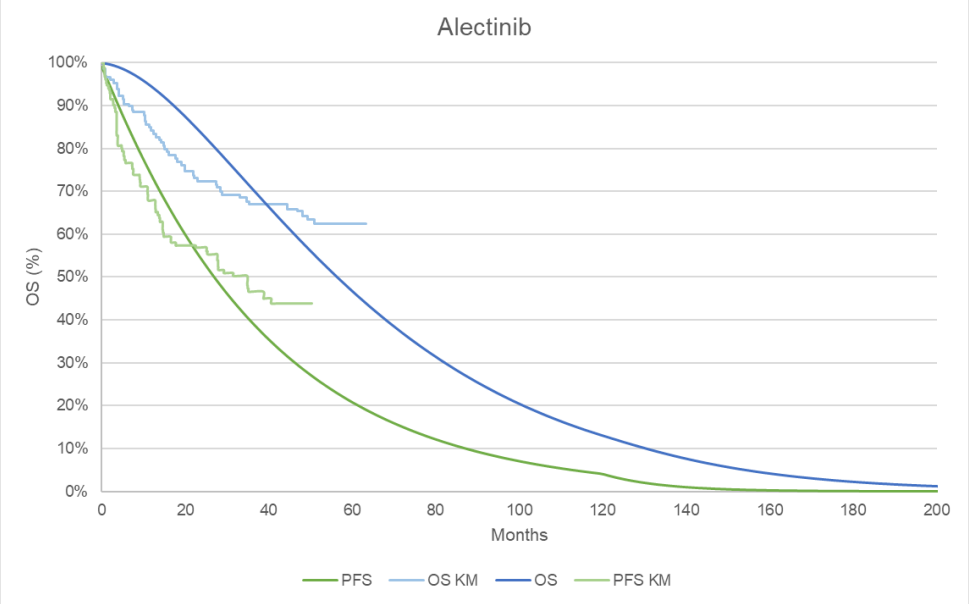


Figure 5. Alectinib Markov traces using lorlatinib as a reference

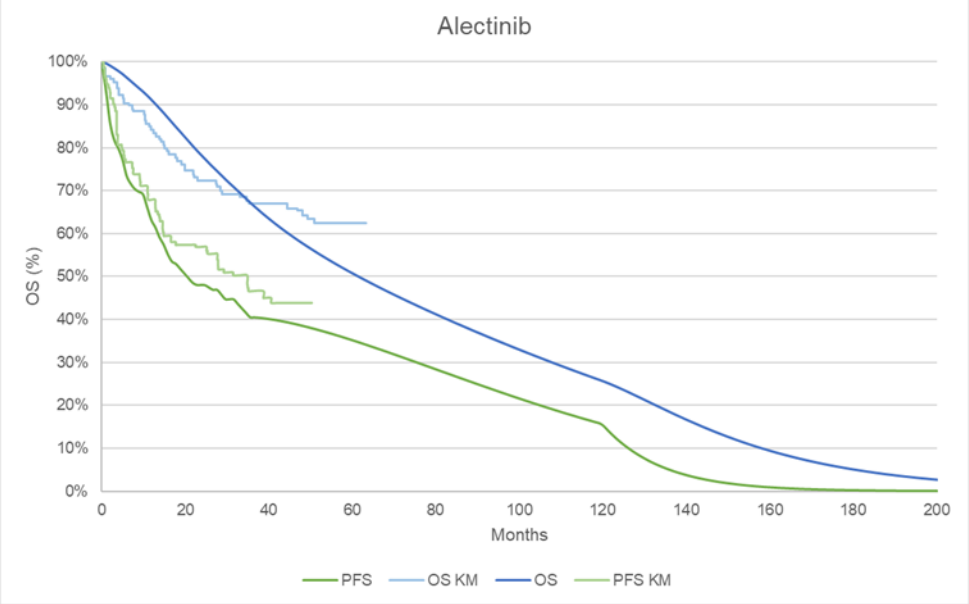


Table 5 shows the results when the hazard ratios versus lorlatinib are applied (deterministic as well as probabilistic results). Applying the hazard ratios versus lorlatinib based on the 36-months piecewise Weibull reduces significantly the ICER, from £19,138 to £11,018. The decrease in the ICER is explained by the longer PFS, which increases the acquisition costs. Although the OS is higher than in the base case, the increase in acquisition cost outweighs the higher life years gained, and the ICER decreases significantly. Based on the 36-months piecewise gamma (also considered a plausible extrapolation), the ICER is £11,098.

Table 5. Deterministic scenario analysis applying HRs using lorlatinib as a reference (versus alectinib)

#	Parameter varied	Deterministic ICER	Probabilistic ICER
	Base case	£19,138	£15,558
1	HRs using lorlatinib as a reference (PFS INV and IC-TTP) PFS INV using 36-months PW Weibull IC-TTP using exponential (used for determining intercurrent CNS events)	£11,018	£7,988
2	HRs using lorlatinib as a reference (PFS INV and IC-TTP) PFS INV using 36-months PW gamma IC-TTP using exponential (used for determining intercurrent CNS events)	£11,098	£8,655

Although not selected as the base case, given concerns around proportional hazards assumptions, using lorlatinib as the reference treatment in the NMA can be considered a plausible scenario and factored into decision making. See the response to A13 but particularly B4 below, it is not obvious from these plots that the proportional hazards assumption is necessarily rejected for alectinib versus lorlatinib (i.e. although they differ in absolute terms hazards are a similar shape for second generation ALK inhibitors versus lorlatinib).

B3. Priority question: Please fit standard parametric function to Study 1001 (Cohorts EXP3B-5) OS data. Please use these to operationalise alternative parametric extrapolations using the approach taken in the base case for the exponential curve.

Incorporation of time varying post-progression survival (PPS) would have required multiple tunnel states. Therefore, exponential curves using data from Study 1001 and Ou et al. were used to model PPS using EXP3B-5 data in line with TA909.

All the extrapolations (Figure 6), the mean and median overall survival within the considered time horizon (Table 6), landmark values (Table 8) and Akaike information

criterion (AIC) and Bayesian information criterion (BIC) statistics (Table 7) for all second-line lorlatinib OS parametric survival models are shown below.

Figure 6. Lorlatinib second-line overall survival extrapolations

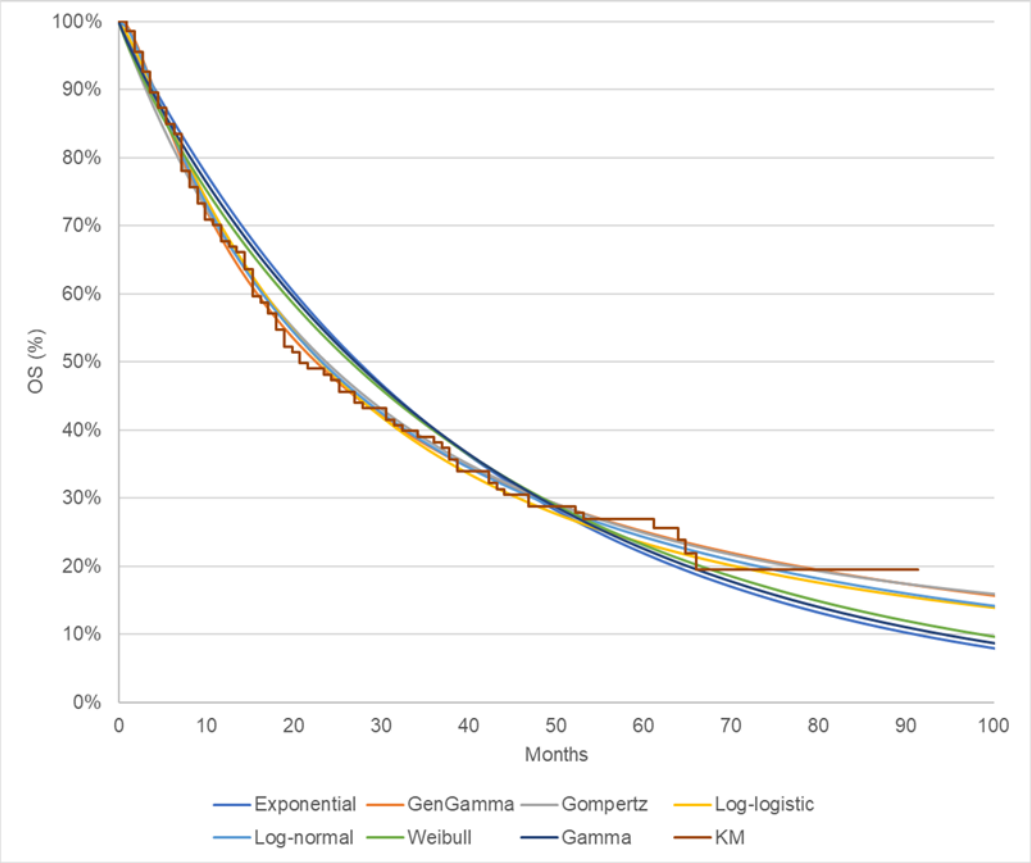


Table 6. Mean and median overall survival by extrapolation curve

Distribution	Median (months)	Mean (months)
Exponential	26.61	39.87
Generalized gamma	21.68	51.03
Gompertz	23.66	54.14
Log-logistic	22.67	48.36
Log-normal	22.67	48.34
Weibull	25.63	41.43
Gamma	26.61	40.52

Table 7. Fit statistics of second-line lorlatinib overall survival

Distribution	AIC	AIC_rank	BIC	BIC_rank
Exponential	890.34	5	893.27	5
Generalized gamma	892.00	7	897.87	7
Gompertz	882.15	2	890.95	3
Log-logistic	886.44	4	892.31	4

Log-normal	883.13	3	889.00	2
Weibull	880.64	1	886.51	1
Gamma	891.20	6	897.07	6

Table 8. Proportion of patients alive at key time points in second-line lorlatinib

	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
Exponential	74.1%	22.3%	4.9%	1.1%	0.2%	0.0%
Generalized gamma	67.9%	25.4%	13.1%	8.4%	6.0%	3.6%
Gompertz	68.7%	25.3%	13.9%	10.8%	9.7%	9.1%
Log-logistic	69.7%	23.7%	11.5%	7.2%	5.1%	3.2%
Log-normal	69.0%	24.6%	11.5%	6.7%	4.3%	2.2%
Weibull	71.8%	23.5%	6.4%	1.8%	0.5%	0.1%
Gamma	73.0%	23.0%	5.5%	1.3%	0.3%	0.0%

Alternative parametric extrapolations to the exponential were explored and included in the model, to allow for the mean PPS to vary and reflect the uncertainty in the ICER. To incorporate this, the goal seek function was used to find the exponential rate that equates to the mean PPS for alternative distributions (again in the same way as TA909).

Figure 7. Lorlatinib second-line overall survival extrapolations using exponential equivalent curves

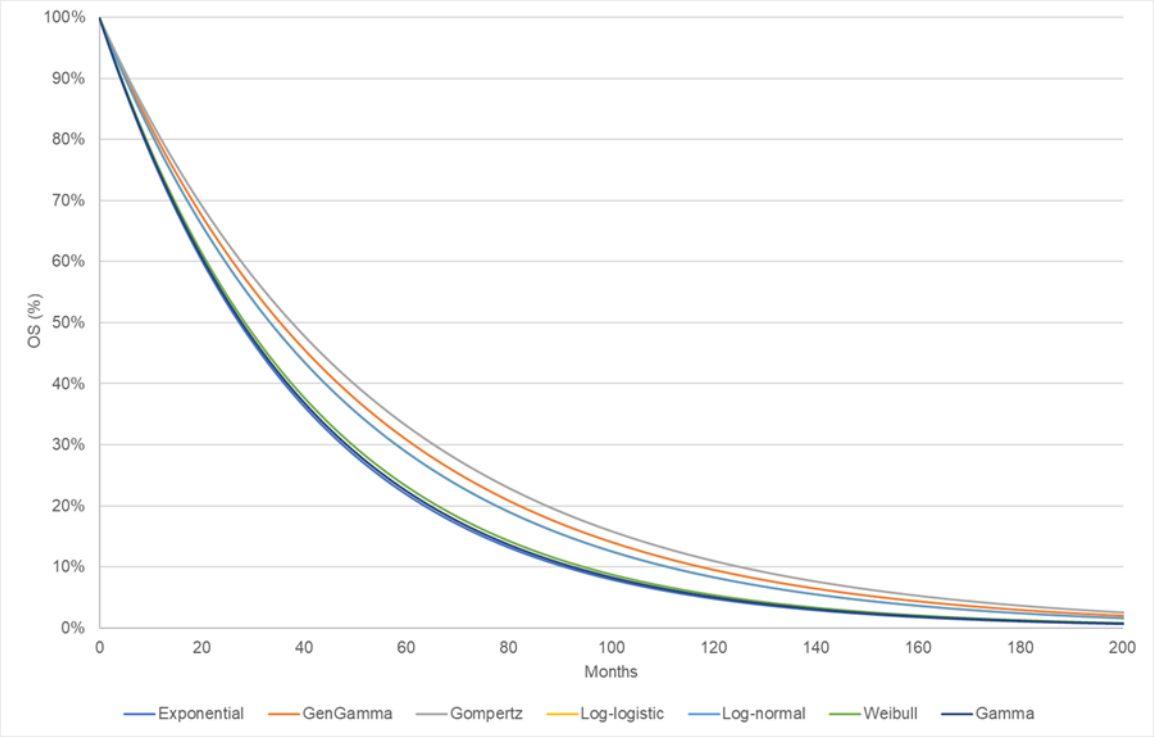


Table 9. Exponential rates to obtain the mean OS for alternative distributions

Distribution	Exponential coefficient	Exponential rate
Exponential	-3.6755	0.0253
Generalized Gamma	-3.9318	0.0196
Gompertz	-3.9944	0.0184
Log-logistic	-3.8754	0.0207
Log-normal	-3.8749	0.0208
Weibull	-3.7148	0.0244
Gamma	-3.6921	0.0249

The updated model structure allows for alternative parametric distributions to be explored to extrapolate PPS as discussed above. In NICE TA628 (Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer), there was a consensus among clinicians and the committee that lorlatinib OS would be more consistent with around 10% alive at 10 years and so the generalized gamma was considered the most optimistic but plausible at the time. With the more mature OS the generalized gamma also gives similar results. Therefore, deterministic and probabilistic results for the exponential curve and generalized gamma are shown in Table 10 to quantify the uncertainty around the post-progression survival. As a sensitivity test, the deterministic ICER for the Gompertz (lowest mortality rate and highest ICER) is £20,102. Note no account of the impact of different PPS assumptions on duration of treatment of second line lorlatinib has been made in these scenarios; however, modelled duration of treatment of second line lorlatinib was based on the agreed ToT curve selection from TA628 and this is unlikely to make much difference.

Table 10. Deterministic scenario analysis using alternative second-line overall survival extrapolation curves

#	Parameter varied	Deterministic ICER	Probabilistic ICER
	Base case (PPS curve exponential)	£19,138	£15,558
1	PPS curve - Generalised gamma	£19,885	£15,719
2	PPS curve - Gompertz	£20,102	£16,078

B4. Can the company elaborate on their position on the clinical plausibility of the treatment waning assumptions applied in the company base case analysis,

citing relevant evidence of treatment resistance for Lorlatinib and other ALK inhibitors in 1L?

Treatment waning is used to explore implied treatment effects over the long run, given the inherent uncertainty in treatment effect over the long-term that are beyond the observed trial period and even outside clinical experience (i.e. ALK inhibitors have only been in widespread use for no more than a decade). Broadly, the main reasons for 10-year waning in the base case are:

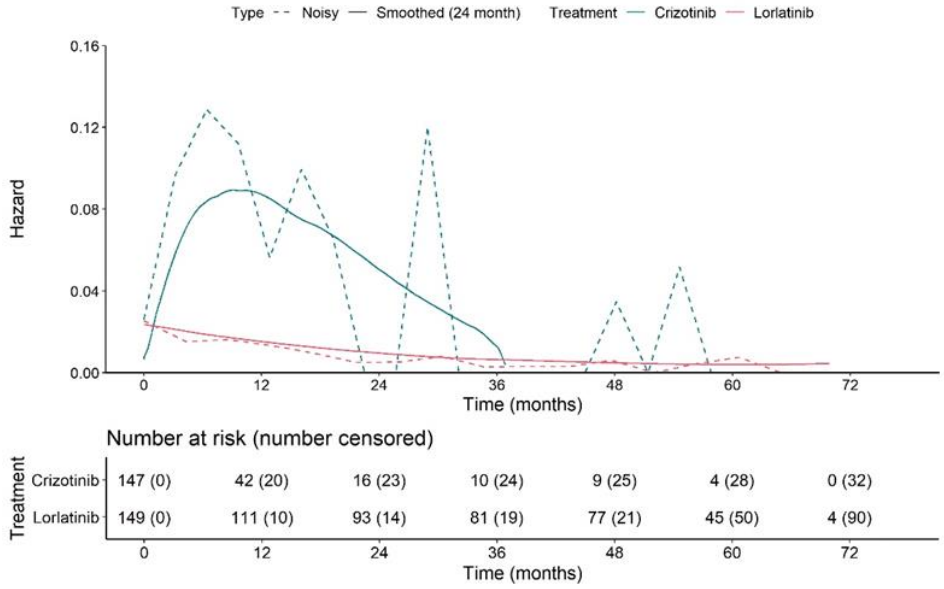
- 10-year waning was considered a reasonable compromise in the previous appraisal (TA909), with the committee taking account of clinical opinion at the time
    - As discussed in detail in Document B.3.3.2 and B.3.3.3 clinicians had a reasonably high certainty of expected lorlatinib PFS closer to the observed data: 60% PFS at 60 months (5 years) and a median of around 8 years would be plausible. However, longer term PFS for lorlatinib would be uncertain and hence the need to explore waning
    - Pfizer also explored other waning options and has retained this functionality in the model. Twelve and 15 years were included in scenario analyses. Interestingly, it should be noted that much earlier waning was explored in the brigatinib (TA670) and alectinib (TA536).
- All three clinicians consulted for this submission suggested 10 years is a reasonable point at which to assume (PFS and OS/PPS) hazards of ALK inhibitors equalize (versus say 8 or 12 years). This is a period after which “fast progressors” will have already progressed on less efficacious ALK inhibitors (e.g. crizotinib versus the second or third generation) and at the point at which there would be a set of “stable” or “durable” long-term responders for which hazards of progression (on treatment) and PPS (off treatment) will be similar
    - Pfizer acknowledges that the shape of the lorlatinib PFS curve after waning is perhaps not intuitive (i.e. a relatively sharp drop) and this was also discussed with clinicians. Despite this, there was a view that the equalizing of hazards at this point is reasonable from a clinical perspective and for simplicity given the previous committee’s view this hard point at which hazards equalize should be retained. Pfizer also considered smoother waning approaches (e.g. gradual waning from 8

to say 13 years at which point hazards fully equalize) but these would not impact cost-effectiveness greatly with the area under the PFS curve remaining similar

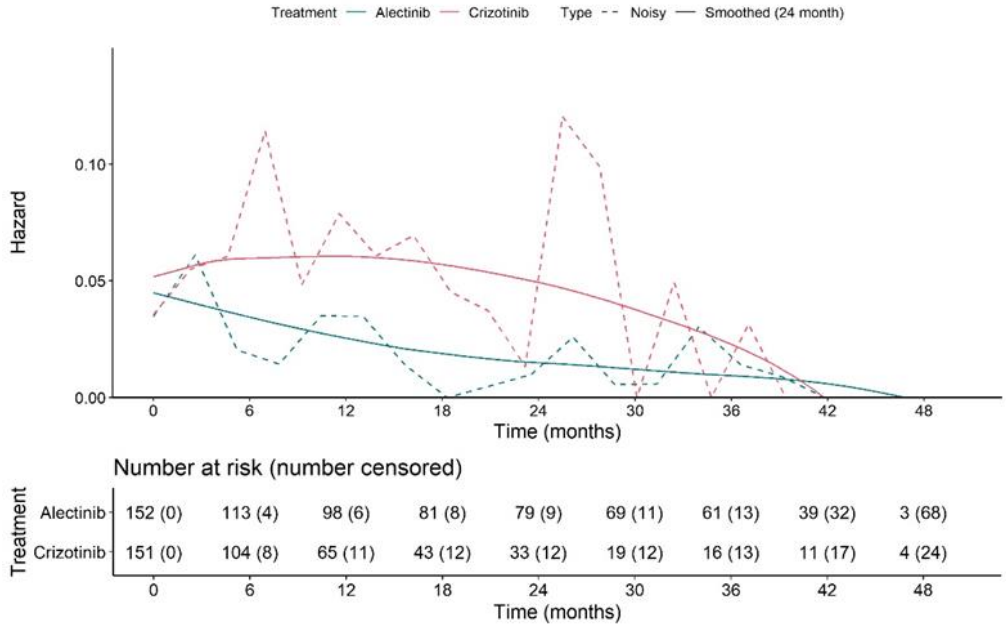
- Observed trial period (investigator assessed) PFS smoothed hazard plots for all trials are shown below. Crizotinib hazards tend to increase then decrease over time in all trials before settling at a relatively low level, which is unsurprising given the shape and uniformity of crizotinib PFS Kaplan–Meier curves across the trials (a sharp decrease in PFS and then a levelling off to a low tail). The second generation (alectinib, brigatinib) and third generation (lorlatinib) hazards are not a dissimilar shape: flatter hazards, but in general decreasing over time (apart from ALESIA, but these are presented for a shorter duration). Lorlatinib PFS hazards in absolute terms are consistently lower than the second generation inhibitors and this again is not a surprise given the unique shape of the lorlatinib PFS curve (i.e. a higher PFS curve and higher tail than other ALK inhibitors)
    - In relation to waning, these plots do not contradict the explanation for waning at 10 years: patients at risk are lower by the end of the trial periods and so there is uncertainty, but crizotinib smoothed hazards tend towards the second/third generation hazards by the end of the observed period. This is consistent with a view of longer term stable or durable responders: hazards become similar, but the absolute S(t) or observed PFS tails will be different between treatments which is what is observed

Figure 8. Smoothed PFS observed hazards from all trials:

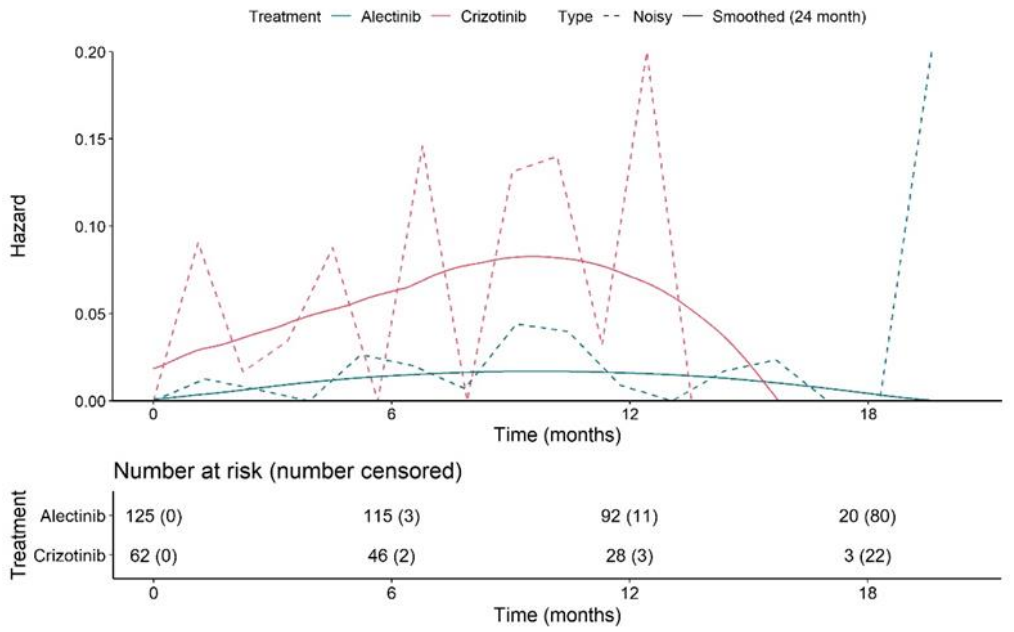
Smoothed hazard plot for CROWN – progression-free survival (INV)



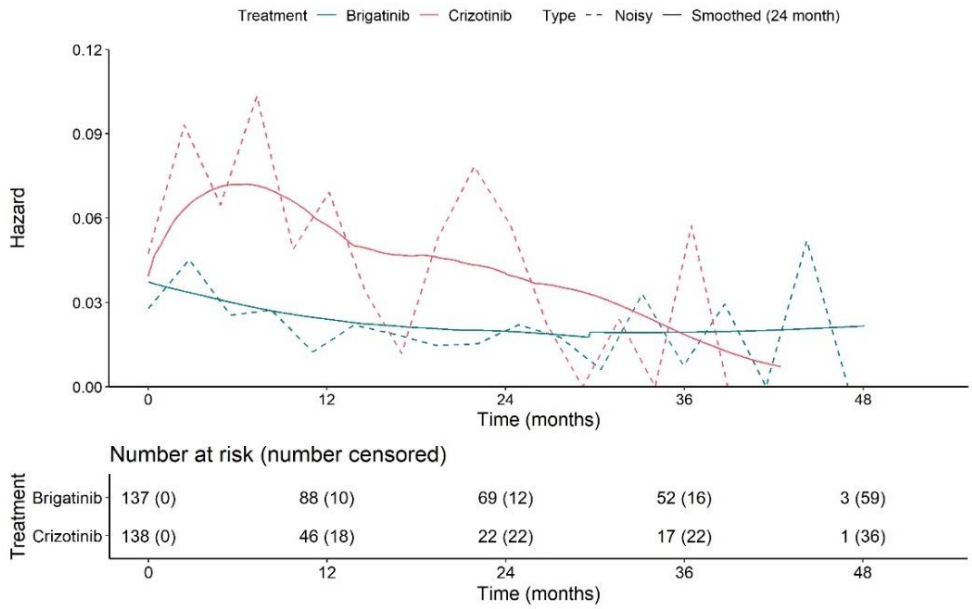
Smoothed hazard plot for ALEX – progression-free survival (INV)



Smoothed hazard plot for ALESIA – progression-free survival (INV)



[Smoothed hazard plot for ALTA-1L – progression-free survival (INV)]



B5. Priority question: In the company base case economic analysis PFS is extrapolated using two different approaches: a piecewise approach in the lorlatinib arm and a standard parametric extrapolation in the

alectinib/brigatinib arms. This is highly unusual, and it is not clear that this is consistent with recommendations in NICE DSU TSD 14.

a. Please justify this approach and its clinical plausibility.

b. Additionally, please provide appropriate statistical analysis to support this approach e.g. comparison of hazard trends.

As discussed in Document B.3.3.3 (and shown in Figure 22 of Document B) the fit of standard parametric models to the crizotinib PFS Kaplan–Meier curves is remarkably good given that most events have occurred by the October 2023 data cut. Therefore, for these no advanced survival methods beyond the standard methods were explored. Based on a reasonable assessment of PFS proportional hazards assumptions (see response to A13 and the submitted appendices) and a pragmatic way of combining the two trial sources of efficacy for alectinib it was decided that the modelled PFS for alectinib/brigatinib would be determined by applying NMA derived HRs to crizotinib survival. Therefore, there was no requirement for alternative survival models in this case.

The relevant curve selection sections in B.3.3 discuss the projected alectinib/brigatinib curves in the context of trial Kaplan–Meier curves and clinical plausibility. An alternative flatiron RWE alectinib arm is also presented in an addendum (with related documents) and integrated into the model to provide additional validation for the main comparator survival projections.

In TA909, the feedback from the EAG and first committee was that the lorlatinib survival analysis had “failed” given that only the exponential function gave the most plausible (or least implausible) long-term projections, meaning it was difficult to explore the impact of different long-term survival projections on cost-effectiveness. Therefore, there was a need to explore more advanced methods. The same issues persist even with the later 2023 data cut of PFS given the lack of PFS events and even longer (high) tail: with standard methods again perhaps only one function is plausible in the long-term. As discussed in Document B.3.3.2 and B.3.3.3 many alternative methods were explored with more detail provided in appendices. The conclusion was that the piecewise models provided more curve selection options that fit the observed tail well, were consistent with clinical estimates up to 8 years (higher certainty) and gave plausible long-term extrapolations (more uncertain).

Piecewise cut-point selection is explained in Document B.3.3.2 and associated appendices and relates to hazard shape and responder to PFS status over time.

Referencing observed period hazards, the high PFS tail and small events accrual for lorlatinib is reflected in the absolute low and flat hazards (see response to B4) and particularly compared with the second generation ALK inhibitors. Therefore, these hazards are consistent with the practical need to explore alternative survival methods that both capture the unique lorlatinib PFS while giving plausible long-term projections.

It should be noted that, in response to B2 we provide functionality and results for an analysis that uses lorlatinib PFS as the base to apply NMA derived HRs. This would mean applying HRs to the piecewise lorlatinib selected curves to derive alectinib and brigatinib curves which would avoid any argument about the use of advanced survival methods for only one model arm.

B6. Priority question: The base case extrapolation of crizotinib progression-free INV using Weibull distribution appears to be particularly pessimistic predicting 5 years PFS that is significantly below that observed in CROWN (1.9% vs 7.5%). Moreover, the model predictions for alectinib and brigatinib PFS appear to underestimate the observed data in the ALEX and ALTA-1 studies.

a. **Please present tables comparing the predictions of the model with relevant pivotal trial data for PFS and OS for crizotinib, alectinib and brigatinib at key time points and justify any departure from the observed data.**

b. **Please provide digitized KM data for ALEX and ALTA-1 and plot them against the Markov trace from the model.**

Table 11 and Figure 9 show the crizotinib PFS predictions compared to the Kaplan–Meier curve. During the initial 30 months the extrapolations marginally overestimate survival. However, after 30 months, the extrapolations are marginally below the Kaplan–Meier data, possibly due to the low numbers at risk.

Table 11. Proportion of patients alive and progression-free INV assessed at key time points – crizotinib

Distribution	12 months	24 months	36 months	48 months	60 months
Exponential	46.6%	21.7%	10.1%	4.7%	2.2%
Generalized gamma	40.1%	18.4%	10.5%	6.8%	4.7%
Gompertz	41.6%	21.2%	12.6%	8.4%	6.2%
Log-logistic	38.9%	14.9%	7.6%	4.6%	3.1%
Log-normal	41.9%	17.9%	9.1%	5.1%	3.1%
Weibull	**47.2%**	**21.5%**	**9.7%**	**4.3%**	**1.9%**
Gamma	48.2%	20.4%	8.3%	3.3%	1.3%
KM curve	**34.4%**	**14.7%**	**10.1%**	**10.1%**	**7.5%**

Figure 9. INV assessed PFS for crizotinib

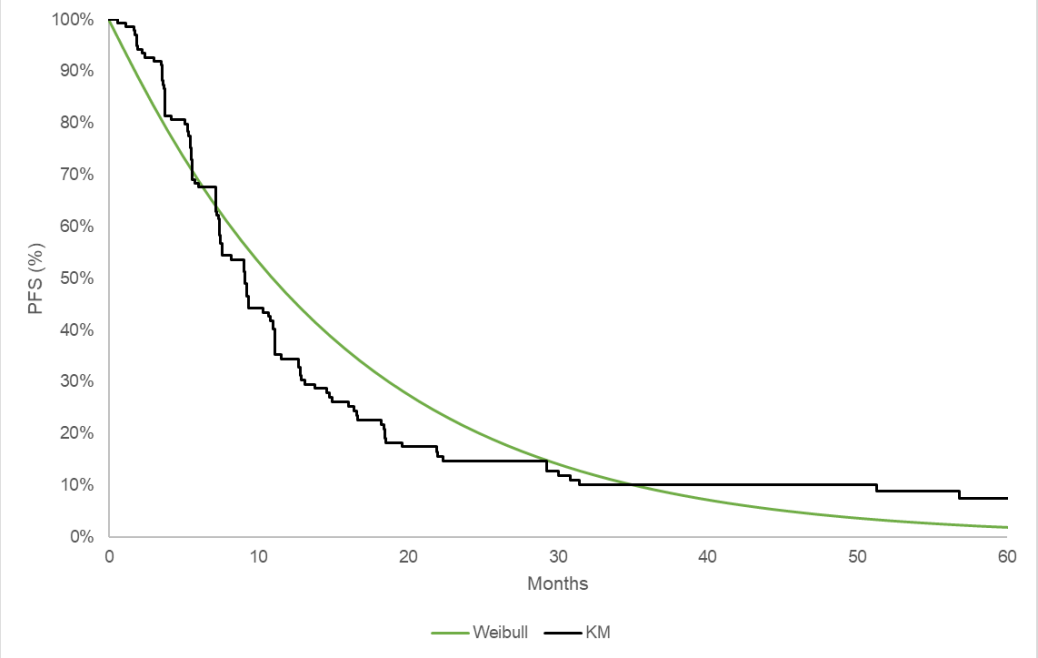


Table 12 and Figure 10 show the crizotinib OS predictions compared to the Kaplan–Meier curve. Extrapolations fit the data well. Note again that the pseudo state transition approach for OS was used for alectinib and brigatinib and so some of these comparisons do not reflect the modelling approach used.

Table 12. Proportion of patients alive at key time points – crizotinib

Distribution	6 months	12 months	18 months
Exponential	93.5%	87.5%	81.8%
Generalized gamma	93.9%	86.2%	80.9%
Gompertz	93.0%	86.9%	81.5%
Log-logistic	94.5%	87.9%	81.6%
Log-normal	94.6%	87.6%	81.3%

Weibull	**94.5%**	**88.2%**	**82.0%**
Gamma	94.7%	88.4%	82.0%
KM curve	**94.9%**	**86.6%**	**79.4%**

Figure 10. OS for crizotinib

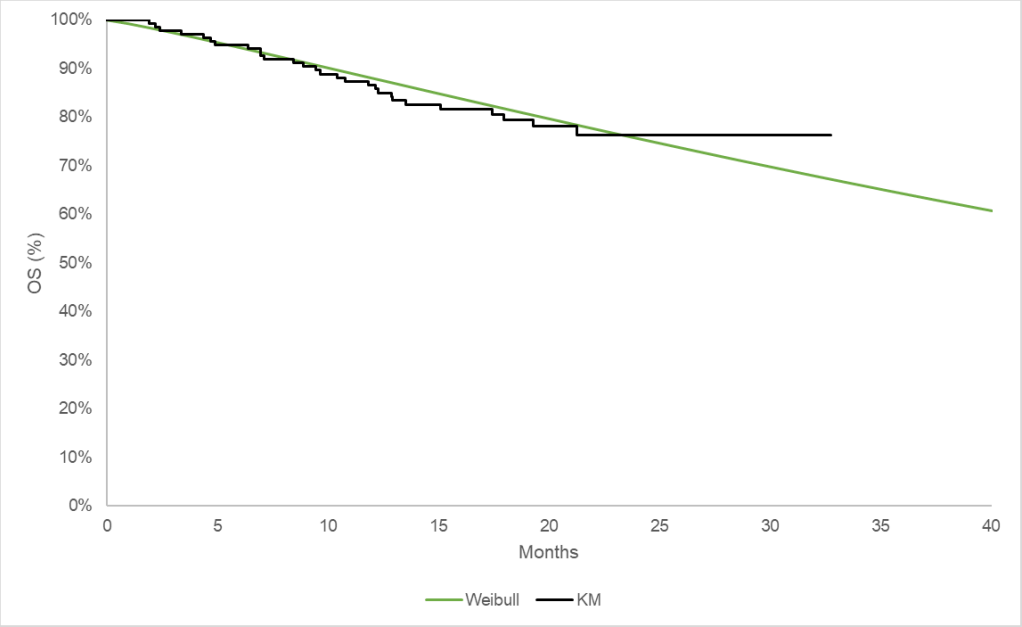
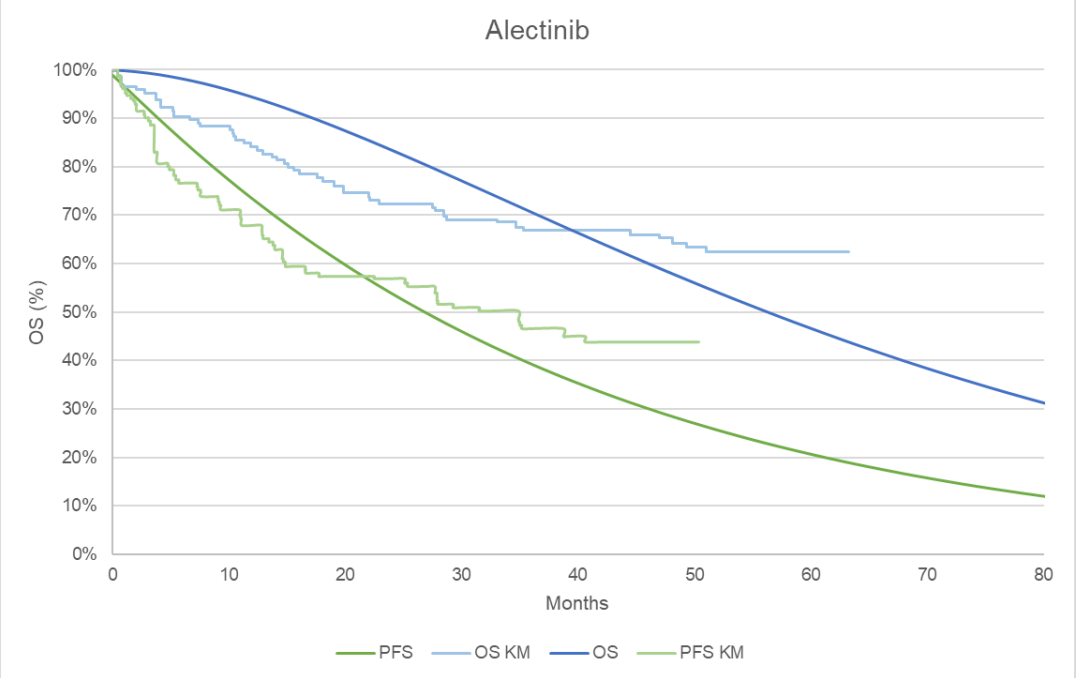


Table 13 and Figure 11 display the OS and PFS extrapolations and the Kaplan–Meier curves from the ALEX trial. As mentioned in the company submission, direct comparisons versus ALEX and ALTA-1 Kaplan–Meier curves should be interpreted in the context of the PFS curves being produced using the results of NMA analyses and OS from the pseudo state transition approach. The extrapolated curves show some differences compared to the KM data. OS is overestimated until month 40, and PFS until month 22.

Table 13. Proportion of patients alive and progression-free INV assessed at key time points – alectinib

	12 months	24 months	36 months	48 months	60 months
PFS extrapolation	73.8%	54.4%	39.9%	29.1%	21.2%
PFS KM	67.9%	56.9%	46.6%	43.8%	NA
OS extrapolation	94.5%	83.8%	71.2%	58.7%	47.4%
OS KM	84.1%	72.3%	66.9%	65.3%	62.4%

Figure 11. Alectinib survival extrapolations



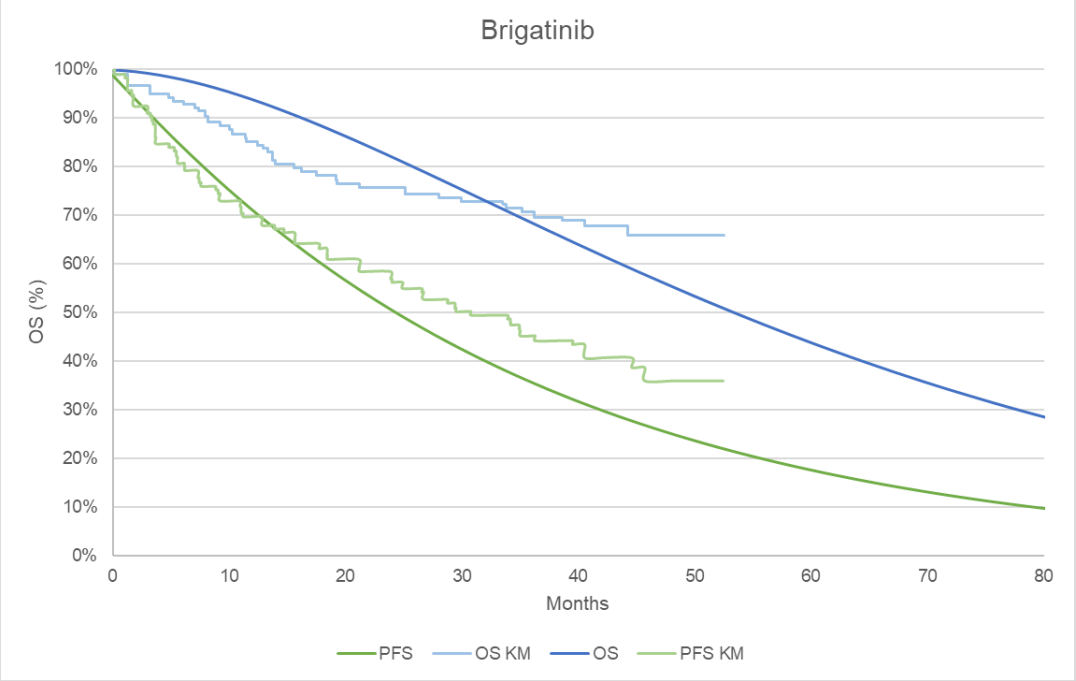
Differences were also observed during NICE TA570 but the exponential was selected due to clinical plausibility. “Therefore, it was deemed the exponential is the most appropriate distribution to utilize. However, visual fit to the curves is poor, driven by the delay in the separation of the curves. Therefore, it was deemed more appropriate to utilize the KM data up to 18 months (where censoring increases), with the exponential tail added afterward.”

Table 14 and Figure 12 display the OS and PFS extrapolations and the Kaplan–Meier curves from ALTA-1L trial. A similar trend is observed from brigatinib. OS is overestimated until month 35, while PFS is aligned with the KM data until month 12.

Table 14. Proportion of patients alive and progression-free INV assessed at key time points – brigatinib

	12 months	24 months	36 months	48 months	60 months
PFS extrapolation	71.4%	50.9%	36.1%	25.5%	18.0%
PFS KM	69.7%	56.1%	45.1%	35.8%	NA
OS extrapolation	94.0%	82.4%	69.1%	56.1%	44.6%
OS KM	85.2%	75.6%	70.6%	65.8%	NA

Figure 12. Brigatinib survival extrapolations



Health-related quality of life

B7. Priority question: The committee for brigatinib (TA670) did not consider the Roughley et al. 2014 (Reference 42 of the CS), to be a reliable source to calculate the multiplier applied to the progressive disease utility value to estimate the impact of brain metastases due to the small number of people with brain metastases (n = 29) and the fact that treatment-related adverse events, comorbidities or age were not reported.

a. Please re-run your HRQoL regression model described in Section B3.4.1 with the addition of CNS metastases as a covariate.

b. Please also present a comparison of observed disutilities associated with different types of metastases i.e. other than CNS metastases.

In response to Part A, this analysis has already been conducted at the most recent data cut for which health-related quality of life (HRQoL) is available (September 2021) and is published as a poster. Please see Document B.3.4.2.3 and reference 134 (Liu G et al. 2022) which forms the basis of scenario analysis 14. Applying a mixed effect (longitudinal model), the study shows a 0.10 difference in the EQ-5D baseline utility values of those patients with brain metastases in comparison to those without brain metastases (versus 0.69-0.52=0.17 with Roughley et al. 2014). No

differences in EQ-5D-5L index scores between treatment arms were observed in patients with and without brain metastases; however, there were absolute differences between those with and without brain metastases in the lorlatinib arm.

In response to Part B, other metastatic sites beyond the brain/CNS were not of special interest to clinicians and so have not been treated as a special group in any pivotal ALK targeting TKIs (including CROWN). This contrasts with progression in the brain. Clinical consultations carried out by Pfizer recently and presented in the submission (advisory board, Delphi panel, individual clinical consultations) also reflect this emphasis on progression in the brain among clinicians and patients. Beyond those specific to each patient (i.e. target tumours reflected in RECIST criteria) these were not captured in the trial dataset as independent time-to-event outcomes (i.e. as with IC-TTP for progression specific to the brain) and so such an analysis would be challenging.

B8. The EAG is concerned that the relatively high utilities generated in the CROWN trial may be a consequence of high rates of attrition in the HRQoL data, which may be particularly affecting patients experiencing adverse events.

a. Please provide further information on the patients contributing HRQoL data, including baseline characteristics and the number of patients. Please also provide the number of observations included in the analyses at each time point.

b. Please provide evidence that patients experiencing adverse events continued to contribute to HRQoL data collected. In particular please comment on the participation of patients suffering peripheral neuropathy, and cognitive, mood, speech, and psychotic affects associated with treatment.

c. Please provide information on the number of missing observations in the HRQoL analyses at each time point. Provide details on how these were

handled in the regression analysis (e.g. complete case analysis or multiple imputation).

A) A summary of baseline characteristics for patients included in the utility analyses are presented in Table 15. To illustrate attrition rates, Table 14.5.1.1.2 of the CROWN 18-month CSR details the number of patients who reported utility questionnaires at each timepoint, along with the number of patients who should have provided responses to the questionnaires (note: utility analyses were done using 3-year CROWN data).

Table 15: Baseline characteristic summary for patients included in the utility analysis

Category	Crizotinib	Lorlatinib
Total	140	148
Age – years, n (%)		
18–44	34 (24.3)	26 (17.6)
45–64	65 (46.4)	64 (43.2)
≥65	41 (29.3)	58 (39.2)
Baseline ECOG PS, n (%)		
0	52 (37.1)	67 (45.3)
1	79 (56.4)	78 (52.7)
2	9 (6.4)	3 (2.0)
Baseline brain metastases, n (%)		
No	102 (72.9)	110 (74.3)
Yes	38 (27.1)	38 (25.7)
Race, n (%)		
Asian	63 (45.0)	65 (43.9)
Non-Asian or unknown	77 (55.0)	83 (56.1)
Sex, n (%)		
Female	86 (61.4)	84 (56.8)
Male	54 (38.6)	64 (43.2)
Smoking status, n (%)		
Current	9 (6.4)	13 (8.8)
Former	40 (28.6)	54 (36.5)
Never	90 (64.3)	81 (54.7)
Key: ECOG PS, Eastern Cooperative Oncology Group Performance Status.		

B) In the time available to respond to EAG questions it was not possible to summarize the available and missing data by occurrence of adverse events. However, as acknowledged in response to B9, Pfizer agrees that the CROWN derived utilities available (i.e. at the September 2021 data cut) may be less realistic

than the alternative ALEX and ALTA-1L, which provide a more reasonable range of utility estimates to be explored (and could form part of the EAG base case).

C) In the utility regression model, a complete case analysis was conducted where all available records were used, using 3-year CROWN data. As mentioned in Part A, Table 14.5.1.1.2 of the CROWN 18-month CSR details the total number of utility records and expected number of utility records at each timepoint. Questionnaire adherence was above 90% for all visits while the patient was on treatment. The adherence was lower at the end of treatment and follow-up visits. Questionnaires were administered after treatment was finished every 4 weeks at the follow-up visit, only if the patient visited the clinic. There was no clear pattern in the reasons for non-completion for one treatment arm or the other. Since the level of missing data was low for the majority of visits and there was no obvious reason why the patients were missing the observation a complete cases analysis was conducted.

B9. Priority question: Please justify why different progression-free health state utility values have been used for each treatment (Table 61, company submission Document B, page 149). Clinical advice to the EAG did not believe that quality of life would differ in these health states by treatment. The EAG also notes that these assumptions are inconsistent with those made in TA 536, TA 670 and TA 909.

TA670 look to have applied ALTA-1L derived utilities to both brigatinib and alectinib PFS, but different PPS utilities (variable by CNS substates). The earlier TA536 looks to have done something similar (versus crizotinib). The Pfizer position was that separate PFS utilities (with trial specific AE decrements) were thought to better reflect patient experience on each ALK inhibitor.

However, Pfizer acknowledges that the CROWN derived PFS utility using the latest available data for HRQoL from CROWN (September 2021 data cut) is probably too similar to general population norms and so alternatives were explored in scenario analyses in the submission. Both the ALEX and ALTA-1L derived utilities for PFS are options in the model and do not make a great deal of difference to cost-effectiveness results (holding other settings constant). Pfizer accepts that the alternative sources provide a plausible range of PFS utilities (the ALTA-1L derived utilities are already in the base case for PPS) and would accept them as part of an updated base case.

Resource use and costs

B10. Priority question: In TA909 the NICE committee concluded that it was appropriate to model treatment beyond progression recognizing that treatment beyond progression is common for all ALK TKIs in this disease area.

a. Please justify why the company base case does not include treatment beyond progression.

b. Please present a scenario analysis implementing treatment beyond progression as described in the guidance documents for TA909.

In response to Part A, the Pfizer view of this issue is explained in detail in Document B.3.3.5 and summarized in detail in Document A.11.4. Also explained in those sections (and summarized below), using the trial observed relationship between time on treatment (ToT) and PFS was retained in the alectinib and brigatinib appraisals and is consistent with the NICE view of the hierarchy of evidence. With even more mature ToT and (BICR or IA) PFS CROWN data, there continues to be a ToT < PFS observed relationship (again discussed in detail in Document B.3.3.5).

TA670 looks to have resolved this issue in technical engagement with the conclusion that treatment duration should be determined by independently fitted ToT curves, but this did not make much difference given that in ALTA-1L ToT is very similar to PFS (as explained in B.3.3.5). Clinicians there also suggested that treatment for some may go beyond progression, but the technical team report concluded (and this was supported by the committee): “However, the committee was aware that ToT data were available from trials and concluded that data from the available evidence was preferred”.

In TA536 this was not identified as a technical issue and is not discussed in the ERG report or final appraisal document (FAD; or accompanying committee slides). This suggests that the company presentation of the ToT Kaplan–Meier curves atop PFS Kaplan–Meier curves, showing that they are very similar and that PFS can be used as a ToT proxy, was accepted.

Guidance in TA909 recommended using a duration of treatment beyond progression based on Ou et al. in which the median duration of treatment after progressive disease is 5.7 months. However, in the study, it is explained that only patients with

the best overall response of complete or partial response or stable disease were included (N=74). Among the 74 patients considered, only 56 patients continued lorlatinib beyond progressive disease (LBPD), where LBPD is defined as greater than 3 weeks of lorlatinib treatment after investigator assessed progressive disease. Therefore, only 56 out of 278 patients received lorlatinib beyond progression (20.1%) with a median duration of 5.7 months (Figure 13). This is equivalent to only 1.14 months of treatment beyond progression, including this for all treatments including lorlatinib (i.e. equivalent to applying a HR ToT Vs PFS of 1.263) makes a very small difference to the ICER. However, Pfizer strongly disagree that even such a scenario is consistent with good modelling practice as discussed above and in Document B.

Figure 13. Lorlatinib treatment beyond progression from Ou et al.

Table 2. Duration of Treatment, OS, and Overall and Postprogression DoT

	Group A		Group B	
Treatment Outcomes	LBPD (n = 21)	Non-LBPD (n = 7)	LBPD (n = 56)	Non-LBPD (n = 18)
Median DoT, mo (range)	32.4 (4.6-41.9)	12.5 (0.4-38.8)	16.4 (3.7-43.2)	7.7 (2.8-38.2)
Median DoT post-PD, mo (range)	11.8 (0.8-36.8)	0.1 (0-0.3)	5.7 (0.8-32.7)	0.3 (0-0.6)
Median OS, mo (95% CI)	NR (NR-NR)	24.4 (12.1-NR)	26.5 (18.7-35.5)	14.7 (9.3-38.5)
Median OS post-PD, mo (95% CI)	NR (21.4-NR)	8.0 (1.5-NR)	14.6 (11.2-19.2)	5.3 (2.8-14.3)

CI, confidence interval; DoT, duration of treatment; LBPD, lorlatinib beyond progressive disease; NR, not reached; OS, overall survival; PD, progressive disease.

Severity Modifier

B11. Priority question: The company's submission does not include an assessment of the disease severity modifier criteria. Please provide an evaluation of these criteria in line with the NICE methods manual.

This is a first-line NSCLC trial with established TKIs and so no severity modifier is achievable. To verify, under the following conditions a quality-adjusted life year (QALY) proportional (absolute) shortfall of 75% (10.3) is achieved:

- Age (57) and proportion female (59%) consistent with the model and CROWN trial
- Total discounted QALYs for standard of care (SoC) from the base case model (alectinib which is the main comparator)
- Reference case utility set from the York shortfall calculator to calculate general population QALYs

In addition, using probabilistic QALY results or the alternative base case based on Flatiron derived OS and PFS for alectinib, which is arguably a better reflection of

real-world SoC accrued QALYs, does not make much difference to these calculations.

Section C: Textual clarification and additional points

Systematic Literature Searches

C1. The searches for clinical evidence (CS, Appendix D) were last updated in February 2024. Please clarify if any relevant evidence has been published in the last 7 months or could be available from unpublished sources (e.g. conference presentations).

Two relevant publications have recently been published, but the results from these publications have already been included in this submission:

- CROWN 5-year data (Solomon et al. 2024)[4], already included in this submission
- ALESIA 5-year data (Zhou et al. 2024)[6], previously published as abstract/poster that was included in this submission.[7]

No additional publications have been published in the past 7 months. For the ALEX study, Mok 2020 reported the final PFS results and the final OS analysis is expected in 2026.[1, 8]. For ALTA-1L, Camidge 2021 reported final results of this study.[9]

C2. The searches for cost-effectiveness evidence (CS, Appendix G), Health-Related Quality of Life evidence (CS, Appendix H) and cost and healthcare resource identification, measurement and valuation evidence (CS, Appendix I), were last updated in 2019, in the context of the 2022 appraisal of Lorlatinib. Please provide updated searches or clarify that no relevant evidence has been published since the dates of the last searches.

Although the clinical SLR was fully updated on 27 February 2024, the cost-effectiveness SLR was not updated due to the very low probability that an alternative cost-effectiveness analysis related to lorlatinib had been published since that time. The HCRU SLR was not updated because of the very low probability that an alternative set of health state costs (or similar) would have been published since that time that could be useful or impact cost-effectiveness. In the context of this being a

resubmission, the HRQoL SLR was not updated given the abundance of ALK trial reported utilities available in previous submissions that determine what have been seen as the plausible range of PFS/PPS utilities (and available as options in the submitted model).

C3. Within the clinical evidence searches (CS, Appendix D, Tables 1 to 6), please clarify if any relevant evidence was missed as a result of:

a. Missing various drug brand names (e.g. Lorbena, Lorviqua, and Alunbrig);

b. Not searching dedicated HTA databases (e.g. INAHTA), trial registries (e.g. ClinicalTrials.gov) or guidelines and regulatory bodies (e.g. NICE)

'Lorlatinib', 'brigatinib' was searched in Embase using /syn functionality which should include all the studies indexed with relevant brand names as soon as the brand names are recognized. All investigational and other generic names were searched using 'kw' options in Cochrane, so it is highly unlikely that any study using the brand names would have been missed. In addition, re-running the searches using the missing brand names, does not result in any additional records.

Trail registries were searched as part of the Cochrane search strategy to identify the unique trials not otherwise captured in Embase.com. Other HTA bodies and regulatory agencies' websites were not searched since only pivotal studies are captured in those and they are comprehensively searched in electronic databases and grey literature searches.

C4. Within the clinical evidence MEDLINE and Embase search (CS, Appendix D, Table 4), line 28 removes reviews using various subject headings and free-text terms, yet the inclusion criteria of the SLR of clinical evidence includes systematic reviews of RCTs and non-RCTs (CS, Appendix D, Table 8). Please clarify whether any relevant evidence was missed as a result.

Line 28 removes all narrative reviews and narrative synthesis which are not conducted systematically but NOT the systematic reviews which are searched and included as per PICOS. Since there is some overlap expected between the two and hence, a 'NOT' functionality is added to ensure systematic reviews are retained while removing the narrative reviews.

C5. Within the clinical evidence MEDLINE In-Process search (CS, Appendix D, Table 5), line 9 which pools together all the results searching for the condition is orphaned. There is therefore either an error or missing line(s) from the documentation. Please provide a correct version of the search strategy, and explain which publication types line 27 is including and excluding.

Line 9 pools the evidence base for the indication 'non-small-cell lung cancer' which is pooled in different ways i.e. 'Lung cancer' terms (Line 2, 3 and 5) are pooled with 'non-small cell' terms (line 7) in line 8, which is then combined with MeSH terms for NSCLC (line 1). "ALK+" terms were not added in the search terms so as not make the search strategy restrictive and ensuring the searches are sensitive and specific enough. Therefore, only the terms for non-small-cell lung cancer were searched.

Line 27 of Table 5 provides records for all In-process evidence and publications which are ahead of print in MEDLINE.

References

1. ClinicalTrials.gov. NCT02075840. A Study Comparing Alectinib With Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Participants (ALEX). Available at: https://clinicaltrials.gov/study/NCT02075840?term=ALEX%20alectinib&rank=1. Accessed: October 2024.
2. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2018; 379(21):2027-39.
3. Pfizer Inc. Data on file: Pfizer UK Lorlatinib Advisory Board - Analysis and Recommendations Report. 2024.
4. Solomon BJ, Liu G, Felip E, et al. Lorlatinib Versus Crizotinib in Patients With Advanced ALK -Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. *Journal of Clinical Oncology*. 2024; 42(29):3400-9.
5. Ou. Lorlatinib in patients with ALK-positive non-small cell lung cancer: a brief report on final results from the Phase 2 study. *Manuscript in preparation*. In press.
6. Zhou C, Lu Y, Kim SW, et al. Alectinib Versus Crizotinib in Asian Patients With Treatment-Naive Advanced ALK-Positive NSCLC: Five-Year Update From the Phase 3 ALESIA Study. *JTO Clin Res Rep*. 2024; 5(9):100700.
7. Zhou C, Lu Y, Kim SW, et al. LBA11 Alectinib (ALC) vs crizotinib (CRZ) in Asian patients (pts) with treatment-naïve advanced ALK+ non-small cell lung cancer (NSCLC): 5-year update from the phase III ALESIA study. *Annals of Oncology*. 2022; 33:S1563.
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positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020; 31(8):1056-64.
9. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib Versus Crizotinib in ALK Inhibitor–Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. *JTO*. 2021; 16(12):2091-108.

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by [redacted]
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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Study details

Reference	Solomon BJ, Liu G, Felip E, et al. Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. J Clin Oncol. 2024:JCO2400581.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Lorlatinib Comparator: Crizotinib

Specify which outcome is being assessed for risk of bias	PFS, by investigator assessment (5-year data cut)
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	HR: 0.19 (95% CI: 0.13, 0.27) mPFS: Lorlatinib: not reached (95% CI: 64.3, NR) vs crizotinib: 9.1 months (95% CI: 7.4, 10.9) Table 1 and Figure 5 in the Company Submission

Is the review team's aim for this result…?

- X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
X Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Yes, patients were randomly assigned 1:1 to receive lorlatinib 100 mg once daily or crizotinib 250 mg twice daily in 28-day cycles.[1] Randomization codes were centrally allocated across all centers via an IRT system. Allocation sequence was only available at the IRT system until database release for interim analysis.	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	The baseline patient demographics were well-balanced between treatment arms, with no major differences with respect to gender, race, presence of brain metastases or other clinically important characteristics (see Table 9 in the Company Submission).[1] There were numerically slightly fewer female patients in the lorlatinib arm compared with the crizotinib arm.	No
Risk-of-bias judgement	-	Low
Optional: What is the predicted direction of bias arising from the randomization process?	-	NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	The study was open-label, but the BICR (terminated after 3 years of follow up) and the sponsor's study team were blinded to the randomized treatment.[2]	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Yes
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No	No
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	n/a	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	n/a	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes, intention-to-treat analysis. Five patients in the crizotinib group did not receive treatment but were included in the intention-to-treat population.	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	n/a	NA
Risk-of-bias judgement	-	Low risk
Optional: What is the predicted direction of bias due to deviations from intended interventions?	-	NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	The study was open-label, but the BICR (terminated after 3 years of follow up) and the sponsor's study team were blinded to the randomized treatment.	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Yes
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	At 5-year data cut, similar number of patients were censored from PFS analysis due to start of new anti-cancer therapy: 7 (4.7%) patients in the lorlatinib arm and 9 (6.1%) in the crizotinib arm Source: Table 14.2.1.1 in the CROWN 5-year Clinical Study Report Tables and Figures[3]	Yes
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	No	No
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	No	No
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	n/a	NA
Risk-of-bias judgement	-	Low risk
Optional: What is the predicted direction of bias due to deviations from intended interventions?	-	NA

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Intention to treat analysis; outcomes available for > 95% patients and similar number of patients with missing outcome data were censored across both arms. Patients with missing data (who were censored for PFS analysis) in lorlatinib and crizotinib arms: - No adequate baseline assessment: 1 (0.7%) vs 0 (0%) - Event after ≥ 2 missing or inadequate post-baseline assessments: 5 (3.4%) vs 3 (2.0%) - Lost to follow-up: 2 (1.3%) vs 1 (0.7%) - No adequate post-baseline tumour assessment: 0 vs 0	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	n/a	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement	n/a	Low
Optional: What is the predicted direction of bias due to missing outcome data?	a/n	NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	No	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes, open-label design. Only BICR assessment was blinded.	Yes
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes, theoretically possible, but unlikely	Yes
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		No
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?	Theoretically could favour intervention, but unlikely. Assessment of PFS by blinded independent central review (BICR) at 3 years (per-protocol, BICR assessment of PFS, IC-TTP and ORR finished after 3 years) confirmed the PFS benefit of lorlatinib (at 3 years, mPFS by BICR was NR (NR–NR) for lorlatinib vs 9.3 (7.6–11.1) for crizotinib; HR 0.27 (0.18–0.39))[4]	Favours experimental

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No	No
5.3 ... multiple eligible analyses of the data?	No	No
Risk-of-bias judgement	-	Low
Optional: What is the predicted direction of bias due to selection of the reported result?	-	NA

Overall risk of bias

Risk-of-bias judgement	The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.	Some concerns
Optional: What is the overall predicted direction of bias for this outcome?	As mentioned in Domain 4, lack of investigator blinding for the PFS assessment could theoretically favour intervention, but this is unlikely. Assessment of PFS by blinded independent central review (BICR) at 3 years (per-protocol, BICR assessment of PFS, IC-TTP and ORR finished after 3 years) confirmed the PFS benefit of lorlatinib (at 3 years, mPFS by BICR was NR (NR–NR) for lorlatinib vs 9.3 (7.6–11.1) for crizotinib; HR 0.27 (0.18–0.39))[4]	Favours experimental

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References:

1. Solomon B, Liu G, Felip E, et al. Lorlatinib vs Crizotinib in Treatment-Naive Patients With Advanced ALK+ Non-Small Cell Lung Cancer: 5-Year Progression-Free Survival and Safety From the CROWN Study. ASCO. Chicago: USA; 2024.
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Appendix 1: Study 1001

Summary of trial design and methodology

Study 1001 was a Phase I/II, multicentre, open-label, single-arm trial in which patients with ALK-positive advanced NSCLC received lorlatinib monotherapy.(1) The study completed in March 2023.(2) Patients in Study 1001 were grouped based on their prior exposure to ALK inhibitors into six expansion cohorts (EXP)-1–6. The data and outcomes presented in this appendix focuses on the treatment naïve population (EXP-1, n = 30) in line with the population relevant to ID6434 Company Submission.

A summary of the Study 1001 design and methodology is presented in Table 1.

Table 1: Summary of methodology for Study 1001

Study 1001 (NCT01970865)	
Location	Australia (2), Canada (1), France (4), Germany (1), Hong Kong (1), Italy (4), Japan (10), Korea (1), Singapore (2), Spain (4), Switzerland (2), Taiwan (1), US (11)
Trial design	Phase I/II, open-label, multicentre, single-arm study
Duration of study and follow-up	• Treatment continued until investigator assessed disease progression, unacceptable toxicity, withdrawal of consent, or death • Patients were allowed to continue treatment with lorlatinib after objective progression as long as there was evidence of clinical benefit in the investigator's opinion • Survival and subsequent therapy follow-up continued every 2 months after discontinuation of treatment
Method of randomization	Patients were not randomized, instead they were enrolled into expansion cohorts on the basis of their ALK or ROS1 status and previous treatment history
Trial drugs and method of administration	Lorlatinib was administered orally in tablet form at a 100 mg dose once daily in 21 day cycles
Permitted and disallowed concomitant medication	Allowed concomitant therapies included: • Bisphosphonate therapy for metastatic bone disease • Palliative radiotherapy for the treatment of painful bony lesions • Granulocyte-colony stimulating factors for treatment-emergent neutropenia • Erythropoietin for the supportive treatment of anaemia • Anti-diarrhoeal, anti-emetic and acid-reducing therapy, except in the first cycle of Phase I • Anti-inflammatory or narcotic analgesics • Palliative and supportive care for disease related symptoms • Topical or oral corticosteroids

	• Testosterone replacement therapy • Statins (recommended at the first signs of elevated cholesterol and/or triglycerides. Statins of choice were pitavastatin or pravastatin, followed by rosuvastatin. Similarly, if hypertriglyceridemia required treatment, fenofibrate or fish oils, followed by nicotinic acid were recommended) The following concomitant therapies were disallowed, or caution warranted: • Additional systemic anti-tumour therapy • Strong/moderate CYP3A4 inhibitors or strong CYP3A4 inducers • CYP2C9 or CYP2B6 substrates • CYP3A4 or P-gp substrates with a narrow therapeutic index • Surgical procedures
Primary outcomes[a]	• ORR • IC-ORR
Secondary outcomes[a]	• TTR and IC-TTR • DOR and IC-DOR • DCR and IC-DCR at 12 weeks and 24 weeks • TTP and IC-TTP • PFS • OS • AEs

Key: AE, adverse event; ALK, anaplastic lymphoma kinase; CYP3A4, cytochrome P450 3A4; CYP2B6, cytochrome P450 2B6; CYP2C9, cytochrome P450 2C9; DCR, disease control rate; DOR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; IC, intracranial; N/A not applicable; NSCLC, non-small-cell lung cancer; ORR = objective response rate; OS, overall survival; P-gp, P-glycoprotein; PFS, progression-free survival; PK, pharmacokinetic; PS, performance status; QLQ-C30, Quality of Life Questionnaire – Cancer; QLQ-LC13, Quality of Life Questionnaire – Lung Cancer; QD, once daily; RECIST v1.1,Response Evaluation Criteria in Solid Tumour version 1.1; ROS1, ROS proto-oncogene 1; TTP, time to tumour progression; TTR, time to tumour response.
Source: Pfizer Inc, Study 1001 CSR, 2017; Soloman et al. 2018.(1)

Eligibility criteria

A summary of the key eligibility criteria for Study 1001 is presented in **Table 2**.

Please refer to 1001 Clinical Study Report for the full eligibility criteria.

Table 2: Eligibility criteria for Study 1001

Inclusion criteria	• Age ≥ 18 years (or ≥ 20 years, if required by local regulations) • Histologically or cytologically confirmed diagnosis of metastatic (Stage IV) NSCLC • Confirmed presence of an ALK or ROS1 gene rearrangement • At least one measurable target extracranial lesion according to RECIST version 1.1 • Adequate bone marrow, renal and hepatic function • ECOG PS of: 0 or 1 in Phase I or 0, 1, or 2 in Phase II • Prior treatment: – Phase I: treatment naïve in the advanced setting (focus of this submission) or disease progression after at least one previous ALK or ROS1 inhibitor – Phase II: treatment naïve in the metastatic setting or disease progression after 1–3 ALK TKIs, with or without prior chemotherapy (ALK-positive patients), or any number of ROS1 therapies • Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤ 1 (except for AEs that did not constitute a safety risk) • Serum pregnancy test negative at screening (for females of childbearing potential) and the use of two highly effective methods of contraception from screening, until 90 days after the last dose
Exclusion criteria	• Spinal cord compression, unless the patient demonstrated good pain control with therapy and stabilization or recovery of neurological function for four weeks prior to study entry • Major surgery within four weeks of study entry • Radiation therapy within two weeks of study entry, unless palliative to relieve bone pain and completed at least 48 hours prior to study entry. Stereotactic/small field brain irradiation and whole brain radiation had to be completed at least two or four weeks prior to study entry, respectively • Systemic anti-cancer therapy completed within five half-lives of study entry • Prior T-cell co-stimulation- or immune checkpoint pathway targeted therapy (including, but not limited to anti-PD-1, PD-L1, PD-L2, CD137 or CTLA-4 therapy) • Previous high-dose chemotherapy requiring stem cell rescue • Prior irradiation to >25% of the bone marrow • Active and clinically significant bacterial, fungal, or viral infection including HBV, HCV, HIV or AIDS-related illness • Clinically significant cardiovascular disease or abnormal LVEF • Predisposing characteristics for acute pancreatitis • History of extensive, disseminated, bilateral or presence of Grade 3/4 interstitial fibrosis or interstitial lung disease

	• Active inflammatory gastrointestinal disease, chronic diarrhoea, symptomatic diverticular disease or previous gastric resection or lap band • Other severe acute or chronic medical or psychiatric condition

Key: AIDS, Acquired Immunodeficiency Syndrome; ALK, anaplastic lymphoma kinase; CD137, TNF receptor superfamily member 9; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; CTLA 4, cytotoxic T-lymphocyte-associated antigen 4; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; NSCLC, non-small-cell lung cancer; PD, pharmacodynamic; PD-1, programmed cell death receptor-1; PD-L1, programmed cell death receptor-ligand-1; PD-L2, programmed cell death receptor-ligand-2; RP2D, recommended Phase II dose; SAE, serious adverse event; TKI, tyrosine kinase inhibitor; ROS1, ROS proto-oncogene 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1.
Source: Pfizer Inc, Study 1001 CSR, 2017; Solomon et al., 2018.(1)

Baseline characteristics

A summary of the baseline characteristics of ALK inhibitor treatment naïve patients (n = 30) in Study 1001 is presented in **Table 3**. Median age was 59 years (IQR: 48–68) and 57% of participants were male.(1) Twenty-seven percent of patients had brain metastases at baseline with the average number being 1–3 in 50% of patients. One patient had received previous chemotherapy and eight had had radiotherapy.(1) Baseline characteristics for the whole trial population are presented in 1001 Clinical Study Report.

Table 3: Baseline characteristics for the treatment naïve population of Study 1001

Characteristics	**Treatment naïve patients (n = 30)**
Age, years	
Median (IQR)	59 (48.0–68.0)
Sex (%)	
Female	13 (43)
Male	17 (57)
Race (%)	
White	10 (33)
Black	1 (3)
Asian	17 (57)
Other	1 (3)
Unspecified †	1 (3)
ECOG performance status (%)	
0	13 (43)
1	16 (53)
2	1 (3)
Brain metastases at baseline ‡	8 (27)
Number of brain metastases at baseline‡	

1–3	4 (50)
4–6	2 (25)
7–9	2 (25)
≥ 10	0
Median (IQR)	3 (1–6)
Previous radiotherapy	6 (20)
Previous brain-directed radiotherapy	2 (7)
Number of pervious chemotherapy regimens	
0	29 (97)
1	1 (3)§
> 1	0

Key: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group.
Notes: †In France, information about race was not allowed to be collected per local regulations. ‡By independent central review; includes measurable and non-measurable CNS lesions at baseline. §One patient in EXP1 received previous adjuvant chemotherapy but no previous treatment for metastatic disease.
Source: Solomon et al. 2018.(1)

Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical analysis

A summary of the statistical analysis performed during Study 1001 is provided in **Table 4**.

Table 4: Summary of statistical analyses in Study 1001

Study 1001 (NCT01970865)	
Hypothesis objective	In Phase II, for subpopulations EXP-1–5 the goal of the primary analysis of objective response was to estimate the ORR and their exact 95% confidence intervals (CIs).
Statistical analysis	• **Binary data:** Binary endpoints were summarised by percentage rates along with the 95% CIs using an exact method. • **Continuous data:** Descriptive statistics, including the mean, standard deviation, median, minimum and maximum values, was provided for continuous endpoints. • **Categorical data:** The number and percentage of patients in each category was provided for categorical variables. Missing data for a variable was included in the denominator and a row was included for the number and percent with missing values. • **Time to event data:** For each endpoint, the median, quartiles; and for TTP, IC-TTP, PFS and OS only the probabilities at 1 year, 18 months and 5 years were estimated using the Kaplan–Meier (KM) method. CIs for the median and quartiles were generated using the Brookmeyer-Cowley (B-M) method. Two-sided 95% CIs for the 1-year and 18-month and 5-year survival probability were calculated for the log [-log(1-year (18-month/5 year) survival probability)] using a normal approximation and then back transformed to give a CI for the 1-year (18-month/5 year) survival probability itself.
Sample size, power calculation	The sample size of each cohort was based on an estimation design with no specific hypothesis testing. EXP1* had a target enrolment of 30 patients.
Patient withdrawals	Patients were allowed to withdraw from treatment at any time at their own request or withdraw at the discretion of the investigator or sponsor due to safety or behavioural reasons, or to the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.
Key: CI, confidence intervals; EXP, expansion cohorts; ORR, objective response rate; PFS, progression-free survival; PROs, patient-reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumours. **Notes**: * EXP-1 cohort (patients previously untreated with ALK inhibitors) is the focus of this submission. **Source**: Solomon et al. 2018.(1)	

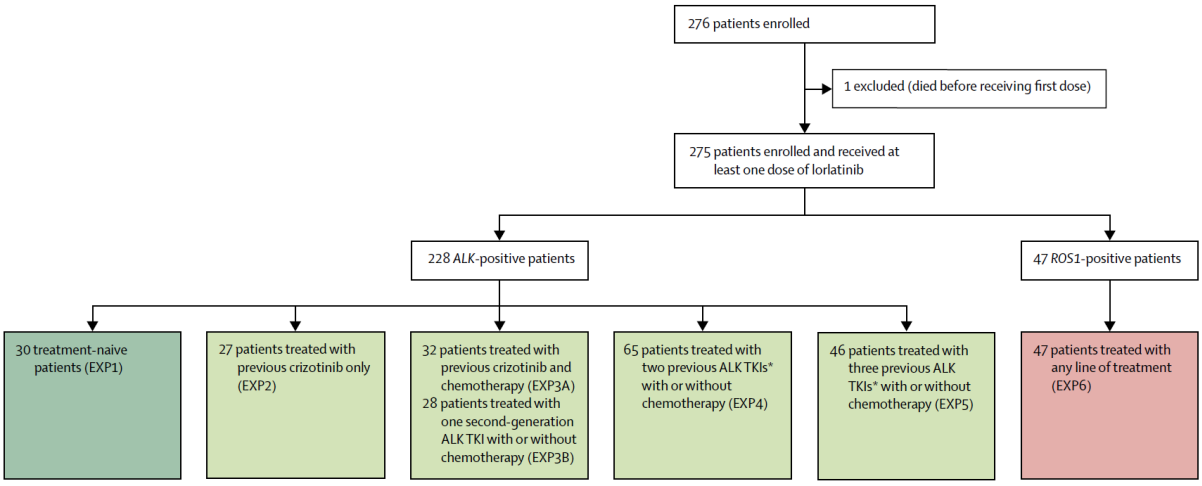
Analysis sets

In Phase II, analyses of efficacy endpoints were conducted by EXP cohorts. Data presented here will focus on the treatment naïve population (n = 30). Details of the full study analysis sets are presented in the 1001 Clinical Study Report.

Patient disposition

In total, 275 patients were enrolled into the Study 1001 trial (**Figure 1**). One patient withdrew before receiving the study drug.(1) Thirty patients were treatment naïve and enrolled into the EXP-1 cohort. All patients received the study drug as planned.

Figure 1. Patient disposition (Study 1001; Phase 2 FAS)



Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; FAS = full anaysis set; ROS1 = c-ROS oncogene 1; TKI = tyrosine kinase inhibitor
*If the same TKI was given twice, it was counted as two previous lines of treatment
Source: Solomon et al. 2018.(1)

Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of Study 1001, based on Solomon et al. 2018, using the risk of bias checklist recommended by NICE is presented in **Table 5**. Study 1001 was methodologically robust, well-reported and considered to be at low risk of bias.(1)

Table 5: Quality assessment of the Study 1001 trial

Question	Study 1001 trial
1. Was randomization carried out appropriately?	Yes
2. Was the concealment of treatment allocation adequate?	No
3. Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	No
5. Were there any unexpected imbalances in drop-outs between groups?	No
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Clinical effectiveness results of the relevant trials

Study 1001 included patients with and without prior exposure to ALK inhibitors.(2) Here we present the ORR, a primary endpoint (March 15, 2017 data cut)(1), and the 5-year long-term follow-up data (July 27, 2023 data cut) for patients that were naïve to treatment with ALK inhibitors (n = 30).(2) At the data cutoff for the 5-year analysis, median duration of treatment with lorlatinib was 64.59 months (range, 1.68-88.21).

Overall response rate (primary endpoint)

At the initial data cut off (March 15, 2017 data cut), of 30 patients who were naïve to treatment with ALK inhibitors, 27 (90.0%; 95% CI 73.5–97.9) had an objective response, with one patient achieving a complete response and 26 achieving a partial response (Table 6).(1) Of the 27 confirmed responses, 23 (85%) were ongoing and the median duration of response was not reached (95% CI 10.0 months–not reached [NR]). Median time to first tumour response was 1.4 months (IQR 1.3–2.7). The estimated median duration of follow-up for response was 6.9 months (IQR 5.6–12.5).

Table 6. Overall responses by independent central review (March 15, 2017 data cut)

Variable	Lorlatinib (treatment-naïve cohort: n = 30)
Best overall response	
Complete response[†], n (%)	1 (3%)
Partial response[†], n (%)	26 (87%)
Stable disease, n (%)	2 (7%)
Objective progression, n (%)	1 (3%)
Indeterminate	0
Patients with confirmed objective response (%; 95% CI)[‡]	27 (90.0%; 73.5–97.9)
Median time to first tumour response, months (IQR)	1.4 (1.3–2.7)
Median duration of response, months (95% CI)[§]	NR (10.0–NR)
Median duration of follow-up for response, months (IQR)[¶]	6.9 (5.6–12.5)

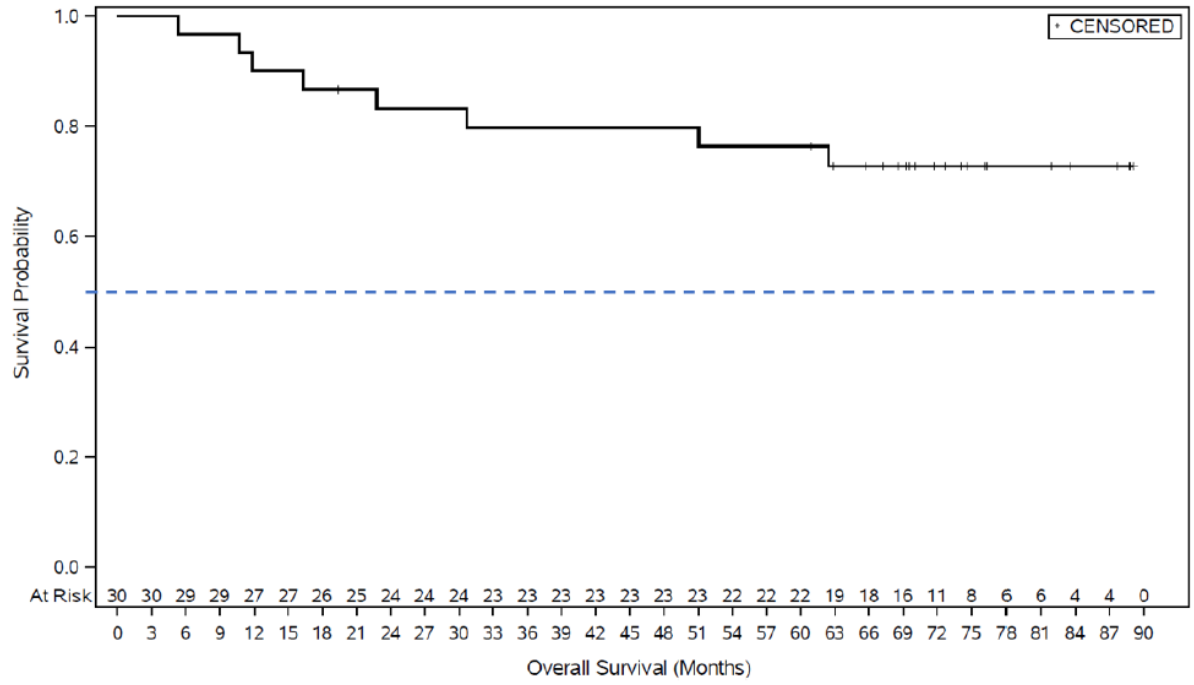
Key: CI, confidence interval; IQR, interquartile range.
Notes : [†]Confirmed response; [‡]Using exact method based on binomial distribution; [§]Using Brookmeyer and Crowley method. [¶]Estimates are based on the reverse Kaplan-Meier method with 95% CIs based on the Brookmeyer and Crowley method.
Source: Solomon et al. 2018.(1)

Overall survival

Patients in the treatment naïve cohort had a median duration of follow-up for OS of 72.7 months (95% CI: 69.3, 76.3).(2) Median OS was not reached (95% CI: NR, NR) while the probability of 5-year OS was 76% (**Figure 2**). The median time to disease progression was 17.7 months (95% CI: 12.5, 40.5).(2)

In patients with baseline CNS metastases (measurable and non-measurable; n = 8), the median OS was NR (95% CI: 51.0, NR). In patients without baseline CNS metastases (n = 22), the median OS was NR (95% CI: NR, NR).(2)

Figure 2: Kaplan–Meier curve for long-term OS in the treatment naïve population in Study 1001



Key: OS, overall survival.
Source: Ou et al. manuscript in preparation.(2)

Time to disease progression

The median time to disease progression in EXP1 was 17.7 months (95% CI, 12.5-40.5).

Subsequent treatments

In the treatment naïve cohort, a total of nine (30%) patients received at least one subsequent anti-cancer therapy; eight (27%) patients received at least one subsequent systemic anti-cancer therapy; two (7%) patients received at least one subsequent radiotherapy treatment and two (7%) patients received at least one subsequent anti-cancer surgery. Most patients received one subsequent systemic anti-cancer therapy, most commonly, another ALK inhibitor.(2)

References

1. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. The Lancet Oncology. 2018;19(12):1654-67.

2. Ou, cartographer Lorlatinib in patients with ALK-positive non-small cell lung cancer: a brief report on final results from the Phase 2 study [[manuscript in preparation]].

NICE 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]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	ALK Positive UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	It is a charity run by patients & carers for the benefit of ALK-positive lung cancer patients across the UK. It is funded by charitable donations, in memorium donations, charity- organised fund-raising events, family members completing sponsored events and restricted grants from pharma' We currently
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	**Our members are regularly surveyed where we gather patient insights, experiences and those of carers.**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It causes constant anxiety having this diagnosis. Most patients aren't diagnosed until they are stage 4, so they know it is life limiting. Most patients have regular CT/PET scans every 3/4mths treatments to ensure they haven't stopped working. All patients are aware that these targeted treatments only hold the cancer at bay and the PFS (progression free survival) data is only a guide as to how long each individual patient will be stable. This makes every scan very scary for both patients and carers. Patients are also aware that up to 70% of ALK-positive patients develop brain metastases. Another anxiety inducing regular scan is the brain MRI, usually at a similar frequency to the CT/PET scan, however very often the appt's are on different days so requiring multiple trips to the hospital. This has a significant impact on both the patient and their family – many women have young families so may need childcare to attend appt's. Working patients need to take time off work – not everyone is paid for the time they attend appt's which impacts the whole family with reduced monies to manage the family budget. If brain metastases develop this has a massive impact on patients & their families as patients need to surrender their driving licence for a minimum of a year. Imagine trying to get young children to school when its raining or having to carry your shopping home on the bus. Those are the realities for some of our members. Carers feel guilt and helplessness. They also experience all the anxieties associated with scans/scan results. A patient isn't diagnosed with cancer, the whole family is – all their dreams for the future are smashed.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Patients generally feel their oncology teams do their very best by them, however they also know there are only a few treatment options in the UK –** **Alectinib 1st line followed by Lorlatinib. Chemo or a trial follow although chemo is rarely successful for any length of time and only a handful are selected for the trial.** **Brigatinib 1st line followed by Lorlatinib. Chemo or a trial follow** **Progression free survival for both 1st line treatments is somewhere between 3-4 yrs for most patients and PFS is usually less for any treated used in the 2nd line setting.**
8. Is there an unmet need for patients with this condition?	There is a real need for treatments that offer a significantly longer PFS time and overall survival OS. This population are generally younger than the average lung cancer patient. Our youngest member is just 18 yrs old, diagnosed on his 18th birthday.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**This treatment would potentially offer them far longer on treatment before progression and reduces the probability of developing brain metastases. Any progression either leads to radiotherapy to stay on current treatment, which comes with its own side effects or switching to the next line of treatment, with the anxiety of not knowing if the 2nd line will work.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	It is known amongst our members to have cognitive effects – loss of memory for words, forgetfulness and sometimes the feeling of 'pins & needles' in hands and/or feet. All patients agree these are side effects worth tolerating for longer with their families.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I think all patients with an ALK-positive lung cancer diagnosis would benefit from this treatment being available as a 1st line choice.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues

13. Are there any other issues that you would like the committee to consider?	I cant think of any I haven't referred to above.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients progress too quickly on current 1st line treatments • Patients need treatments that offer a longer time before progression for a better QoL • Up to 70% ALK+ patients will develop brain metastases which have a sig. impact on quality of life • Patients need greater protection from the risk of developing brain metastases • Patients who have received Lorlatinib as a 2nd line treatment report its an easier to tolerate option than the other TKI's and they feel better on it with a better QoL. •

Thank you for your time.

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Single Technology Appraisal

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

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services; £165 Advisory Meeting Honorarium) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1040 Advisory board Honorarium) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Sanofi (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Astra Zeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £300 for Advisory Board Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium) - Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker Fee) - Janssen (£24,000 grant funding for Ask The Nurse Service)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	none
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lung Cancer symptoms, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. The ALK gene rearrangement is found in about 3% to 5% of patients with NSCLC. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is our observation that, though a younger, fitter patient group (fewer co-morbidities), ALK positive patients tend to be diagnosed later, as they do not fit the 'typical' lung cancer patient profile.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Crizotinib, Certitinib, Alectinib and Brigatinib have all been approved by NICE for untreated ALK positive NSCLC patients. Lorlatinib has previously been approved for ALK positive patients, whose disease has progressed after an initial ALK TKI. Previous NICE appraisal (July 2023), did not recommend Lorlatinib in this setting. However, in the recommendation, NICE indicated that collecting more data may resolve some of the uncertainties they encountered during their appraisal. These drugs work in part by blocking the activity of the ALK protein, ultimately inhibiting the growth of tumour cells. Patients typically develop resistance to these drugs when tumour cells develop new gene alterations, in the ALK gene, which renders the protein insensitive to the inhibitor. It appears that most patients progress under ALK inhibition within a few years, the brain being a common site of relapse. Each ALK inhibitor has a different spectrum of sensitivity to ALK mutations, thus making complex the optimal sequencing of ALK inhibitors.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Outcomes of treatment are seen as an advantage of this technology. We do not have any additional data, beyond that publicly available. We note, however, the updated results of the CROWN trial, presented at ASCO in June 2024. This study compared Lorlatinib and Crizotinib, in untreated ALK positive patients – at the time this study commenced, Crizotinib was the standard of care. This update was a follow up at 5 years. At 5 years, 60% of patients on Lorlatinib were alive and progression free. For Crizotinib, this was 8%. Remarkable! As noted above, brain metastasis is of particular concern with ALK positive lung cancer. In the CROWN study, for patients with brain metastatsis at baseline, five year Progression Free Survival (PFS) in the Lorlatinib arm was 53%. In the Crizotinib arm, all patients with baseline brain mets had progressed or died within 2 years. For patients without brain metastasis at baseline, five year PFS was 63% in the Lorlatinib arm and for Crizotinib, 10%. After 5 years of follow up, median PFS has not yet been reached in the Lorlatinib group. We understand that this represents the longest PFS reported with any single agent molecular targeted treatment in advanced non small cell lung cancer and indeed across all metastatic solid tumours. From a patient perspective, this is good news.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Side effects of the treatment. We understand that common side effects associated with Lorlatinib include oedema, peripheral neuropathy, weight gain, dyspnoea, arthralgia, diarrhea, hypercholesterolemia and cough. In the anecdotal patient experience available to us, it appears to be generally well tolerated.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• At 5 year follow up, median progression free survival with Lorlatinib, in this patient group, has not yet been reached. • This data is really good news for ALK positive patients • Lorlatinib has been shown to have benefit both for those patients who have brain metastasis at diagnosis and those who do not.

Thank you for your time.

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NICE 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]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Funded by sponsorship and registration fees for HCP's working in thoracic oncology
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes sponsorship BTOG 2024 Annual Conference £22,000 + VAT
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prolong survival of patients with advanced ALK positive NSCLC
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in size of tumour Disease control on treatment
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	With 2nd generation ALK inhibitors (Alectinib or Brigatinib)
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE, ESMO Treatment in the NHS is confined to the treatments reimbursed

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are multiple first line treatment options for ALK positive NSCLC. Most professional will be prescribing a 2nd generation ALK inhibitor (Alectinib or Brigatinib)
9c. What impact would the technology have on the current pathway of care?	No change in the pathway. Lorlatinib would become another first line choice
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	n/a
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Centres where SACT is prescribed / dispensed – secondary / tertiary centres
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	n/a
11. Do you expect the technology to provide clinically meaningful	Based on the CROWN trial date - yes

benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	For patients with advanced ALK positive NSCLC

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	Toxicities are different to current standard of care, but not more difficult to manage

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stopping treatment will be upon loss of clinical benefit
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	n/a
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Based on the clinical benefit seen in the trials - yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	It is likely to be a more clinically effective treatment than current standard of care

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Lorlatinib has a well established toxicity profile with effective guidance on management

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	n/a
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	PFS Intracranial disease control Safety
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical	n/a

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	n/a
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA670 and TA536?	n/a
21. How do data on real-world experience compare with the trial data?	n/a

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	n/a
22b. Consider whether these issues are different from issues with current care and why.	n/a

Topic-specific questions

23. Would you expect people given alectinib as adjuvant therapy for locally advanced stage 2/3 NSCLC (if recommended in ID6368) to be eligible for lorlatinib as first-line treatment for advanced/metastatic stage 4/5 NSCLC (as recommended in TA628)?	If they progress while on Alectinib (or within 12 months) then they should be eligible for Lorlaitnib as a 'second line' therapy If the progressed 12 months after stopping Alectinib in the adjuvant setting then they should be eligible for Lorlatinib as a 'first line' therapy

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Based on the CROWN data Lorlatinib appears to be the most efficacious ALK inhibitor in the first line setting • The PFS benefit is one of the most pronounced and impressive data seen in solid tumours • The intracranial efficacy is also highly impressive bearing in mind the high prevalence of brain metastases in this population and the significantly negative impact on quality of life they can have • The toxicity profile is manageable effectively with supportive measures and dose modification •

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with ALK-positive advanced non-small-cell lung cancer or caring for a patient with ALK-positive advanced non-small-cell lung cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **7 February 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with ALK-positive advanced non-small-cell lung cancer

Table 1 About you, ALK-positive advanced non-small-cell lung cancer, current treatments and equality

1. Your name	Debra Montague
2. Are you (please tick all that apply)	☒ A patient with ALK-positive advanced non-small-cell lung cancer ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with ALK-positive advanced non-small-cell lung cancer ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	ALK Positive UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with ALK-positive advanced non-small-cell lung cancer? **If you are a carer (for someone with ALK-positive advanced non-small-cell lung cancer) please share your experience of caring for them**	I have been living with the disease for 8yrs, 4months
7a. What do you think of the current treatments and care available for ALK-positive advanced non-small-cell lung cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**I, and the whole ALK Positive UK community are extremely grateful for the targeted treatments available for this disease.** **Evidence suggests that traditional chemotherapy is only successful in up to 30% of ALK-positive patients, which means that many others and I wouldn't be here today if we hadn't had the opportunity to be prescribed TKI's.**
8. If there are disadvantages for patients of current NHS treatments for ALK-positive advanced non-small-cell lung cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Without current treatments the majority of patients alive today wouldn't be. It would be dishonest to suggest that the side effects of any of the current treatments aren't problematic. The reality is their severity varies for each individual and in fact can vary in an individual patient. However, the alternative for us isn't particularly appealing either. The side effects range from the following – Headaches Nausea Muscle aches Fatigue Sun sensitivity Constipation

	Diarrhoea Hallucinations Mood swings High Cholesterol Raised liver enzymes High Blood Pressure However, most of the time they are manageable, and most patients and I live very fulfilling lives, working, supporting families and contributing to society.
9a. If there are advantages of lorlatinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does lorlatinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**The data for progression free survival and overall survival for Lorlatinib prescribed as the first line of treatment with newly diagnosed patients is extremely compelling.** **It is an unfortunate fact that most patients aren't diagnosed until they are stage 4 and so the only goal is to stay alive as long as possible. Many have young families so the prospect of not living until they have finished school and are at least a little settled as young adults is one many patients agonise over. The prospect of living many years without progression should in my opinion be offered to newly diagnosed patients.** **Being potentially able to live in a 'stable' state for many years would enable many people to care for their elderly relatives (instead of needing care homes), contributing to the economy and I doubt many would argue, children brought up by 2 parents is in all children's best interests.** **I have found taking Lorlatinib to be much easier that other TKI's. the fatigue I listed above isn't just feeling tired, it is where your arms and legs feel like lead and trying to wade through treacle with them. This can take a massive toll on patients who then struggle managing with young families or coping with physically demanding jobs.** **I noticed a discernible difference a week after starting Lorlatinib. I now have much more energy that I did previously. I don't get muscle aches and I'm no longer sensitive to the sun. The sun sensitivity I listed above isn't like sunburn, it occurs when the person is fully covered up and with factor 50**

	applied to hands and face (difficult to cover up). I experienced it several times and the pain is intense and can last for a few days on each occasion.
10. If there are disadvantages of lorlatinib over current treatments on the NHS please describe these. For example, are there any risks with lorlatinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	**There can be cognitive effects with Lorlatinib and myself and many members of the ALK Positive UK community have found 75mg to be a much easier dose to tolerate.**
11. Are there any groups of patients who might benefit more from lorlatinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients with diagnosed cognitive impairments may require closer monitoring. I am not medically qualified so not in a position to offer further comment.
12. Are there any potential equality issues that should be taken into account when considering ALK-positive advanced non-small-cell lung cancer and lorlatinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	I see no potential equality issues that should be taken into account when considering ALK-positive advanced non-small-cell lung cancer and Lorlatinib.

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No thank you.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Lorlatinib offers a longer progression free time on treatment, so no need for radiotherapy or surgical interventions which are costly to the NHS
- Lorlatinib offers patients the potential to live longer overall, contributing to the economy and society longer
- Patients experience fewer side effects on Lorlatinib
- Lorlatinib is easy to take being O.D.
- Click or tap here to enter text.

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Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **7 February 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Part 1: Treating ALK-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Shobhit Baijal
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with ALK-positive advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for ALK-positive advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a

8. What is the main aim of treatment for ALK-positive advanced non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Prolong survival and maintain quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	PFS greater than 3 years
10. In your view, is there an unmet need for patients and healthcare professionals in ALK-positive advanced non-small-cell lung cancer?	Yes
11. How is ALK-positive advanced non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Standard of care is to treat with a second generation ALK inhibitor (Alectinib or Brigatinib) No impact of technology on current pathway
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Yes Will be used in centres that can deliver SACT No added investment required

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Based on the CROWN data the technology provides a significant clinically meaningful increment in efficacy / survival outcomes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	n/a
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	n/a
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would stop when loss of clinical benefit
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Significant reduction in development of progression of brain metastases

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes – step change in terms of the incremental benefit in efficacy / survival outcomes
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Drug has its own toxicity profile. However this is well documented with effective toxicity management guidance available. Trial demonstrated that dose modification is effective in managing toxicities
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Comparator arm is no longer SOC in the UK (but this is a result of the timing of the trial opening) Most important outcomes are PFS and CNS data
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no

22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA670, TA536]?	no
23. How do data on real-world experience compare with the trial data?	n/a
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	n/a

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Lorlatinib is a step change in the management of this condition

Efficacy outcomes some of the most impressive seen for an advanced solid tumour

CNS data is very impactful and meaningful for this population

Click or tap here to enter text.

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Single Technology Appraisal

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

Clinical expert statement

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send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Part 1: Treating ALK-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Alastair Greystoke
2. Name of organisation	Newcastle University
3. Job title or position	Professor of Oncology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with ALK-positive advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for ALK-positive advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for ALK-positive advanced non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Prolong overall survival Prevent and control CNS disease
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Three month improvement in overall survival, Six month improvement in disease free survival, Reduction in occurrence of CNS metastases or progression in CNDS disease by 5% at a suitable landmark (ie 12 or 24 months into treatment)
10. In your view, is there an unmet need for patients and healthcare professionals in ALK-positive advanced non-small-cell lung cancer?	Yes. Despite advances and improvement in prognosis these patients are young, have extensive disease burden in particular affecting the brain and will lose many years of life due to the development of resistant disease. This is normally by progressive brain or leptomeningeal disease which is associated with significant symptom burden and cost to the NHS .
11. How is ALK-positive advanced non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients are usually treated with alectinib or brigatinib as an upfront treatment. This is based on NICE Technology appraisal guidance TA536 and TA670. There is some variability in which clinicians will choose. On progression, most patients will be offered second line lorlatinib based on NICE Technology appraisal guidance TA628. On further progression patients may be offered chemotherapy with carboplatin, and pemetrexed or carboplatin, paclitaxel, atezolizumab and bevacizumab based on NICE Technology appraisal guidance TA584. There is some variability in which clinicians will choose.

	On further progression patients may be offered nintedanib and docetaxel based on NICE Technology appraisal guidance TA347. The number of patients who get to this line of therapy in reality is small. In the case of progression in one or a small number of sites patients may be offered radiotherapy (normally stereotactic)to try and preserve the time on a targeted therapy such as briagtinib, alectinib or lorlatinib, especially if this disease is in the brain. The expertise and willingness to offer this will vary by centre. Clinicians are also guided by the ESMO guidance "Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up .Ann Oncol. 2023;34(4):339-357." 1st line Lorlatinib would replace the strategy of sequential alectinib or brigatinib followed by 2nd line lorlatinib if approved
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	As above lorlatinib Is routinely used in the second line setting. this would move it into the frontline setting. It would be routinely used in tertiary Oncology centres. No extra facilities or training would be required.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It is difficult to know the exact survival benefit. However, the CROWN study presented very provocative long-term disease control in the brain both in those patients presenting with CNS disease and those without. Given that this drives life expectancy particularly in the real world, I would expect that this could be associated with a significant survival benefit despite lorlatinibs availability already in the second line setting. However, it is associated with side-effects and these will be known need to be borne in mind when choosing suitable patients. There will be a payoff from additional side effects of treatment versus the significant impact on patients of subsequent disease and progression in the brain.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It may be more suitable for younger patients in those with CNS disease but impact seems to be seen in all disease types and those with and without CNS disease at presentation.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	We are already routinely used to using lorlatinib in the second line setting. It does often require treatment with appropriate statins for the elevated cholesterol which is unknown side-effect of this agent. It is also with significant weight gain and this will be something to bear in mind in patient choice and acceptability.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clinicians may prefer to use it in those patients with known CNS disease at baseline. Most guidelines would suggest brain imaging anyway as part of the work up of these patients given the high proportion of patients who develop CNSdisease but this is not always done in the real world based on patient surveys. If done this may need to an overall improvement in care if the NHS.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The study suggested that was a significant proportion of patients more than 50% who got long-term disease control on first line lorlatinib. This will be an extremely important outcome in this young patient population with heavy symptomatic burden where in general with present treatments disease becomes resistant after 2 to 3 years and subsequent treatments are less effective. This is the first time this length of disease control has ever been seen with a targeted therapy in a solid tumour, and dfinitiely the 1st time it has been seen in lung cancer.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As described above elevated cholesterol is commonly seen. This can be treated with appropriate statins.

	The main side effects that impact on patient quality of life are a number of patients experience mood disturbance which can lead in a small number to significant psychiatric illness. We are used to looking for this and managing it appropriately in the community. It normally improves with dose suspension and dose reduction appropriately. In addition significant weight can be seen with these agents and that is more difficult to manage both in acute and particularly the chronic setting.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, this does reflect the UK population. The most important outcomes including progression free, overall survival and disease control in the brain were measured along with patient reported outcomes and quality of life. The acute and long-term toxicity has been well described and are similar to what we have seen in real world practice.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA670, TA536]?	No
23. How do data on real-world experience compare with the trial data?	We do not know outcomes with first line or Latin as this is not been available. Real world outcomes with first line Alectinib and brigatinib normally match relatively closely the clinical trial data but we don't always reach the same length

	of responses. Conversion onto subsequent lines of treatment is significantly less in the real world setting than is observed in clinical trials.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	No

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Data from Crown suggests long-term responses which are not seen with the present strategy of first line ALK inhibitors followed by lorlatinib in the second line setting.
This may be a particularly good strategy to control or prevent CNS metastases.
Lorlatinib is associated with more side-effects, including mood disturbance and weight gain which may be problematic.
This would not be the preferred option for all patients, but would meet a unmet need in a significant proportion
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External Assessment Group Report
Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (Review of TA909) [ID6434]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Alexis Llewellyn, Research Fellow, CRD, University of York Diarmuid Coughlan, Research Fellow, CRD, University of York Chinyereugo Umemneku-Chikere, Research Fellow, CRD, University of York Helen Fulbright, Information Specialist, CRD, University of York Sarah Nevitt, Senior Research Fellow, CRD, University of York Robert Hodgson, Senior Research Fellow, CRD, University of York
Correspondence to	Robert Hodgson, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD
Date completed	15/11/2024

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Declared competing interests of the authors

None

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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.

This report should be referenced as follows:

Llewellyn A, Coughlan D, Umemneku-Chikere C, Fulbright H, Nevitt S, Hodgson R. Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (Review of TA909): A Single Technology Appraisal. CRD and CHE Technology Assessment Group, 2024

Contributions of authors

Alexis Llewellyn performed the critical review of the clinical effectiveness evidence, drafted Section 1 and Section 3 and contributed to drafting Section 2 of the report.

Diarmuid Coughlan performed the critical review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 1, 4, 5, 6 and 7 of the report.

Chinyereugo Umemneku-Chikere performed the critical review of the clinical effectiveness evidence, conducted EAG additional analyses, drafted Section 2 and contributed to drafting Section 3 of the report.

Helen Fulbright reviewed the systematic review searches, wrote sections of the report pertaining to the searches and provided editorial support.

Sarah Nevitt oversaw the review of the clinical effectiveness evidence, wrote and commented on drafts of the report and takes joint responsibility for the report as a whole.

Robert Hodgson oversaw the review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 1, 4, 5, 6 and 7 of the report, commented on drafts of the report and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been redacted

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Table of Contents

Table of Tables

Table of Figures

List of abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
3L	Third line
AE	Adverse event
AEDC	Discontinuation due to adverse events
ALK	Anaplastic lymphoma kinase
BICR	Blinded independent central review
BID	Twice daily
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CNS-PD	Central nervous system progressed disease
CrI	Credible interval
CS	Company submission (Document B)
DOR	Duration of response
EAG	External Assessment group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EoL	End of life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
FAD	Final appraisal document
FAS	Full Analysis Set
FHRD	Flatiron Health research Database
FTA	Fast track appraisal
HCRU	Healthcare resources Utilisation
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IC-TTP	Intracranial Time to Progression
IMD-PE	Intracranial metastatic disease in the context of progressive extracranial disease
IMD-SE	Intracranial metastatic disease in the context of stable extracranial disease
INHB	Incremental Net Health Benefit
INV	Investigator
IPD	Individual patient data
KM	Kaplan–Meier
LY	Life years
MAIC	Matched adjusted indirect comparisons
MHRA	Medicines and Healthcare products Regulatory Agency
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for health and care Excellence
NMA	Network meta-analysis
NR	Nor reached
NSCLC	Non-small cell lung cancer

ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PFS	Progression-free survival
PH	Proportional hazard
PPS	Post-progression survival
PSM	Partitioned survival model
PSSRU	Personal Social Services research Unit
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumour
RR	Relative risk
rwPFS	Real world PFS
rwOS	Real world OS
SLR	Systematic Literature Review
SmPC	Summary of product characteristics
STM	State transition model
TA	Technology Appraisal
TEM	Treatment effect modifier
TKI	Tyrosine Kinase Inhibitor
ToT	Time on treatment
TRAE	Treatment related adverse event
QALY	Quality-adjusted life year
UK	United Kingdom

EXTERNAL ASSESSMENT GROUP REPORT

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report. All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

Issue ID	Summary of issue	Report sections
1	Accounting for treatment sequences in the decision problem: The decision problem is framed as a comparison of lorlatinib against alectinib or brigatinib in the 1L setting but does not account for subsequent therapies in the treatment pathway.	2.2, 2.3
2	Applicability of treatment sequences in CROWN and comparator trials: Treatment sequences in the lorlatinib trial (CROWN) and comparator trials are not applicable to current or future practice.	3.2.2, 3.5.5
3	Immature overall survival (OS) data from the CROWN trial: Although progression-free survival (PFS) looks highly promising for lorlatinib compared with crizotinib in the CROWN trial, the OS is very immature, and there is no evidence that increased PFS from lorlatinib leads to increased OS.	3.2.1, 3.4.1, 3.4.5
4	Validity of OS estimates from the company's network meta-analysis (NMA): The validity OS estimates in the NMA is limited due to the immaturity of the CROWN OS data, violation of the proportional hazard assumption, and risk of confounding due to treatment crossover and use of subsequent therapies following progression.	3.3.1, 3.4.4.1
5	Inconsistent model structure: The modelling approach between treatment and comparator arms is inconsistent. There is uncertainty regarding the most appropriate modelling approach and structure.	4.2.2
6	Time on treatment (ToT) and treatment beyond progression: ToT is modelled inconsistently across intervention and comparators arms. Continued treatment beyond progression with lorlatinib is likely and is not restricted by its marketing authorisation.	4.2.4
7	PFS extrapolations and waning assumptions: Immaturity of PFS outcome data and uncertainty in choice of extrapolations.	4.2.6.2
8	Utility values in the progression-free health state: Differential utility values are applied within the progression-free health state without proper justification. Post-progression utility values do not capture the benefits of 2L lorlatinib	4.2.7
9	Implementation of Patient Access Scheme (PAS) discount for lorlatinib: Inconsistent application of the PAS discount for lorlatinib.	4.2.8.7

1.2 Overview of key model outcomes

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company prefers to use a partition survival model (PSM) structure for the lorlatinib arm, the EAG prefers to use a state transition model (STM) consistent with the comparator arms.
- The company prefers to use time on treatment (ToT) from CROWN to model ToT for lorlatinib (first-line [1L]), the EAG prefers to assume ToT equals PFS.
- The company prefers to assume no treatment beyond progression, the EAG prefers to include treatment beyond progression.
- The company prefers to the crizotinib arm from CROWN as the reference arm to which relative treatment effects are applied, the EAG prefers to use the lorlatinib arm.
- The company prefers to use a 36-month piecewise Weibull function to extrapolate PFS, the EAG prefers to use a Gompertz function.
- The company prefers the differential utilities in the progression-free health state, the EAG prefers to apply the same utility value to all treatments.
- The company prefers to apply the same utility value for patients on/ off treatment in PD health state, the EAG prefers to apply higher utility value for patients receiving lorlatinib in the PD health state.
- The company applies a different PAS discount to lorlatinib in the 1L setting to that applied in the second-line (2L) setting, the EAG prefers to apply the same discount across both treatment lines.

Overall, the technology is modelled to affect QALYs by:

- Improved quality of life in the progression free health state
- Increasing PFS
- Increasing OS

Overall, the technology is modelled to affect costs by:

- Higher first-line treatment costs
- Lower subsequent treatment costs.

The modelling assumptions that have the greatest effect on the ICER are:

- The model structure adopted in the lorlatinib arm (PSM vs STM)
- The size of the PFS benefit for lorlatinib
- How ToT is modelled and whether treatment beyond progression is assumed

- How the PAS is applied to 2L lorlatinib.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Accounting for treatment sequences in the decision problem

Report section	2.2, 2.3
Description of issue and why the EAG has identified it as important	Current standard of care in the NHS for newly diagnosed advanced anaplastic ALK-positive NSCLC includes alectinib or brigatinib 1L therapy, followed by lorlatinib 2L therapy. EAG clinical advisers note that if lorlatinib was recommended by NICE as 1L, a subset of patients with limited progression (e.g. to a single site) would likely remain on lorlatinib, and subsequent treatment would likely be limited to chemotherapy or best supportive care. The decision problem outlined by the company is framed as a comparison of lorlatinib against alectinib or brigatinib in the 1L setting but does not account for subsequent therapies. This is important as is it fails to recognise the importance of subsequent treatment and significantly impacts how the available clinical evidence is interpreted. For example, in isolation, PFS for lorlatinib looks highly impressive but potentially less so when recognising the limited treatment options following progression and the availability of lorlatinib as 2L treatment in comparator sequences. It also underemphasises the importance of clinical evidence supporting the effectiveness of 2L treatment options which contribute significantly to determining outcomes in the economic model.
What alternative approach has the EAG suggested?	The EAG considers it important to frame the decision problem appropriately and that it reflects the following treatment sequences: - Lorlatinib 1L (with a subset of patients continuing on lorlatinib following progression), chemotherapy 2L. - Alectinib or brigatinib 1L, lorlatinib 2L, chemotherapy 3L The EAG further proposes that the company implement a four-state economic model to better reflect the treatment sequences being modelled.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Implementation of four state economic model as proposed by the EAG. See Issue 2 below.
Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ALK, anaplastic lymphoma kinase, EAG, evidence assessment group; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PFS, progression free survival	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Applicability of treatment sequences in CROWN and comparator trials

Report section	3.2.1, 3.4.1, 3.4.5
Description of issue and why the EAG has identified it as important	The ALK inhibitor treatment sequences used in both arms of the CROWN trial and in comparator trials have very limited applicability to both current NHS practice and to future practice if 1L lorlatinib were to be recommended by NICE (see Issue 1). Subsequent therapies used 2L following a 1L ALK inhibitor (i.e. lorlatinib, alectinib or brigatinib) will impact on post progression outcomes including OS, and subsequently confound comparisons between 1L lorlatinib and alectinib or brigatinib.
What alternative approach has the EAG suggested?	No alternative trial data exists currently. Although the additional US FHRD analysis presented by the company includes a cohort with a more representative sequence of treatments following alectinib 1L, a MAIC between CROWN and FHRD would have substantial limitations and would not resolve this issue.
What is the expected effect on the cost effectiveness estimates?	Unknown. The economic analysis presented by the company attempts to account for this confounding by using external data from PROFILE 1001/1005 and Study 1001 to reflect the outcomes in patients following progression. This approach is however, associated with significant limitations as the model is no longer informed by randomised evidence and both the PROFILE 1001/1005 and Study 1001 do not fully represent current or future NHS practice.
What additional evidence or analyses might help to resolve this key issue?	A trial that compares 1L lorlatinib (with eligible patients continuing on lorlatinib after progression) with 1L alectinib (or brigatinib) followed by lorlatinib at 2L would be most applicable to inform NHS practice. However, such a trial is not currently ongoing or planned to the knowledge of the EAG.
Abbreviations: 1L, first-line; 2L, second-line; ALK, anaplastic lymphoma kinase, EAG, evidence assessment group; FHRD, Flatiron Health Research Database; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival	

Issue 3 Immature overall survival data from the CROWN trial

Report section	3.2.1.2
Description of issue and why the EAG has identified it as important	The latest available data-cut for OS data from the CROWN trial is at 18-months follow-up. No updated OS data cut is available since the previous appraisal of lorlatinib in 2022 (TA909). The OS data remains very immature; the median OS is not estimable in either treatment arm. Although PFS at 5-years looks highly promising for lorlatinib compared with crizotinib in CROWN, including in patients with brain metastases, the company have provided no evidence that this leads to increased OS. A cohort of 30 ALK-TKI-naïve patients with a median follow-up of 72.7 months from a single-arm trial (Study 1001) was pooled with CROWN to inform longer-term OS extrapolations. However, given the design limitations of Study 1001, and its limited comparability with CROWN in terms of PFS, the value of this pooled analysis to the clinical evidence is relatively limited and the long-term OS benefit of lorlatinib remains highly uncertain.
What alternative approach has the EAG suggested?	No alternative is proposed. Uncertainties in long-term OS benefits should be reflected in decision making.
What is the expected effect on the cost effectiveness estimates?	Unknown. The EAG's preferred model does not use OS data from CROWN due to concerns about the reliability of NMA estimates (Issue 4) and inconsistencies in the company's modelling approach (Issue 5).
What additional evidence or analyses might help to resolve this key issue?	The CROWN trial final analysis for OS is anticipated in December 2028. While an updated data cut would be valuable as it would provide more mature OS data to inform longer-term extrapolations, OS data from the CROWN trial will be confounded by subsequent therapies that are not reflective of NHS practice.
Abbreviations: ALK, anaplastic lymphoma kinase, EAG, evidence assessment group; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitor	

Issue 4 Validity of OS estimates from the NMA

Report section	3.3.1, 3.4.4.1
Description of issue and why the EAG has identified it as important	In the absence of direct, head-to-head comparisons, the company conducted an NMA to indirectly compare lorlatinib against alectinib and brigatinib. The OS NMA analyses showed no statistically significant differences between lorlatinib and alectinib/brigatinib. However, the validity of these estimates is limited due to the immaturity of the CROWN OS data, violation of the PH assumption, and risk of confounding due to treatment crossover and use of subsequent therapies following progression.
What alternative approach has the EAG suggested?	The company and EAG ran additional NMAs adjusting for treatment cross-over from the brigatinib trial (ALTA-1L) comparator arm. No adjustments could be made to account for other subsequent therapies, including treatment sequences which are not reflective of NHS practice (see Issue 2). In addition, the immaturity of the OS data from CROWN and the violation of the proportional hazard assumption mean that OS estimates from the NMA remain highly uncertain and no conclusions can be made from these analyses.
What is the expected effect on the cost effectiveness estimates?	Increased uncertainty in the cost effectiveness estimates. The EAG's preferred model relies on non-randomised comparison using external data to estimate OS benefits.
What additional evidence or analyses might help to resolve this key issue?	An NMA with updated OS data from CROWN may resolve some uncertainty relating to the immaturity of OS data for lorlatinb versus comparators. An NMA approach which allows for the estimation of time-varying hazard ratios or flexible survival curves may resolve some uncertainty relating to violation of the PH assumption, but incorporation of such estimates into the economic model would not be straightforward and would likely generate more uncertainty than is resolved. No trial data exists for lorlatinib or comparators which reflects the treatment sequences used in NHS, and the EAG is not aware of suitable statistical methods which could adjust for the confounding effect of these subsequent treatments. Therefore uncertainty in comparative estimates of OS for lorlatinib versus alectinib and brigatinib as 1L treatments cannot be fully resolved.
Abbreviations: EAG, evidence assessment group; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PH, proportional hazards	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 5 Inconsistent model structure

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The company base case uses an inconsistent approach to determine transitions between health states using a PSM in the lorlatinib arm and an STM in the alectinib and brigatinib arms. The EAG does not consider it appropriate to use a differential modelling approach. A PSM and STM adopt fundamentally different assumptions and derive OS as the main driver of modelled health benefits differently. Due to these differences, the EAG recommends using the same modelling approach across all treatment arms to maintain consistency in the underlying assumptions. The EAG considers the STM approach the most appropriate modelling approach and should be applied in all model arms. This is primarily because of the substantive issues with the available OS data from CROWN and the NMA, which neither reflects UK practice nor provides reliable estimates of relative effectiveness, see Issue 2 and Issue 4. Additionally, the EAG notes that using a PSM (in all model arms) produces predictions that lack clinical validity. Specifically, the PSM predicts that patients in the alectinib/ rigatinib model arms spend substantively longer in the PD health state than in the PFS health state.
What alternative approach has the EAG suggested?	The EAG suggests using an STM in all treatment arms.
What is the expected effect on the cost effectiveness estimates?	Using an STM in all treatment arms increases incremental cost savings relative to alectinib and reduces incremental QALYs. [redacted]
What additional evidence or analyses might help to resolve this key issue?	Updated OS data from the CROWN trial may improve the viability of implementing a PSM. This would, however, not resolve the EAG's concerns with the NMA of OS (see Issue 4) which would likely require a head-to-head trial of lorlatinib vs alectinb/brigatinb followed by lorlatinb.
Abbreviations: EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PSM, partitioned survival model; STM, state transition model	

Issue 6 Time on treatment and treatment beyond progression

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The company's base case uses observed ToT from the CROWN trial to inform modelled ToT in the lorlatinib arm. This is inconsistent with the model assumptions in the alectinib and brigatinib arms, where ToT is assumed to align with PFS. This approach implies that ToT is substantially shorter than PFS for lorlatinib and also suggests that no patient will receive treatment beyond progression. The EAG does not consider this inconsistent approach appropriate and believes it is likely that the CROWN trial underestimates how long patients will spend on treatment in the NHS. Factors contributing to this include improved knowledge of the effectiveness of lorlatinib, fewer 2L options in the NHS, and greater experience in managing adverse events. The EAG is also concerned that this implies no treatment beyond progression in the lorlatinib arm. Clinical advice received by the EAG indicated that many patients are expected to be treated beyond clinical progression, in line with historical practices for other TKIs used to treat ALK-positive NSCLC. The EAG also highlights that previous TAs for crizotinib, ceritinib, brigatinib, and lorlatinib have all assumed treatment beyond progression.
What alternative approach has the EAG suggested?	The EAG suggests a consistent approach to modelling ToT, in which the modelled PFS curve is used across all treatment arms. The EAG further considers that treatment beyond progression should be applied in the model, consistent with the committee-preferred assumptions in TA909.
What is the expected effect on the cost effectiveness estimates?	Assuming ToT for lolatininb equals PFS increases the total costs associated with lorlatinb substantially. [redacted]. Assuming treatment beyond progression increases the total costs associated with lorlatinb. [redacted]
What additional evidence or analyses might help to resolve this key issue?	The current scenario does not consider the impact of further treatment, including treatment beyond progression, on the modelled benefits of lorlatinib. It is therefore necessary to balance the uncertainty in cost effectiveness estimates resulting from reflecting likely NHS practice against the desirability of an approach that is more consistent with the current trial evidence.
Abbreviations: 2L, second-line; ALK, anaplastic lymphoma kinase, EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressed disease; PFS, progression-free survival; ToT, time on treatment; TA, technology appraisal; TKI, tyrosine kinase inhibitor	

Issue 7 Extrapolation of PFS and treatment waning

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The company base case uses a 36-month piecewise Weibull distribution to extrapolate PFS. To reflect uncertainty in long-term predictions, the company additionally applies waning from 10 years, during which hazards are waned to crizotinib PFS data (CROWN trial) extrapolated using a standard Weibull function. The EAG is concerned that the clinical plausibility of model predictions heavily depends on the implementation of waning assumptions. In the absence of waning, the company's preferred extrapolation produces predictions that do not align with clinical expectations and predicts that a substantial proportion of patients will be alive even at 20 years. The EAG is also concerned that adjusting hazards through the application of waning relies on using a standard Weibull function to extrapolate crizotinib PFS. If alternative, better-fitting parametric functions are chosen, the correction to model predictions provided by waning is significantly diminished, leading the model to produce overly optimistic forecasts that do not align with clinical expectations. Additionally, the EAG is concerned that the company's extrapolation approach is inconsistent, as it uses a piecewise approach in the lorlatinib arm and a standard parametric function in the comparator arms. This is inconsistent with DSU guidance, which suggests that the same approach should be used in all treatment arms to ensure survival trajectories remain consistent and do not assume underlying differences in hazard trends.
What alternative approach has the EAG suggested?	The EAG proposes using the lorlatinib arm as the reference arm in the model, to which relative treatment effects are applied. This approach resolves the inconsistent extrapolation method. The EAG also prefers using a 36-month piecewise Gompertz distribution to extrapolate PFS. The EAG considers the application of waning reasonable, but it should be implemented to address concerns about the durability of the treatment effect, rather than to "correct" otherwise implausible PFS extrapolations.
What is the expected effect on the cost effectiveness estimates?	Using lorlatinib as the reference arm increases total costs associated with comparator treatment and increases total QALYs. [redacted] Using the Gompertz curve to extrapolate lorlatinib PFS increases cost savings associated with lorlatinib and reduces QALY benefits. [redacted] Altering waning assumptions to apply waning to the alectinib arm at 10 years increases cost savings associated with lorlatinib and increase reduces QALY benefits. [redacted]
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up of PFS on lorlatinib would be beneficial in determining the most appropriate extrapolation of PFS. Additional clinical insights into the plausibility of alternative extrapolations may

	also help guide the selection of alternative parametric extrapolations given the current evidence.
Abbreviations: DSU, decision support unit; EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; PFS, progression-free survival	

Issue 8 Utility values in the progression-free health state

Report section	4.2.7
Description of issue and why the EAG has identified it as important	The utility values used in the model may not reflect real-world HRQL experiences. In the PFS health state, the company uses treatment-specific utility values. The company also uses on/off treatment values. For the PD health state, the values used may be too conservative for those just entering that health state.
What alternative approach has the EAG suggested?	The EAG proposes that a PFS treatment agnostic utility value is used and proposes using values from TA670 as this is consistent with values applied in the PD health state. To account for the HRQL benefits of loraltinib in a post-progression setting the EAG suggests applying a utility value of 0.725 for patients on lorlatinib in the PD health state. This value is approximately halfway between the PF and PD utility values from TA670.
What is the expected effect on the cost effectiveness estimates?	Using the utility values from TA670 reduces incremental QALYs from [redacted] to [redacted] when compared to alectinib. [redacted] Using a utility value of 0.725 to model the on treatment HRQL benefits of being lorlatinib reduces incremental QALYs from [redacted] to [redacted] when compared to alectinib. [redacted]
What additional evidence or analyses might help to resolve this key issue?	The EAG suggests using utility values from TA670. Further evidence on HRQL with lorlatinib in a post-progression setting would be useful and could be informed by Study 1001.
Abbreviations: CNS, central nervous system; EAG, evidence assessment group; HRQL, health related quality of life; ICER, incremental cost effectiveness ratio; PD, progressed disease; PFS, progression-free survival	

Issue 9 Implementation of PAS discount for lorlatinib

Report section	4.2.8.7
Description of issue and why the EAG has identified it as important	The company has provided an updated PAS discount on lorlatinib of [redacted] conditional on its approval as 1L treatment. This PAS discount is higher than the [redacted] currently applied for 2L lorlatinib (indication agnostic) and in the event of lorlatinib's recommendation as a 1L treatment, will be available to the NHS regardless of whether a patient is receiving lorlatinib in the 1L or 2L. To reflect the conditionality of the PAS the company has only implemented the new PAS discount in the lorlatinib arm of the model and the current (lower) PAS discount is applied for subsequent (i.e. 2L) lorlatinib treatment in the comparator arms of the model. The economic analysis therefore includes two separate prices for lorlatinib. Advice from the NICE technical team suggests this is the correct approach. The EAG does not consider the conditional status of the PAS relevant to its integration into the economic model. The EAG considers that this approach inaccurately frames the committee's decision, presenting both practical and methodological issues. The EAG is particularly concerned that this approach could render a positive NICE recommendation self-invalidating; since the enhanced PAS also would extend to 2L use. This would mean that lorlatinib 2L becomes substantially cheaper.
What alternative approach has the EAG suggested?	The same (updated) PAS should apply to both arms of the model.
What is the expected effect on the cost effectiveness estimates?	Applying the updated PAS for lorlatinib to the 2L setting reduces incremental cost savings from [redacted] to [redacted] relative to alectinib. [redacted]
What additional evidence or analyses might help to resolve this key issue?	Not applicable. The EAG has provided additional analysis implementing PAS using both the company preferred and EAG preferred approaches.
Abbreviations: 1L, first-line; 2L, second-line; EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; NICE, National Institute for Health and Care Excellence, PAS, patient access scheme	

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 summarises the scenario analysis undertaken by the EAG. Table 3 summarises the EAG's preferred assumptions and presents additional scenario analysis exploring the impact of apply a different discount for lorlatinib in the 1L and 2L. These results include the PAS discount for lorlatinib only. Results inclusive of all available PAS discounts and other commercial arrangements are provided in the confidential appendix to this report.

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6. All ICERs are deterministic and are exclusive of severity weighting.

Table 2 EAG Exploratory fully incremental scenario analyses (deterministic)

Scenario		Technology	Total		Incremental		Fully incremental ICER
			Costs	QALYs	Costs	QALYs	
Company base case		Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1a	**Model Structure (STM)**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1b	**Model Structure (PSM)**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	**ToT = PFS (Both arms)**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	**Treatment beyond progression**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	**Log-logistic extrapolation for crizotinib PFS**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5a	**Using lorlatinib as reference arm in PFS**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5b	**5a+ Gompertz extrapolation +no waning**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6a	**5b+ no waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6b	**5b+7-yr waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6c	**5b+ 10-yr waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6d	**5b+15-year waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	**Weibull for PPS**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8a		Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ALTA-1L pre-progression utilities	Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8b	**Using a utility score half-way between pre-and post-progression for time on lorlatinib 2L and beyond progression**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8c	**8a + 8b**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9a	**Increase duration of chemotherapy to 5.9 months**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9b	**Increase duration of chemotherapy to 8.0 months**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	**Lorlatinib PAS same for 1L & 2L**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line; 2L, second line, Ext., extended; HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; PSM, partitioned survival model; PPS, post-progression survival; QALY, quality-adjusted life-year; STM, state transition model; ToT, time on treatment.

Table 3 EAG's preferred model assumptions selected scenario analysis (Deterministic)

Technology	**Total**		**Incremental**		**Fully incremental ICER**
	Costs	**QALYs**	**Costs**	**QALYs**	
EAG base case					
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case without Scenario 10					
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

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report reviews the clinical and cost effectiveness evidence submitted by Pfizer to the National Institute for Health and Care Excellence (NICE) in support of lorlatinib (100 mg) as a monotherapy for untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC).

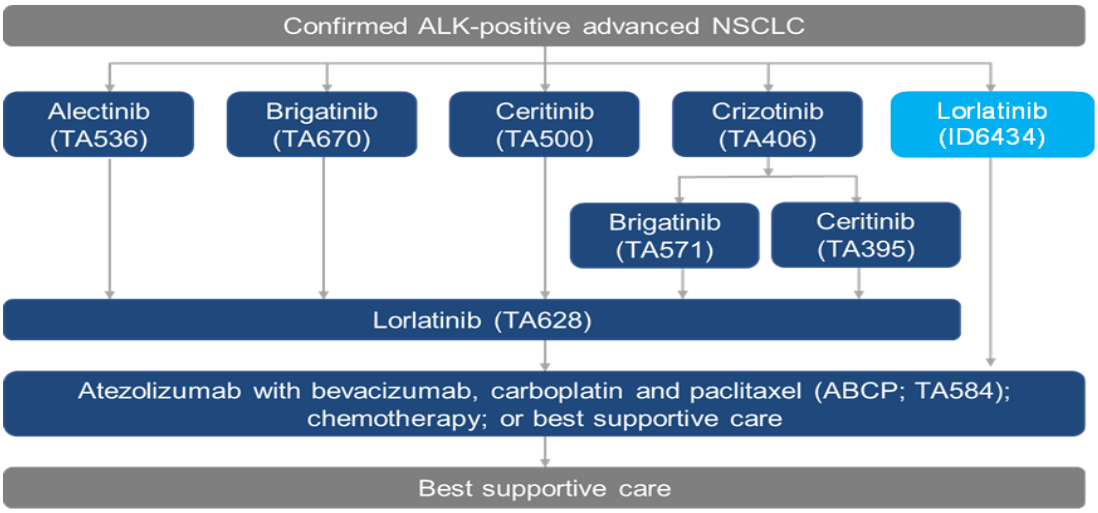
Lorlatinib is a 3rd generation (previously PF-06463922, [Lorviqua®]) small molecular inhibitor of ALK and ROS proto-oncogene receptor tyrosine kinase (RTK) specifically designed to cross the blood – brain barrier to achieve high CNS (central nervous system) exposure. It is administered to patients orally, once daily. The Medicines and Healthcare Products Regulatory Agency's (MHRA) marketing authorisation for lorlatinib to be used as first-line (1L) and subsequent treatment was granted on 23 September 2021.[1] This extended the existing marketing authorisation for lorlatinib as a second-line (2L) of treatment in the UK which was granted in May 2020 (TA628)[2].

This report is a review of TA909[3] published on 12 July 2023 in which lorlatinib was not recommended. This submission provides additional clinical effectiveness results from an unplanned 5-year data cut for clinical effectiveness outcomes progression-free survival (PFS) by investigator (INV), objective response rate (ORR), duration of response (DOR), intracranial time to progression (IC-TTP) by INV and adverse events. This submission also aims to address some of the issues relating to the cost effectiveness approach raised in TA909[3]. This EAG report considers all the evidence submitted by the company in September 2024, with focus on the new evidence generated since the previous assessment.

2.2 Treatment pathway

The EAG considers the company's description of the health condition to be appropriate and relevant to the decision problem. The proposed position of lorlatinib in the NHS clinical pathway, if approved by NICE as a 1L treatment, is presented in Figure 1.

Figure 1 Current treatments and proposed positioning of lorlatinib in the NHS clinical pathway



Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer.
Source: CS, Document B, Figure 2

In the NHS clinical pathway, alectinib, brigatinib, ceritinib and crizotinib are recommended by NICE [4-6]as 1L treatment for ALK-positive NSCLC and, lorlatinib is currently recommended by NICE as a 2L treatment following disease progression.[2] The EAG's clinical advisers broadly agree with the CS treatment pathway and the proposed positioning of lorlatinib as 1L treatment. In their experience of NHS practice, most ALK-positive NSCLC patients will be offered alectinib as a 1L treatment and brigatinib 1L is less commonly used in NHS practice. Other (1st generation) ALK inhibitors ceritinib and crizotinib are no longer used in practice (and do not form part of the NICE final scope). Additionally, most patients who have received alectinib or brigatinib 1L and have experienced disease progression will then go on to receive lorlatinib as 2L treatment.

According to Figure 1, the proposed 1L positioning of lorlatinib in the treatment pathway is in addition to current 2L positioning. Clinical advice to the EAG suggests that if recommended as a 1L treatment by NICE, lorlatinib would likely become first choice 1L treatment offered to patients with ALK-positive NSCLC in the NHS due to its impressive and unprecedented effect on PFS as demonstrated in the CROWN trial[7]; therefore 2L lorlatinib treatment would rarely be offered on the NHS. Consequently, a NICE recommendation of lorlatinib in a 1L setting would effectively displace the current NICE recommendation in the 2L setting. Hence, the EAG believes that to align with the proposed pathway, the decision problem (CS Document B, Table 1) should seek to address whether lorlatinib should be a 1L or a 2L treatment and the comparisons of lorlatinib versus alectinib (then lorlatinib) or lorlatinib versus brigatinib (then lorlatinib), which is not as simple as a straight comparison of all drugs in the 1L.

The MHRA summary of product characteristics (SmPC) for lorlatinib states that treatment is recommended if the patient is deriving clinical benefits without unacceptable toxicity. However, it should be discontinued if the patient is unable to tolerate the 50mg dose taken orally daily[1]. The EAG's clinical advisers anticipate that patients who experience progression on 1L lorlatinib would continue with lorlatinib if the progression was limited (e.g. to a single site) with local therapy such as radiotherapy given to the progressive site of disease. However, patients with multi-focal progression are unlikely to continue with lorlatinib and may move to chemotherapy or may receive a fourth-generation ALK inhibitor as part of a clinical trial. 2L treatments with a 2nd generation TKI inhibitor (e.g., alectinib or brigatinib) are not currently recommended by NICE in the NHS and would not be appropriate due to their reduced ability to cross the blood-brain barrier and reduced coverage of complex mutations.

2.3 Critique of company's definition of decision problem

CS Document B, Table 1 presents a description of the NICE final scope, the decision problem addressed within the CS and the rationale for any differences between the two. This information, along with the EAG comments, is presented in Table 4.

Population

The population addressed in the company decision problem is wider than NICE's final scope in terms of the previous treatments received (i.e. no previous treatment with an ALK inhibitor). The evidence submitted from the CROWN trial of lorlatinib includes patients with ALK-positive advanced NSCLC who had received no previous systemic treatment for metastatic disease including molecularly targeted agents, angiogenesis inhibitors, immunotherapy or chemotherapy (CS, Document B, Table 8) and patients who received chemotherapy either before or after ALK-positive NSCLC was genetically identified were excluded. The EAG's clinical advisers, however, consider the slightly broader population proposed in the CS to be appropriate and relevant.

Intervention

The intervention, lorlatinib (100mg, oral once daily), is in line with the NICE final scope. However, as described in Section 2.2 and in the 'Comparators' section below, the EAG considers that 2L therapies (i.e. chemotherapy or best supportive care) following lorlatinib 1L treatment should be reflected in the decision problem.

Comparators

The comparators included (alectinib and brigatinib) in the CS are in line with the NICE final scope. The company states that alectinib is the major comparator and brigatinib is a minor comparator based on market share data (around 80% market share for alectinib) and clinical opinion. The EAG's clinical advisers agree that brigatinib is less commonly used in NHS practice.

The comparison included in the decision problem reflects a comparison of lorlatinib with alectinib or brigatinib in the 1L setting. The EAG considers that only clinical effectiveness evidence collected prior to disease progression (i.e., PFS) can be meaningfully interpreted for a comparison of lorlatinib with alectinib or brigatinib in the 1L setting only.

As described in Section 2.2, the current NHS pathway includes lorlatinib as a 2L treatment following disease progression after treatment with alectinib or brigatinib 1L. This subsequent use of lorlatinib as a 2L treatment will impact on post-progression outcomes, such as OS, and consequently will confound comparisons of lorlatinib to alectinib and brigatinib as 1L treatments. Therefore, to allow for clinical effectiveness outcomes collected post disease progression to be meaningfully interpreted, the EAG believe that a comparison between lorlatinib 1L followed by chemotherapy or best supportive care 2L against alectinib or brigatinib 1L followed by lorlatinib 2L would be most appropriate to address the decision problem.

Outcomes

The company reported seven outcomes, including all five outcomes listed in the NICE final scope. Discontinuation rate due to adverse events and the intracranial outcomes were additional outcomes presented. The EAG's clinical advisers agree with the company's inclusion of the discontinuation rate

due to adverse events as well as the presentation of intracranial outcomes given that the treatment and prevention of CNS lesions is a priority in patients with ALK- positive advanced NSCLC. New evidence from a 5-year unplanned analysis of CROWN was provided for PFS by INV, ORR, DOR and IC-TTP by INV and adverse events. No additional data are available for OS beyond 18 months of follow-up; therefore, OS data remains immature.

Table 4 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	n/a	The population addressed in the CS decision problem was wider than NICE's final scope in terms of the previous treatments received The EAG's clinical adviser consider the slightly broader population proposed in the CS to be appropriate and relevant.
Intervention	Lorlatinib	Lorlatinib	n/a	Lorlatinib (100mg, oral once daily), is in line with NICE's final and it was reflected in the CROWN trial. The EAG considers that 2L therapies (i.e. chemotherapy or BSC) following lorlatinib 1L treatment should also be reflected in the decision problem
Comparator(s)	• Alectinib • Brigatinib	• Alectinib • Brigatinib	Based on market share data and clinical opinion, alectinib is considered the main comparator (around 80% market share). Brigatinib is considered a minor comparator but comparisons are provided for completeness.[8, 9]	The comparators presented in the CS, alecitinib and brigatinib, are in line with NICE's final scope. However, due to the use of lorlatlib as a 2L treatment following disease progression after alectinib and brigatinib 1L treatment, the EAG considers that a comparison between lorlatinib 1L followed by chemotherapy or BSC 2L against alectinib or brigatinib 1L followed by lorlatinib 2L would be most appropriate to address the decision problem.
Outcomes	• OS • PFS • Response rates • Adverse effects of treatment • HRQL	• OS • PFS • Response rates • Intracranial outcomes • Adverse effects of treatment • Discontinuation rate due to adverse events • HRQL	Intracranial endpoints were reported as secondary outcomes in the CROWN study and are reported because preventing and treating brain metastases are a priority in the treatment of ALK-positive NSCLC	The outcomes reported in the CS covered all the outcomes required in NICE's final scope. The CS presented unplanned 5 year analysis for PFS (INV), response rates, intracranial outcomes and adverse events. No further data are provided for OS beyond 18 months of follow-up, therefore OS data remains immature.
Economic analysis	Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	n/a	The economic analysis aligns with the NICE scope and NICE reference case.
Subgroups	None	None	n/a	None

Abbreviations: 1L, first-line; 2L, second-line; ALK, anaplastic lymphoma kinase; BSC, best supportive care; CNS, central nervous system; HRQL, health-related quality of life; INV; investigator assessed; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival.

Source: NICE [ID6434], CS, Document B, Table 1, Solomon et al. 2023, Solomon et al. 2024.[10-12]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify all relevant evidence regarding the clinical efficacy and safety of 1L treatments for patients with ALK-positive advanced NSCLC. Details of the review are reported in CS, Appendix D. This section presents a critique of the SLR methods for bibliographic searches, study selection, data extraction and quality assessment.

Searches

The search strategies to identify studies of lorlatinib and comparator drugs for the treatment of ALK positive advanced NSCLC were reported in CS, Appendix D, and additional information was provided in response to clarification questions C1 to C5. The search strategy was previously used to inform SLRs for TA909 (October 31, 2019, and April 22, 2021) and the updated literature search was conducted on February 27, 2024. The EAG appraisal of the literature searches can be found in Table 5.

Table 5 EAG appraisal of evidence identification

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	The search strategy documented in CS, Appendix D, Table 5 had an orphaned line (line 9). The company explained the function of the line in response to clarification question C5 but did not provide the reason it was orphaned or correcting the error.
Were appropriate sources searched?	PARTLY	The searches were conducted using a very limited range of relevant databases and conference proceedings. No dedicated HTA databases (e.g. INAHTA) or dedicated trials registries were searched, nor were there searches of websites of bodies such as NICE, etc.
Was the timespan of the searches appropriate?	YES	The sources searched for clinical evidence were seven months old at the time of submission. The company confirmed that the results of two recent relevant publications (5-year data of the CROWN and ALESIA trials)[12] have been included in the CS (response to clarification question C1).
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with interventions and the study types.
Were appropriate search terms used?	PARTLY	Trade names for lorlatinib (Lorbena and Lorviqua), and brigatinib (Alunbrig) were missing from the search strategies. The company clarified that including these terms yielded no additional records (response to clarification question C3a). The EAG considers that including these search terms would have made the searches more comprehensive.
Were any search restrictions applied appropriate?	PARTLY	Animal studies were removed appropriately. However, the EAG considers that it is more appropriate to limit to study types of interest and not to attempt to remove study types not of interest (e.g., as with the removal of narrative reviews in several of the database searches), as this may result in over exclusion. Rather, it is more appropriate to remove ineligible study types identified in the search during study screening.
Were any search filters used validated and referenced?	UNCLEAR	Filters were used but were not referenced and it was unclear if they were validated.
EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE		

Inclusion criteria

The eligibility criteria used to select studies included in the clinical effectiveness SLR were presented in CS Appendix D, Table 8. The company's inclusion criteria were appropriate to inform their decision problem (Table 4). The list of eligible treatments in the company's inclusion criteria included alectinib and brigatinib (1L), as well as interventions outside the NICE final scope (crizotinib, certinib, ensartinib, iruplinalkib, envonalkib), but does not inform the selection of studies of 2L treatments which impact on post-progression outcomes (Section 2.3).

The CS did not report whether the study selection was performed in duplicate and how disagreements in the study selection process (if any) was resolved. However, the EAG clinical advisers believe that all relevant trials were identified, therefore it is unlikely that any relevant evidence was excluded.

Non-randomised studies, as well as single-arm studies, prospective and retrospective cohort studies and long-term follow-up studies were included in the current SLR. However, company network meta-analyses (NMAs) were restricted to RCT evidence only.

Data extraction

The data extraction process was performed by one reviewer and independently checked for errors by a second reviewer, minimising the possibility of errors or bias.

Quality assessment

The quality of the RCTs included in the SLR was assessed using NICE's quality assessment checklist (CS Appendix D, Table 15). The CS did not report whether the quality assessment was performed in duplicate and how disagreements (if any) in quality assessments were resolved.

Evidence synthesis

To inform OS extrapolations in the company model, a pooled analysis combining lorlatinib OS data from the CROWN trial and Study 1001 was performed by the company (CS, Section B.2.8.1). A critique of this analysis is presented in Section 3.2.3.

In the absence of direct evidence comparing lorlatinib with the relevant comparators, an NMA was conducted (CS, Section B.2.9). A critique of the company NMAs is presented in Section 3.4.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The CS included one RCT of lorlatinib: the phase 3 CROWN trial (NCT03052608).[12] The company also presented the results of a cohort (EXP1) of 1L patients from a phase 2, non-randomised, single-arm trial (NCT01970865, hereafter referred to as Study 1001),[13] that was pooled with CROWN and included in the company's economic model to inform long-term OS projections (CS, Section B.2.8.1). This section provides a critique of CROWN, Study 1001 and the pooling of these two studies.

3.2.1 CROWN trial

3.2.1.1 Methods

CROWN is an ongoing phase 3, multicentre, open-label trial in patients with previously untreated advanced ALK-positive NSCLC. A total of 296 patients were randomised in a 1:1 ratio to either lorlatinib (100mg, oral once daily) or crizotinib (250 mg, oral twice daily). Randomisation was stratified by the presence of brain metastases and by ethnic origin (Asian versus non-Asian). Design details and eligibility criteria were reported in CS Document B, Tables 7 and 8, respectively. The primary outcome was PFS assessed using blinded independent central review (BICR). Secondary outcomes included PFS assessed by investigator (INV), OS, response rates, intracranial outcomes, adverse events of treatment and health-related quality of life (HRQL). The final study completion date is estimated to be in December 2028.

Baseline characteristics

Baseline characteristics of the CROWN trial participants are reported in CS Document B, Table 9. There were no notable imbalances in the baseline characteristics, other than the lorlatinib arm being somewhat older than the crizotinib arm (median age 61 versus 56).

Risk of bias

The company's quality assessment of the CROWN trial is presented in CS Document B, Section 2.5. The company concluded that CROWN was at low risk of bias. The EAG agrees that the methodology of CROWN appeared generally robust and to have minimised the risk of most biases. However, the somewhat higher age of lorlatinib arm participants at baseline may slightly favour outcomes for the crizotinib arm.

In addition, the EAG has concerns that the unblinded design of the trial may have introduced bias for investigator-assessed and patient-reported outcomes: PFS (INV), ORR, DOR (INV), IC-TTP (INV), HRQL, and adverse events. Whilst progression and response outcomes were measured against RECIST v1.1 criteria, there remains a risk that knowledge of the intervention may have influenced the assessment of these outcomes.

Of the 147 patients who were randomised to receive crizotinib, all patients randomised to lorlatinib received lorlatinib, and five patients randomised to crizotinib were not treated with crizotinib (CS, Document B, Figure 4). Of those five patients, four withdrew, and one patient was not eligible, was randomised by mistake, and received crizotinib outside of the study.[3] Given the lack of data on subsequent treatments for all five patients, it is unclear whether this imbalance (likely a consequence of the lack of blinding) may have biased results, although any impact is likely to be small.

Applicability to NHS setting

No formal appraisal of applicability (or external validity) was presented in the CS. Three of the 104 trial sites were based in the UK; the countries with the most sites were Japan (17), Italy (13), Spain (10), China (9) and France (8). Patients who had received prior systemic NSCLC treatment were excluded from CROWN. Lorlatinib's license is broader as it covers patients who have not been previously treated with an ALK inhibitor (i.e. prior chemotherapy is allowed). However, the EAG's clinical advisers estimate this would constitute only a very small minority of the ALK-TKI-eligible population as ALK testing is integrated into the current patient pathway to identify these patients early, and ALK targeted therapy is preferred over chemotherapy. The other trial eligibility criteria appeared largely appropriate and relevant.

Although participants with an ECOG performance status of 0-2 were eligible for inclusion in CROWN, only 4% of patients had ECOG 2, so CROWN provides very little data on the efficacy and safety of lorlatinib these patients. The EAG's clinical advisers consider that if approved as 1L therapy, lorlatinib would likely be prescribed to ECOG 2 patients. The TA909 NICE committee concluded that evidence from CROWN may be applicable to people with an ECOG of 2 in the NHS, although they acknowledged uncertainty associated with the lack of evidence for this population. Although the proportion of Asian patients (44%) is higher than would be seen in the NHS, the EAG' s clinical advisers did not feel this raised significant concerns about the applicability of the trial population to UK practice. It is uncertain the extent to which clinical practice and disease management in the majority of the CROWN trial sites outside of the UK may limit the applicability of the study results to the NHS.

The EAG has significant concerns about the applicability of the comparator arm in CROWN. Clinical advice to the EAG is that crizotinib is very rarely used to treat ALK-positive NSCLC patients in practice and is an obsolete comparator. This is corroborated by the company's market research. [9] Furthermore, the treatment sequences used in both trial arms of CROWN are not reflective of NHS practice as described in Section 2.2. CS Document B, Table 25 summarises subsequent therapies by treatment arm in CROWN. In total, of patients whose disease progressed on lorlatinib, only 6.5% continued to receive lorlatinib, and 43% received a second-or-first generation TKI (most commonly alectinib, which falls outside of its MHRA marketing authorisation).[14] The EAG's clinical advisers consider that, if approved, some patients would continue to receive lorlatinib at 1L following progression (notably in case of oligoprogression, see Section 2.2). They note that the use of a 1st or 2nd generation TKI following

progression on lorlatinib is unlikely to occur in practice, given their mechanisms of action and reduced mutation coverage compared with later generation TKIs. In the crizotinib arm, only 3.6% of progressed patients received lorlatinib as 2L TKI, and 89% subsequently received a 2nd generation TKI (mostly alectinib or brigatinib). EAG clinical advisers note that this is not reflective of UK clinical practice, where they would expect most patients to receive lorlatinib (or chemotherapy) as 2L treatment.

3.2.1.2 Results

Clinical effectiveness results for CROWN are presented in CS Section B.2.6. Table 6 compares the data cuts provided in the current CS against the TA909 CS (2022).

Table 6 Data cuts in the current company submission (2024) and for TA909 (2022)

Outcome	Data cut-off presented in 2024 submission	Data cut-off presented in 2022 submission
Primary outcome		
PFS by BICR (RECIST v1.1)	September 2021 data cut-off (3-year follow-up)[a]	September 2021 data cut-off (3-year follow-up)[a]
Secondary Outcomes		
PFS by INV (RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]	September 2021 data cut-off (3-year follow-up)[a]
OS	March 2020 data cut-off (18-month follow-up)[c,d]	March 2020 data cut-off (18-month follow-up)[c,d]
Response rates (ORR, DOR and TTP) by BICR (RECIST v1.1)	September 2021 data cut-off (3-year follow-up)[a]	September 2021 data cut-off (3-year follow-up)[a]
Response rates (ORR and DOR) by INV (RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]	September 2021 data cut-off (3-year follow-up
Intracranial Outcomes		
IC-TTP by BICR (modified RECIST v1.1)	September 2021 data cut-off (3-year follow-up)[a]	September 2021 data cut-off (3-year follow-up)
IC-TTP by INV (modified RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]	NA
IC-OR by BICR (modified RECIST v1.1)	September 2021 data cut-off (3-year follow-up)[a]	September 2021 data cut-off (3-year follow-up)[a]
IC-OR by INV (modified RECIST v1.1)	October 2023 data cut-off (5-year follow-up)[b]	NA
HRQL (all measures)	September 2021 data cut-off (3-year follow-up)[b]	September 2021 data cut-off (3-year follow-up)[b]
Adverse events (all event types)	October 2023 data cut-off (5-year follow-up)[c]	March 2020 data cut-off (18-month follow-up)[c]

Abbreviations: BICR, blinded independent central review; DOR, duration of response; HRQL, health-related quality of life; IC, intracranial; INV, investigator assessment; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1; TTP, time to progression; NA: not available
Footnotes: [a] unplanned data cut; [b] unplanned data cut using INV as BICR was stopped by this date (per protocol); [c] planned, primary analysis set; [d] the number of deaths required to achieve 70% power has not yet been met and therefore OS data were not analysed.
Source: Shaw *et al*. 2020;[15] Solomon *et al.* 2023 ;[11] Solomon *et al*. 2024[12]

Overall, three different data cut-offs were reported; March 2020, September 2021, and October 2023, representing a median of 18 months, 3 years and 5 years of follow-up respectively. The data cut available varied by outcome and measurement method. The latest data cut (October 2023, 5-year follow-up) is an unplanned data cut using INV assessment for progression and response outcomes, as BICR was stopped by this date. This represents the new evidence (not included in the TA909 CS in 2022) and was presented for the following outcomes in the current submission: PFS (INV), response rates, IC-TTP, IC-OR, and adverse events.

The latest available data cut for OS was March 2020 data cut-off (18-month follow-up), as per the TA909 CS. In response to clarification question A2, the company stated that they were unable to provide a later OS data cut, because OS is an alpha protected endpoint, and that the required number of OS events (at least 139 deaths, or 70% of randomised participants) for a protocol-specified second interim analysis was not met. The company stated that this approach was meant to avoid selective and biased reporting of trial results. They noted that, unlike OS, the reporting of non-protocol specified descriptive analyses for PFS "did not break trial reporting convention" as it only occurred after protocol-specified final analyses in which the primary endpoint was met.

The EAG considers that the lack of updated cut-off and substantial immaturity of the OS data from CROWN means that the evidence for any OS benefits from lorlatinib compared with crizotinib remains significantly uncertain.

Progression-free survival

At the October 2023 (5-year) data cut, the median follow-up for PFS (INV) was 60.2 months for lorlatinib and 55.1 months for crizotinib. Median PFS was not reached for lorlatinib (95% CI: 64.3 to NR) and was 9.1 months (95% CI: 7.4 to 10.9) for crizotinib. The 5-year PFS rate for 60% (95% CI 51 to 68) for lorlatinib, and 8% (95% CI 3 to 14) for crizotinib. There was a statistically significant difference in PFS favouring lorlatinib compared with crizotinib (HR 0.19; 95% CI 0.13 to 0.27). Clinical advisers to the EAG agree with the company that the magnitude of PFS benefit for lorlatinib at up to 5-years is highly clinically significant. However, the EAG notes that the proportional hazard (PH) assumption is unlikely to hold for the comparison between lorlatinib and crizotinib (see Section 3.3.2), therefore the interpretation of the magnitude of benefit in terms of a constant HR is uncertain.

Results of subgroup analyses for PFS are reported in CS Appendix E, with further details in the company's clarification response document to questions A5 and A6. Subgroup analyses by brain metastases (CS, Appendix E, Figure 2) showed a numerically greater relative benefit from lorlatinib against crizotinib in patients with brain metastases (HR 0.08; 95% CI 0.035 to 0.188) compared with patients without brain metastases at baseline (HR 0.24; 95% CI 0.164 to 0.362). Other subgroup analyses showed no difference in PFS (INV) at the 5-year data cut by ethnic origin (Asian/non-Asian),

ECOG status, gender, age, smoking status, disease burden and histology. There was no evidence of an interaction effect on PFS (INV) between any of these variables and the presence of CNS at baseline.

An analysis for the discordance between BICR and INV for PFS (reported in the CROWN Interim CSR,[16] Table 14.2.1.3) showed that the overall discrepancy rate was 22.1% in the lorlatinib arm and 46.9% in the crizotinib arm (Chi-squared p value <0.0001). At the 18-month data-cut, PFS (INV) estimates (HR 0.21; 95% CI, 0.14 to 0.31) favoured lorlatinib over crizotinib slightly more than the BICR estimates (HR 0.28; 95% CI, 0.19 to 0.41); at 3 years, PFS (INV) estimates were also more favourable to lorlatinib (HR 0.19; 95% CI 0.13 to 0.27) compared with PFS (BICR) (HR 0.27; 95% CI 0.18 to 0.39). However, 95% CIs between these estimates overlap, and no formal comparison between PFS (BICR) and PFS (INV) at 3 years is available. Visual inspection of Kaplan-Meier (KM) curves at the latest available data cuts (i.e. 5 years for PFS [INV] and 3 years for PFS [BICR]) suggests that the difference between PFS outcomes by INV and BICR is in part driven by a larger discrepancy in events rates by measurement method in the crizotinib arm after approximately 16 months of treatment (CS Document B, Figure 24). Visual inspection of KM curves for IC-TTP by INV and BICR at 5 years and 3 years respectively (CS Document B, Figure 7, and CS Appendix M, Figure 10) showed a similar pattern at up to 3 years (the last data cut for BICR assessments). As BICR data has only been collected up to 3 years, any differences between INV and BICR beyond 3 years are unknown. The potential magnitude of bias associated with the lack of blinding of study personnel and patients for investigator-assessed outcomes in CROWN at 5-years is uncertain.

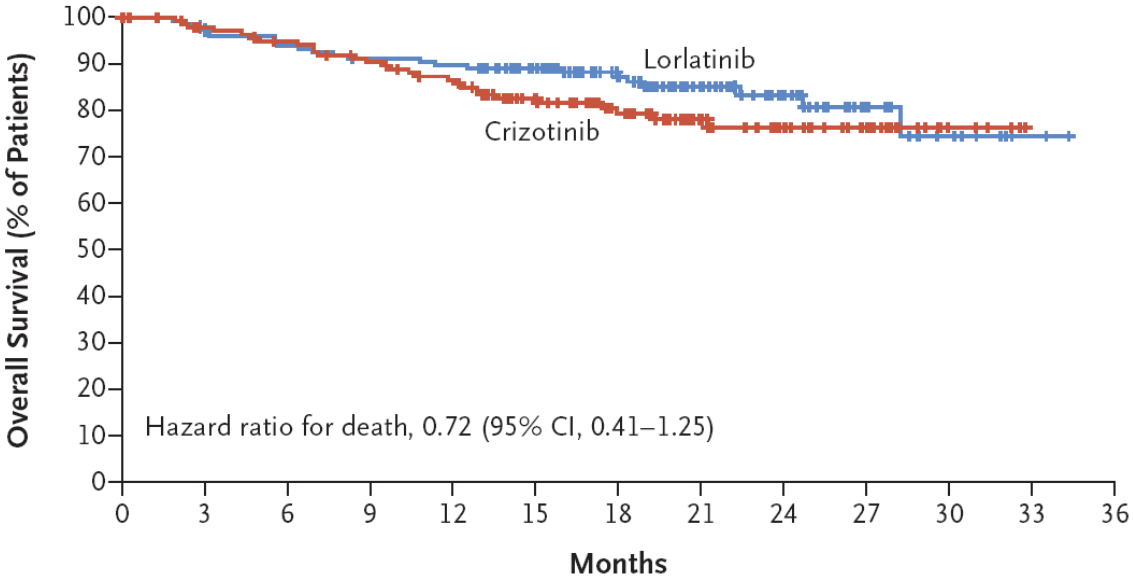
As discussed in Section 3.2.1.1 the EAG has concerns that the magnitude of PFS (INV) benefit at 5 years may be biased in favour of lorlatinib due to the lack of blinding of outcome assessors and evidence of a discrepancy between PFS (INV) and PFC (BICR) at earlier data cut-offs.

Overall survival

At the March 2020 (18-month) data-cut, the median OS was not estimable in either treatment arm. No statistically significant difference in OS was found between lorlatinib and crizotinib (HR 0.72, 95%: CI 0.41 to 1.25). The KM plot is reproduced from the CS below in Figure 2. A separation of the curves appears from approximately 10 months of follow-up. The company's assessment of the PH assumption is discussed in Section 3.3.2, the EAG considers that the PH assumption is unlikely to hold. The EAG agrees with the company that, as the 18-month OS data is still very immature, no conclusions can be drawn from this analysis.

Despite the highly clinically significant PFS benefit for lorlatinib up to 5-years is, there is currently no evidence to support an OS benefit for lorlatinib relative to crizotinib. Furthermore, as discussed in Section 3.2.1.1, subsequent treatments received 2L following progression by patients in the CROWN trial, which are not reflective current NHS practice, will confound currently available OS data and all future data-cuts of OS.

Figure 2 Kaplan-Meier curve for OS in CROWN (FAS, March 2020 data cut-off)



No. at Risk																			
Lorlatinib	149	148	141	138	135	133	131	122	101	85	63	50	38	27	13	8	4	1	0
Crizotinib	147	139	133	127	122	116	111	97	85	68	55	40	31	22	12	5	3	0	0

Abbreviations: CI, confidence interval; OS: overall survival; FAS, full analysis set

Source: CS Document B, Figure 6.

Response rates

At the October 2023 (5-year) data cut, the proportion of patients with a confirmed objective response, defined as either complete or partial response as assessed by investigator based on RECIST v.1.1 criteria, was statistically significantly higher with lorlatinib compared with crizotinib (odds ratio [OR] 2.43; 95% CI 1.43 to 4.43). Most participants in both arms experienced a partial response. Further details are presented in CS Document B, Table 16. Subgroup analyses (response to clarification question A6) showed that response rates were similar between patients with and without baseline CNS metastases in the lorlatinib arm (78.4% and 76.8% respectively) but differed in the crizotinib arm (43.6% and 63.9% respectively). As discussed in Section 3.2.1.1, the EAG has concerns that investigator-assessed rates of response may be biased due to the lack of blinding of outcome assessors.

Duration of response

At the 5-year data cut, the median DOR was not reached (95% CI: NR to NR) with lorlatinib and was 9.2 months (95% CI: 7.5 to 11.1) with crizotinib. The probability of being event-free at 5 years was 68.8% (95% CI: 58.9% to 76.8%) in the lorlatinib arm and 9.5% (95% CI: 3.9% to 18.2%) in the crizotinib arm.

Intracranial outcomes

At the October 2023 (5-year) data cut, median IC-TTP assessed by investigator using modified RECIST v1.1 was not estimable with lorlatinib (95% CI NE to NE) and 16.4 months (95% CI 12.7 to 21.9) with crizotinib (CS Document B, Figure 7). The probability of being free of intracranial progression at 5

years was 92% (95% CI 85 to 96) with lorlatinib and 21% (95% CI 10 to 33) with crizotinib. The difference between groups was statistically significant; HR 0.06 (95% CI 0.03 to 0.12).

In the subgroup of patients with measurable and/or non-measurable baseline brain metastases, intracranial objective response was 60% in the lorlatinib arm and 11% in the crizotinib arm. Intracranial complete response was reported in 49% and 5% of patients, respectively (CS Document B, Table 19). Median duration of intracranial response was NR (95% CI: NR to NR) and 12.8 months (95% CI: 7.5 to NR) respectively.

Clinical advisers to the EAG note that the magnitude of intracranial outcomes for lorlatinib at up to 5-years was highly clinically significant. As with PFS (above in Section 3.2.1.2), the EAG has concerns that the magnitude of IC-TTP benefit may be biased in favour of lorlatinib due to the lack of blinding of outcome assessors.

Health-related quality of life

HRQL was assessed at the September 2021 (3-year) data cut and is presented in CS, Appendix M.2. Outcomes were measured on Day 1 of each cycle, at the end of treatment, and at post-treatment follow-up using the European Organisation for Research and Treatment of Lung Cancer Quality of Life Questionnaire (EORTC QLQ-C30). A statistically significant improvement in global quality of life was reported favouring lorlatinib compared with crizotinib (mean difference of 4.51, 95% CI 0.83 to 8.19). The summary estimate did not reach a minimally important difference for lung cancer: a between-group difference ranging between 5 and 10 points may be considered clinically meaningful.[17] The difference in global quality of life may have been inflated by the impact of detection bias; patients were not blinded to their randomised treatment and may have anticipated experiencing greater benefit from lorlatinib.

Safety

Safety outcomes are presented in CS Document B, Section 2.10 for the October 2023 (5-year) data cut. Further information is available in the Study Output Report for the 5-year data-cut (CS, Appendix M3, Table 14.3.1.1.2 and 14.3.1.4.1). The CS reported no new safety signals since TA909.

Median time on treatment was 57.0 months (IQR: 13.9 to 63.3) in the lorlatinib arm compared with 9.6 months (IQR: 4.7 to 17.1) in the crizotinib arm. Dose reductions (23% versus 15%) and temporary treatment discontinuation (62% versus 48%) were more common in the lorlatinib arm, whilst permanent discontinuations rates were identical between arms (11% in both groups).

All-cause any-Grade AEs occurred in 100% of lorlatinib patients and 99% of crizotinib patients. All-cause Grade 5 AEs were experienced by 9% in the lorlatinib arm, compared with 5% in the crizotinib arm. Two deaths were attributed to study treatment toxicity (both in the lorlatinib arm). All-cause Grade 3/4 AEs occurred in 77% of patients in the lorlatinib arm and 57% of patients in the crizotinib arm, driven by higher rates of hypertriglyceridemia (25% versus 0%), hypercholesterolemia (21% versus

0%), weight gain (23% versus 2%) and hypertension (12% versus 1%). All-cause serious AEs occurred more frequently in the lorlatinib arm (44% versus 32%).

All-cause cardiovascular AEs were reported in 28% of patients in both study arms; of those, grade 3 and 4 rates of cardiovascular events were similar between arms (8% versus 9%). All-cause CNS AEs were reported in 42% of patients in the lorlatinib group; of those, 86% were Grade 1 or 2 and 13% were Grade 3. In comparison, all-cause CNS AEs were reported in [redacted] of the crizotinib group, [redacted] of which were Grade 1 or 2.

Overall, the evidence from CROWN suggests that lorlatinib is more toxic than crizotinib, particularly in terms of CNS AEs. However, EAG clinical advisers note that AEs (all-cause and all types) tend to be more frequently reported in trial settings. This is supported by meta-analytic evidence.[18] Therefore, the CNS toxicity of lorlatinib may have been overestimated in CROWN. The EAG clinical advisers consider the safety profile of lorlatinib to be acceptable and manageable.

It is difficult to predict the magnitude and direction of any bias arising from the lack of blinding of outcome assessors for safety outcomes. Knowledge of the safety profiles of the two drugs and lack of blinding may have affected the rates of discontinuation and switching to newer generation TKIs in the crizotinib arm.

3.2.2 Study 1001: cohort EXP1

The company presents a brief summary of Study 1001 in CS, Section B.2.8.1 and further details in response to clarification question A9 (Clarification Response Appendix 2).

3.2.2.1 Methods and participants

Study 1001 is a phase 2, uncontrolled, open-label multi-centre trial of lorlatinib including a total of 275 patients with *ALK*- or *ROS1*-positive advanced NSCLC who received at least 1 dose of lorlatinib 100mg once daily. Design details and eligibility criteria were reported in Clarification Response Appendix 2, Tables 1 and 2 respectively. The primary endpoint was overall and intracranial tumor response (BICR). Secondary endpoints included OS, PFS and safety.

Of these, the EXP1 cohort included 30 patients who were ALK-positive and treatment naïve. Other cohorts of Study 1001 (EXP2-5) included patients who received lorlatinib 2L. Study 1001 cohorts EXP3B-5 informed post-progression outcomes in the company model (see Section 4.2.2, Table 12); methods, patient characteristics and results for these cohorts are provided in Appendix 1 (Section 9.1).

Baseline characteristics of cohort EXP1

Baseline characteristics of Study 1001 participants are reported in Clarification Response Appendix 2, Table 3. Overall, the characteristics of the EXP1 cohort were broadly comparable with those of the CROWN trial. The median age (59 years) was two years younger than the lorlatinib arm of CROWN.

The proportion of patients with ECOG 0-1 was 96%, and the proportion with baseline CNS metastases was 27%; 57% were Asian.

Risk of bias

The company's quality assessment of Study 1001 is presented in Clarification Response Appendix 2, Table 5. The company concluded that Study 1001 was at low risk of bias. The EAG disagrees with the company's quality assessment. As the study was not randomised, items 1 and 2 on randomisation and allocation concealment are not applicable. The lack of blinding of study personnel and study participants may have introduced bias for investigator-assessed and patient-reported outcomes. The EAG considers that a quality assessment tool suitable for the non-randomised design of Study 1001 should have been used, rather than the NICE quality assessment checklist which is designed for RCTs.

Applicability to NHS setting

None of the 44 trial sites were based in the UK; the countries with the most sites were the USA (11), Japan (10), Italy (4), Spain (4) and France (4). The lack of UK sites may limit the applicability of the study results NHS practice. The trial eligibility criteria appeared largely appropriate and relevant to the EAG clinical advisers. In the EXP1 cohort, only one (3%) patient had an ECOG 2; although the proportion of Asian patients was high (57%), clinical advisers do not think this raises significant concerns about the applicability of the trial population to UK practice. At a median follow-up of 72.7 months, only 9 (30%) patients received subsequent systemic therapy; 3 received alectinib, 2 crizotinib, 1 had lorlatinib and 2 had 2L chemotherapy. EAG clinical advisers note that the rate of patients undergoing subsequent therapy was low compared with clinical practice, and they expect most patients to receive lorlatinib (or chemotherapy) rather than an older generation TKI as 2L treatment.

3.2.2.2 Results

Effectiveness and safety results of Study 1001 are presented in Clarification Response Appendix 2, pp. 8-10. Further details were presented in an unpublished manuscript.[13].

Effectiveness

Median follow-up for OS was 72.7 months (95% CI: 69.3 to 76.3) for the EXP1 cohort. Median OS was not reached (95% CI: NR to NR). The probability of 1-years OS was 90% (as with CROWN); 3-year OS was 80%, and 5-year OS was 76%. Like the CROWN trial, OS data from Study 1001 EXP1 are confounded due to the use of 2L subsequent therapies not reflective of NHS clinical practice,

The median time to disease progression, defined as the median time from treatment initiation to the date of the first documentation of objective tumour progression, was 17.7 months (95% CI: 12.5 to 40.5). At the latest data cut (July 27, 2023), median duration of treatment with lorlatinib was 64.6 months (range, 1.7 to 88.2). The reason for the relatively large difference between reported time to disease progression and treatment duration estimates is unknown. Results for PFS, defined as time from

treatment initiation to first documentation of objective disease progression or to death on study due to any cause, whichever came first, were not reported at the latest data cut.

At the time of the initial data cut (March 15, 2017), 27 patients (90.0%; 95% CI 73.5 to 97.9) had an objective response by independent central review, with one patient achieving a complete response and 26 achieving a partial response.

Although the results of Study 1001 provide significantly longer-term follow-up compared with CROWN, the difference between median time-to progression and time on treatment is unexplained and does not appear to align with equivalent data from CROWN. The reported median time to disease progression appears less favourable to lorlatinib than PFS results reported in CROWN. However, the lack of reporting of PFS results at the latest data cut in Study 1001, as well as the lack of control group and the small number of treatment naïve patients limits comparisons with CROWN.

Safety

Safety results were not presented separately for the EXP1 cohort but were reported for the total study population, therefore it is unknown whether the reported rates of AEs are applicable to the treatment naïve cohort. Overall, 13% discontinued treatment permanently due to AEs. All-cause Grade 5 AEs were reported in 16%, and Grade 3/4 in 76% of patients. Serious AEs were reported in 49%. Most frequent AE types were hypercholesterolemia and hypertriglyceridemia.

3.2.3 Critique of pooled analysis of lorlatinib trials

To strengthen the extrapolations of OS data in the CS model, KM curves for OS from lorlatinib arm of CROWN and the EXP1 (treatment naïve) cohort of Study 1001 were pooled. The methods and results of this pooling are presented in CS Section B.2.8.1, with further details in the company's response to clarification question A11. The analysis involved treating all lorlatinib patients from both studies as a combined trial arm (n=179). The reverse KM method was used to estimate median duration and survival probabilities were calculated using the normal approximation to the log transformed cumulative hazard rate.

The EAG agrees with the company that baseline characteristics were broadly similar between the treatment naïve arm of Study 1001 and the lorlatinib arm of CROWN, including median age, ECOG status and CNS metastases, as described in Sections 3.2.1.1 and 3.2.2.1.

Results of the pooled analysis of OS from CROWN and Study 1001 are reported in CS Document B, Figure 12 and Table 21. These shows that median OS was not reached. One, 3- and 5-year OS rates were 89%, 77% and 73%. The company concluded that this data supports the continued OS benefit of lorlatinib in patients with ALK-positive NSCLC.

The EAG considers that pooling of the OS data from these two studies is acceptable in principle, given the comparability of baseline characteristics between the lorlatinib arms of CROWN and Study 1001. The short-term results of CROWN and 1001 are comparable, as both reported 90% survival at 1-year. Study 1001 included only 30 participants, compared with 149 for the CROWN lorlatinib arm. However, the follow-up duration of Study 1001 (72.7 months) is substantially longer than CROWN (18 months). Consequently, data from Study 1001 is a significant driver of the OS results after 18 months. Given the limitations of Study 1001 as discussed in Section 3.2.2, including the small sample size and therefore small number of OS events in the treatment naïve cohort and confounding due to subsequent treatments, the value of this pooled analysis to the clinical evidence is relatively limited and the long-term OS benefit of lorlatinib remains highly uncertain.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As the CROWN trial only provides evidence on the efficacy and safety of lorlatinib against crizotinib, an NMA was conducted to compare the relative efficacy and safety of lorlatinib to alectinib and brigatinib.

3.3.1 Study selection

The company clinical effectiveness SLR (CS, Section B.2.1) identified 12 RCTs. CS Document B, Table 22 provides an overview. Of these 12 RCTs, eight were deemed not relevant to the decision problem for this appraisal and were excluded from the company's NMA. This included seven studies evaluating comparators outside of the decision problem (ceritinib, chemotherapy, ensartinib, envonalkib, and iruplinalkib), [19-25] and one study (J-ALEX) [26] evaluating a treatment at an unlicensed dose in the UK (alectinib 300mg BID). The EAG found these exclusions to be appropriate.

Four RCTs were included in the company's NMA, including one trial of lorlatinib (CROWN),[12] two trials of alectinib (ALEX, ALESIA), [27, 28] and one of brigatinib (ALTA-1L).[29]

Although the EAG for the brigatinib appraisal (TA670) argued for the inclusion of the ALESIA trial, the NICE committee concluded it should be excluded. The Final Appraisal Document (FAD) for TA670 stated that differences in healthcare systems and subsequent treatment options meant that data from the ALESIA trial were not applicable to UK practice.[4] The EAG and their clinical advisers believe that the inclusion of ALESIA in the NMA for this current appraisal is appropriate. As per TA670 and TA909 EAG reports, if this assumption was applied across all four included RCTs, most trial data in the NMA would have to be judged inapplicable to the UK population. For example, the CROWN trial only included three UK sites out of a total 104 sites (see CS, Document B, Table 7). Many sites were conducted in healthcare systems different from the UK such as Japan (17 sites), China (9 sites), Taiwan (4 sites), Russia (4 sites), and Hong Kong (3 sites). Although PFS is unlikely to be impacted by differences in subsequent treatment options between healthcare systems offered post-progression, the

EAG acknowledges that subsequent management is likely to impact on the validity of OS estimates. The applicability of subsequent therapies to current UK practice is a key issue that does not only affect ALESIA, but the majority of the trial evidence for OS included in the NMA (see Section 3.4.1.2 and Section 3.4.4.1 for further discussion).

Furthermore, the protocol of the ALTA-1L trial of brigatinib versus crizotinib allowed treatment crossover, meaning patients who progressed on crizotinib could go on to receive brigatinib following disease progression. In total, 58.4% of patients who were randomised to crizotinib received brigatinib as a subsequent therapy, including a quarter of patients who were randomised to crizotinib who crossed over to brigatinib according to the trial protocol. This crossover is likely to have significantly impacted OS estimates. Removing ALTA-1L from the OS network would prevent the evaluation of brigatinib against lorlatinib. Therefore, the EAG considers the inclusion of ALTA-1L to be acceptable. The implications of the ALTA-1L design allowing crossover following progression on OS NMA results are further discussed in Section 3.4.4.1

3.3.2 Risk of bias of included trials

Risk of bias assessments for the comparator RCTs included in the NMA were reported in CS Appendix D, Table 15. The results showed that none of the included trials used methods to blind patients or caregivers. Whilst disease progression was assessed using objective criteria (RECIST v1.1), the lack of investigator blinding raises some concerns about assessment bias for these progression and response outcomes. The lack of blinding of study participants also means that there is a high risk of bias for patient reported outcomes. The ALTA-1L trial was by the company assessed as not having adequate allocation concealment, however the EAG for TA670 judged the risk of selection bias relating to allocation concealment in ALTA-1L trial to be low (TA670 EAG report, Table 9).[4]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Consistency and similarity of trials included in the company NMA

Trial and patient characteristics are summarised in CS Section B.2.9.2, with further details provided in the NMA feasibility report.[30]

3.4.1.1 Populations

The trial participant selection criteria of the four RCTs included in the NMAs are summarised in CS Document B, Table 23 and were broadly comparable. All trials included adults with ALK-positive NSCLC who were ALK-inhibitor naïve. ALTA-1L and ALESIA included patients with prior chemotherapy (6–27% across trial arms). No subgroup results were available for treatment naïve populations in ALTA-1L. Clinical advice to the EAG is that the impact of prior chemotherapy on the NMA results is likely to be limited, and therefore would not expect prior chemotherapy to have an important impact on the relative treatment effect in these trials and the NMA results.

Baseline characteristics for each trial arm included in the NMA are presented in CS Document B, Table 24. The median ages of patients within the included trials varied, and also were somewhat imbalanced between arms across the studies; CROWN (lorlatinib: 61 years, crizotinib 56 years), ALEX (alectinib: 58 years, crizotinib: 54 years), ALESIA (alectinib: 51 years, crizotinib: 49 years) and ALTA-1L (brigatinib: 58 years, crizotinib: 60 years). EAG clinical advisers considered that it is unlikely that age differences within and between studies would affect the NMA results.

Most patients had an ECOG performance status of 0 or 1 (93% to 98% across trial arms). The applicability of the evidence to patients with ECOG 2 is therefore uncertain.

The proportion of patients with Asian ethnicity varied between the trials, ranging from 36% to 100%; ALESIA only included patients from Asia. The EAG clinical advisers note that ethnicity is unlikely to be an effect modifier and furthermore, subgroup analyses from ALEX, ALTA-1L and CROWN showed no evidence of a difference in PFS between Asian and non-Asian participants.

The proportion of patients with brain metastases was higher in the ALEX and ALESIA trials than in ALTA-1L and CROWN (CS, Document B, Table 24). Variable analysis results have been reported in the ALEX, ALESIA and ALTA 1L trials regarding any subgroup differences between patients with and without brain metastases in terms of PFS and OS; although none of the trials included in the NMA were powered to detect a difference in subgroups. Clinical advice to the EAG and published evidence suggest that brain metastases are associated with a poorer prognosis and significant morbidities, although it is unclear whether they are an effect modifier. [3, 4]A population-adjusted analysis aimed to explore imbalances in the trials included in the NMA in the percentage of patients with brain metastases at baseline is discussed in Section 3.4.5.1.

3.4.1.2 Interventions

Treatments included in the trials and subsequent treatments are summarised in CS Document B, Table 25. As discussed in Section 3.3.1, ALTA-1L allowed treatment cross-over following progression, and 58.4% who were randomised to crizotinib received brigatinib as subsequent therapy. Overall, the subsequent therapies in the comparator arms poorly reflect the current NHS treatment pathway as described in Section 2.2. The proportion of patients receiving lorlatinib at any line of therapy after alectinib 1L was 13.1% in ALEX and 15% in ALESIA (out of patients who progressed on alectinib). In ALTA-1L, 29.7% of patients who progressed following brigatinib 1L therapy received lorlatinib. Across the comparator trials, up to 5% remained on their initial 2nd generation therapy following progression. These proportions are significantly lower than in UK practice where approximately 87% of patients receive 2L lorlatinib according to the UK advisory board to the company (CS Document B, Table 71).[9] EAG clinical advisers note that in practice, the vast majority of patients who progress on 1L treatment will receive 2L therapy (usually lorlatinib) or many will remain on their initial TKI. This

may lead to underestimating OS estimates for these trial arms, and consequently impact on the 1L lorlatinib and alectinib / brigatinib comparisons in the NMA.

3.4.1.3 Outcomes

Outcome definitions of trials included in the NMA were broadly comparable.[30] However, definitions of IC-TTP differed between CROWN and the comparator trials. In CROWN, the HR for IC-TTP was calculated by censoring patients who received systemic therapy other than lorlatinib, whereas within the comparator trials, other systematic therapies were treated as a competing event in the calculation of HR.

Data cuts and extent of follow-up for OS and PFS differed between trials. The 5-year data cut from the CROWN trial was used for all outcomes included in the NMA except for PFS (BICR) and OS, which were only available at 3 years and 18 months respectively. Unlike the comparator trials, PFS (BICR) was not available at 5 years in CROWN. The median follow-up for alectinib was 48.2 months in ALEX, 61 months in ALESIA, and 40.4 months in ALTA-1L. In ALEX, median PFS for alectinib was reached at 34.8 months versus 10.9 months for crizotinib, whilst at five years median OS was not reached with alectinib versus 57.4 months with crizotinib.[27] In ALESIA, the median PFS (INV) was reached at 41.6 months for alectinib versus 11.1 months for crizotinib, and the 5-year OS rate was 66.4% for alectinib versus 56.0% for crizotinib.[28] For ALTA-1L, the median PFS was reached at 24.0 months versus 11.1 months for crizotinib, and the median OS was not reached in either group; survival probability at four years was 66% in the brigatinib arm, and 60% for the crizotinib arm.[29]

Whilst the extent of follow-up for PFS INV is comparable across the trials, the EAG agrees with the company that the shorter follow-up duration for OS and PFS (BICR) in CROWN compared with other comparator trials is a source of uncertainty in the NMA.[30]

3.4.2 Proportional Hazards Assumptions

The company PH assessment was presented in Appendix N1, pp.143-151, with further details in the company's NMA feasibility assessment report.[30]

To assess the PH assumption, the company produced log-cumulative hazard plots and Schoenfeld residuals using individual participant data (IPD) from CROWN and generated pseudo IPD from KM curves from ALEX, ALESIA and ALTA-1L

3.4.2.1 Progression-free survival

In CROWN, the company consider that the PH assumption is violated for PFS (INV) from the 5-year data cut owing to the crossing of the curves in the log-cumulative hazard plot at several time points up to approximately 6 months (CS Appendix N, Figure 14), and a statistically significant Schoenfeld test result ($p = 0.03$; CS Appendix N, Figure 15). The EAG agrees with the company that the PH assumption is unlikely to hold for the comparison between lorlatinib and crizotinib.

In the ALEX trial for PFS (INV), the curves on the log-cumulative hazard plot cross at several time points up to approximately 6 months (CS Appendix N, Figure 17), and the Schoenfeld test was statistically significant (p = 0.002; CS Appendix N, Figure 18). In response to clarification question A13, the company stated that the scheduled progression assessments per the protocol could mask the treatment effect early in the trial, so these observations are likely to be the product of trial protocol, rather than the treatment effect. However, the company did not provide evidence to support this statement. Whilst the EAG acknowledges that log-cumulative curves appear close to parallel after approximately 10 months (CS Appendix N, Figure 17), the EAG considers that the early crossing of hazard plots and the results of the Schoenfeld test provide sufficient evidence to conclude that the PH assumption is violated. This is consistent with the interpretations by the EAG and submitting company for TA536, who agreed that the PH assumption was violated for PFS (including BICR and INV). [5]

In ALTA-1L for the final analysis of PFS (INV), the curves on the log-cumulative hazard plot cross up to three months follow-up (CS Appendix N, Figure 19), and the Schoenfeld test was not statistically significant (p =0.94; CS Appendix N, Figure 20). As with the ALEX trial, the company consider that these results are likely to be the product of trial protocol, rather than the treatment effect. Whilst the EAG acknowledges that the log-cumulative hazard plots for PFS (INV) appear parallel from approximately four months onwards, the EAG considers that the early crossing of the curves may suggest that the PH assumption does not hold. This is in line with the submitting company's position in the CS for TA670 based on an interim analysis of PFS (INV),[4] however, the EAG for TA670 concluded that there was no statistically significant evidence that the PH assumption was violated. Overall, the EAG considers that the validity of the PH assumption cannot be determined conclusively from the evidence provided.

Based on the company assessments for ALESIA (CS Appendix N, Figures 21 and 22), the EAG agrees with the company that there is no evidence that the PH assumption is violated for PFS (INV).

In summary, based on the evidence presented, the EAG believes that the PH assumption for PFS (INV) may be appropriate for ALESIA but is unlikely to hold for CROWN, ALEX and ALTA-1L.

TA909 concluded that the PH assumption for PFS (BICR) did not hold for CROWN. No PH assessment for PFS (BICR) was performed at the 5-year cut-off for ALEX, ALTA-1L and ALESIA, so the validity of the PH assumption is unknown for PFS (BICR) at the latest available data cut is unknown.

3.4.2.2 Overall survival and intracranial time-to-progression

The PH assessment for OS and IC-TTP is presented in the company's NMA feasibility assessment, pp. 31 to 35.[30] Results of Schoenfeld tests were summarised, but residual plots were not presented for these outcomes. The company found evidence or 'potential evidence' against the PH assumption for both outcomes in CROWN and ALEX. For ALESIA, they reported evidence against the PH assumption for IC-TTP but not OS. For ALTA-1L, evidence against the PH assumption was found for OS, but was

could not be assessed for IC-TTP as no KM curve was available. Visual inspection of the KM curves for IC-TTP suggests some crossing of the curves early in the trial and relatively parallel curves from approximately 6 months onwards, indicating some evidence against the PH assumption. The EAG generally agrees with the company PH assessments indicates that the PH assumption for OS is unlikely to hold for CROWN, ALEX and ALTA-1L, but may hold for ALESIA. The EAG considers that the PH assumption for IC-TTP is unlikely to hold for CROWN, ALEX and ALESIA, and finds there is insufficient evidence to determines whether the PH assumption is violated for ALTA-1L.

3.4.3 Network and methodology

The NMA was conducted for PFS by BICR, PFS by INV, OS and IC-TTP, AEDC and Grade 3/4 AEs, using available data from the most recent data cut-offs for each outcome from each included trials (see Appendix I of the company's NMA feasibility assessment report[30] for NMA input data). A network diagram is presented in CS Document B, Figure 14. It was not possible to assess the consistency (coherence) of direct and indirect evidence statistically as there were no trials directly comparing lorlatinib, alectinib and brigatinib.

A fixed effects model was used for all analyses. The EAG believes this was appropriate due to the small network size, limited number of studies, and a lack of loops in the network. However, fixed effect models may underestimate imprecision, as acknowledged by the company in Section B.2.9.5. The EAG agrees that the choice of a Bayesian NMA was the most appropriate given the small network size. The EAG were able to replicate the results of the NMA using the code provided by the company and had no concerns about implementation.

The EAG notes that the PH assumption is unlikely to hold or was uncertain for all of the time-to-event outcomes included in the NMAs (Section 3.3.2), and therefore the interpretation of NMA results in terms of constant HRs is uncertain. The EAG considers that whilst NMA methods could in theory be used to calculate time-varying HRs, this would likely cause added complexity for modelling PFS, OS and IC-TTP without necessarily resolving uncertainty.

3.4.4 NMA results

3.4.4.1 Progression Free Survival and Intracranial outcomes

PFS (BICR and INV) results and IC-TTP (INV) results are summarised in CS Section B.2.9.4.1 and CS Section B.2.9.4.3 respectively and presented in Table 7.

Lorlatinib showed a statistically significant improvement in PFS (INV), PFS (BICR) and IC-TTP (INV) compared to both alectinib and brigatinib. PFS (INV) results were generally more favourable to lorlatinib over the comparator and had narrower CrIs, indicating greater precision, compared to PFS (BICR). Differences in IC-TTP outcome definitions (see Section 3.4.1.3) are a source of heterogeneity in this NMA, however, the impact on the NMA results is unknown.

Table 7 NMA results: PFS by BICR and INV (fixed effects)

Comparison	PFS (BICR)	PFS (INV)	IC-TTP (INV)
HR (95% CrI) for all treatments versus crizotinib[1]			
Lorlatinib	0.27 (0.18, 0.40)	0.19 (0.13, 0.27)	0.06 (0.03, 0.12)
Alectinib (600mg BID)	0.46 (0.35, 0.60)	0.39 (0.31, 0.49)	0.15 (0.10, 0.24)
Brigatinib	0.48 (0.35, 0.66)	0.43 (0.31, 0.59)	0.30 (0.15, 0.60)
HR (95% CrI) for lorlatinib versus relevant comparators[1]			
Alectinib (600 mg BID)	0.59 (0.37, 0.95)	0.49 (0.32, 0.75)	0.39 (0.17, 0.89)
Brigatinib	0.56 (0.34, 0.93)	0.44 (0.27, 0.72)	0.20 (0.07, 0.54)

Abbreviations: BICR: blinded independent central review; BID, twice daily; CrI, credible interval; HR, hazard ratio; IC-TTP: intracranial time to progression; INV, investigator assessment; PFS, progression-free survival; NMA: network meta-analysis
Footnotes: 1. HR<1 indicates an advantage to the treatment versus the comparator
Source: CS Document B, Table 27 and Table 29

3.4.4.2 Overall Survival

OS results are summarised in CS Section B.2.9.4.2 and Table 8.

Table 8 NMA results: OS unadjusted and adjusted for crossover (fixed effects)

Comparison	Unadjusted analysis[1]	Crossover adjusted analysis[2]
HR (95% CrI) for all treatments versus crizotinib[3]		
Lorlatinib	0.72 (0.41 to 1.25)	0.72 (0.41 to 1.25)
Alectinib (600 mg BID)	0.64 (0.48 to 0.87)	0.60 (0.37 to 0.98)
Brigatinib	0.81 (0.53 to 1.23)	0.50 (0.28 to 0.89)
HR (95% CrI) for lorlatinib versus relevant comparators[3]		
Alectinib (600 mg BID)	1.12 (0.59 to 2.11)	1.20 (0.57 to 2.52)
Brigatinib	0.89 (0.44 to 1.78)	1.44 (0.65 to 3.18)

Abbreviations: BID, twice daily; CrI, credible interval; HR, hazard ratio; IPCW: inverse probability of censoring weighting, OS, overall survival.
Footnotes: 1. Includes OS data from CROWN, ALTA-1L, ALESIA and ALEX trials without adjustment for treatment crossover; 2. Includes OS data from CROWN and ALESIA trials without adjustment for treatment crossover, and OS data from ALTA-1L adjusted for treatment crossover using IPCW analysis; 3. HR<1 indicates an advantage to the treatment versus the comparator
Source: CS Document B. Table 28 and company clarification response, Table 3.

In their unadjusted analysis, the company found no statistically significant differences in OS for lorlatinib compared with alectinib (600mg BID, hereafter referred to as alectinib) and brigatinib. The EAG agrees with the company that, given the immaturity of the OS data from CROWN and the fact that patients in all included trials received subsequent therapies not reflective of UK clinical practice (see Section 3.4.1.2), no definitive conclusions can be drawn from this analysis and no evidence to support an OS benefit for lorlatinib over alectinib or brigatinib is shown.

The company notes that the 5-year OS rates observed in the comparator trials with alectinib was 62.5% in ALEX [at a median follow-up of 48.2 months] [31] and 66.4% in ALESIA trial [at a median follow-up

of 61 months][28] and 4-year OS probability with brigatinib in ALTA-1L was 66% [at a median follow-up of 40.4 months].[29] These were similar to lorlatinib PFS rates of 63% at 4 years and 60% at 5 years observed in CROWN, at a median follow-up of 60.2 months (CS Document B, p83). The company therefore suggest that the OS benefit from lorlatinib has the potential to be of higher magnitude than with 2nd generation TKIs, such as alectinib and brigatinib. Clinical advisers to the EAG note that the latest available PFS results from CROWN were highly clinically significant and show promise of OS benefit. However, in the absence of sufficiently mature OS data, the EAG considers that the extent to which PFS results observed in the CROWN trial may translate into OS benefits relative to 2nd generation TKIs when used as 1L therapies is uncertain.

The EAG considers that design of the ALTA-1L, which permits treatment crossover from crizotinib to brigatinib after disease progression, will introduce bias to the NMA OS estimates for comparisons that include brigatinib. In response to clarification question A17, the company conducted an exploratory crossover-adjusted analysis for OS to mitigate the risk of confounding from treatment crossover. The company performed an additional NMA using the inverse probability of censoring weighting (IPCW) adjusted OS estimate from the ALTA-1L trial from published evidence. [29] However, the company also excluded the ALEX trial from this NMA as it did not include crossover-adjusted data. As CROWN and ALESIA trials also do not present cross-over adjusted OS results, the EAG believe that the exclusion of the ALEX trial was unnecessary. Furthermore, due to the absence of closed loops in the NMA, the EAG does not expect that the potential bias from the design of the ALTA-1L trial will affect the comparisons between lorlatinib and alectinib. The EAG conducted an additional NMA included data from ALEX, and crossover-adjusted data from ALTA-1L (Section 3.5).

Results suggest that unadjusted data for brigatinib in ALTA-1L may underestimate the relative treatment effect of brigatinib versus crizotinib due to treatment switching. Compared with the unadjusted analysis, the crossover-adjusted analysis showed a change in the direction of effect of the HR for lorlatinib versus brigatinib, but still no statistically significant difference between lorlatinib and alectinib or brigatinib (Table 8).

The EAG agrees with the company that this analysis is limited, and results should be interpreted as exploratory. Additionally, this analysis does not adjust for confounding of OS due to other subsequent therapies received by patients' post-progression (i.e. any other therapy aside from switching between trial treatment arms, including treatments which do not reflect the current NHS treatment pathway) in any of the trials included in the NMAs.

In response to clarification, the company provided the results of an additional analysis conducted using observational real-world evidence from the US Flatiron Health Research Database (FHRD) to further investigate the efficacy (in terms of OS and PFS) of the sequence of alectinib or brigatinib (1L) followed by lorlatinib. This is further discussed in Section 3.4.5.2.

3.4.4.3 Safety outcomes

Results for AEDC and Grade 3/4 treatment-related adverse events (TRAE) were presented in the company's NMA results report[32] and are summarised in Table 9.

Table 9 NMA results: safety outcomes

Comparison	AEDC	TRAE Grade 3/4
OR (95% CrI) for all treatments versus crizotinib[1]		
Lorlatinib	0.94 (0.34, 2.66)	3.15 (1.96, 5.13)
Alectinib (600mg BID)	0.90 (0.53, 1.54)	0.81 (0.56, 1.16)
Brigatinib	1.60 (0.75, 3.59)	1.81 (1.10, 3.01)
OR (95% CrI) for lorlatinib versus relevant comparators[1]		
Alectinib (600 mg BID)	1.04 (0.33, 3.34)	3.89 (2.15, 7.16)
Brigatinib	0.59 (0.16, 2.14)	1.74 (0.87, 3.49)
Abbreviations: AEDC: discontinuation due to adverse events; CrI: credible interval; OR: odds ratio; NMA: network meta-analysis; TRAE: treatment-related adverse events **Footnotes**: 1. OR<1 indicates an advantage to the treatment versus the comparator **Source:** Company NMA results report,[32] Table 5 and Table 13		

No statistically significant difference in the odds of AEDC was found between lorlatinib and alectinib/brigatinib. The odds of experiencing a Grade 3/4 TRAE were statistically significantly higher for patients on lorlatinib compared with alectinib and numerically higher compared to brigatinib (although not statistically significant). All NMA results for safety outcomes were imprecise as shown by the wide credible intervals.

3.4.5 Population adjusted analyses

3.4.5.1 Matching-adjusted comparison

To address imbalances in the percentage of patients with brain metastases at baseline between the trials included in the NMA, anchored matching-adjusted indirect comparisons (MAIC) comparing lorlatinib (CROWN) versus alectinib (ALEX and ALESIA, separately) and lorlatinib (CROWN) versus brigatinib (ALTA-1L) was briefly discussed in CS Section B.2.9.5, with further details reported in a separate publication.[33] The following outcomes were assessed: PFS by BICR, PFS by INV, TTP-CNS by BICR, Grade ≥3 AEs, AEs leading to discontinuation, AEs leading to dose reduction, and AEs leading to dose interruption. Analyses were conducted using the 18-month (March 2020) or 3-year data cut (September 2021) for CROWN, to align with the follow-up for each outcome from the ALEX, ALESIA and ALTA-1L trials. A list of prespecified treatment effect modifiers (TEMs) was identified following consultation with clinical experts, a targeted literature review, and a quantitative evidence assessment. The following variables were selected for matching: Asian ethnicity, ECOG PS, and brain/CNS metastases at baseline. Sensitivity analyses included prior chemotherapy and brain radiotherapy as additional matched variables. It is unclear whether other variables, such as age, sex, and smoking status were considered

during the selection of TEMs; the exclusion of any variables considered, and their reasons for their exclusion, were not reported.

The results of the MAICs are summarised in CS Section B.2.9.5 and Garcia (2024).[33] The company concluded that the results of the MAIC analyses are aligned with the current CS NMA results, demonstrating that imbalances in the percentage of brain metastases between trials did not greatly impact the results of the NMA (CS, Document B, p86).

The EAG agrees with the company that the results of the MAICs are generally aligned with the current CS NMA results, showing similar effect estimates for PFS (INV and BICR) and IC-TTP but some variation in the effect estimates generated in the MAICs and CS NMAs for safety outcomes.

However, the reporting of the methods of the MAIC was insufficient to assess the validity of the process used to select the TEMs, and whether the TEMs selected for adjustment were appropriate. The EAG does not consider that the general alignment of the MAICs and CS NMA results provide conclusive evidence regarding whether the presence of brain metastases modifies the treatment effect of lorlatinib compared to alectinib or brigatinib. Furthermore, the omission of OS from the MAICs means that the potential impact of differences in TEMs on OS is uncertain. However, adding population adjustments to the OS NMA would have been unlikely to address current uncertainties associated with the immaturity of the OS data. MAICs did not include the 5-year data cut for PFS from CROWN, which limits its relevance to the decision problem. Additionally, the violation of the PH assumption for PFS and OS (as discussed in Section 3.4.2.1) means that population adjusted HRs are also unlikely to address the uncertainty in the NMA results.

3.4.5.2 Flatiron Health Research Database analysis

In response to clarification, the company provided an addendum including a retrospective analysis of observational data from the US Flatiron Health Research Database (FHRD).[34]

The objectives of this analysis included:

- To examine treatment sequencing from 1L to 2L TKIs.
- To summarize unadjusted real-world overall survival (rwOS) and real-world progression-free survival (rwPFS) for patients who received alectinib or brigatinib at 1L.
- To summarize adjusted (weighted) rwOS and rwPFS for patients who received alectinib or brigatinib at 1L by matching the baseline characteristics to the CROWN study population using a MAIC.

To adjust for known confounders, analyses were conducted using propensity score matching for the following covariates: age, sex, race/ethnicity, ECOG PS, histology and CNS metastases. IPD obtained from FHRD was matched to baseline aggregate data extracted from CROWN [16].

Data from a cohort of 272 ALK-positive metastatic NSCLC patients were extracted from FHRD. The most common 1L treatment was alectinib (88.2%). Only 5% received brigatinib, therefore insufficient data were available to estimate rwPFS and rwOS for brigatinib, 6.2% received either crizotinib or ceritinib. No patients received lorlatinib 1L.

Compared with CROWN, patients in FHRD receiving alectinib were slightly older (median 63.0 vs. 61.0 years), more often white (71.7% vs. 48.6%) and had a higher proportion of ECOG PS of 2 (12.9% vs. 4.0%). Other baseline characteristics were similar.

Following 1L alectinib, 41.7% of patients received 2L treatment; of those, 64.0% received lorlatinib 2L. Following progression on 1L alectinib, 71.8% received a 2L treatment; of those 72.6% received lorlatinib. The EAG agrees with the company that these values are significantly more reflective of UK practice compared with ALEX and ALESIA reported in CS Document B, Table 25.

Median (unadjusted) follow-up duration for OS for the patients in FHRD was 41.7 months. Median OS in the alectinib 1L cohort was 56.5 months (95% CI 48.7 to NR) prior to adjustment, and 54.0 months (95% CI 37.9 to NR) following adjustment. Median PFS alectinib 1L cohort was 28.5 months (24.5 to 36.4) prior to adjustment, and 26.8 months (95% CI 19.6 to 35.8) following adjustment. Sensitivity analyses suggested that the adjusted analyses were robust. These results suggest that propensity score matching adjustment only had a relatively small impact on alectinib's median OS and PFS estimates.

The EAG considers that a strength of the FHRD analysis is that the use and types of subsequent therapies in the alectinib cohort (notably the proportion of patients receiving lorlatinib 2L) are significantly more representative of UK practice than alectinib trials (ALEX and ALESIA). Appropriate methods were employed to extract relevant data and address the risk of biases associated with selection, missing data and confounding. Appropriate population adjustment methods were employed and both adjusted and unadjusted rwOS and rwPFS KM curves for alectinib 1L from FHRD were broadly comparable with the ALEX trial, although the tails of the alectinib FHRD cohort KM curves were lower than in ALEX (see Company Addendum, Figure 2).

The company acknowledged several limitations of the analysis, including that measurement error and misclassification may have occurred with FHRD, as well as the descriptive nature of the retrospective study design. The EAG considers that further limitations of the FHRD analysis include the fact that no actual indirect effect estimates comparing and alectinib with lorlatinib were provided. However, a MAIC between FHRD and CROWN would have important limitations, notably because it would need to be unanchored due to the limited number of patients receiving crizotinib in FHRD, due to differences in study designs between FHRD and CROWN, and the immaturity of OS CROWN data. Due to insufficient data, the FHRD analysis could not inform the comparison between lorlatinib and brigatinib.

3.4.6 Comparison with published NMAs

3.4.6.1 Design and methods of published NMAs

To compare the company's NMA with published evidence, the EAG conducted a pragmatic search of Pubmed from 2021 onwards for NMAs evaluating TKI inhibitors in ALK-positive NSCLC patients. A recent review of previous NMAs funded by Pfizer was identified.[35] This review of eight previous NMAs [36-42] included evidence for 1L treatments of advanced ALK NSCLC in patients naïve to TKI inhibitors. A summary of the eight NMAs included in the Ou *et al.* (2024) review is presented in Appendix 2 (Section 9.2, Table 36).

CROWN, ALEX, ALESIA and ALTA-1L were included in all the NMAs reported in Ou *et al.* (2024). All NMAs included in Ou *et al.* (2024) also included at least one additional study including one or more interventions outside the scope of this appraisal (crizotinib, ensartinib, ceritinib, or chemotherapy). Most of the NMAs used a Bayesian fixed-effect approach [35, 38-42] or a Bayesian random-effects approach[37, 40]. One NMA used a frequentist fixed-effect approach [36]

All eight NMAs included the J-ALEX trial, which compared a lower dose of alectinib (300mg BID, not licensed for UK practice) to crizotinib and within five of these NMAs, [38-42] a merged alectinib dose node (i.e. 300mg BID and 600mg BID) was included. Therefore, comparisons of lorlatinib and alectinib from NMAs with the combined alectinib dose node are not reflective of NHS clinical practice.

The Ou *et al.* (2024) review of NMAs reported the treatment estimates of lorlatinib versus alectinib and lorlatinib versus brigatinib for the following outcomes: PFS (BICR), IC-TTP, Grade ≥ 3 or 3/4 AE and AEDC. However, Ou *et al.* (2024) did not report PFS (INV) or OS results from the eight NMAs so, where reported, the EAG checked for and where available, extracted results for these outcomes from the NMAs included in the Ou *et al.* (2024) review.

3.4.6.2 Results

PFS and OS results of the 8 NMAs[36-42],) included in the Ou (2024) review, with results of the current CS NMA for comparison are presented in Appendix 2 (Section 9.2, Table 36).

Overall survival

Five NMAs reported results for OS.[37, 39-42] Consistent with the OS NMA results presented in the CS, all NMAs found a numerical difference in OS favouring alectinib over lorlatinib that was not statistically significant and all NMAs found a numerical difference in OS favouring lorlatinib over brigatinib that was not statistically significant. However, all NMAs yielded uncertain estimates, reflected in the wide 95% CrIs, OS data from many studies included in the NMAs, including the CROWN study, was immature and none of the NMAs performed any adjusted analyses to account for treatment crossover or subsequent therapies following disease progression.

Progression-free survival

All eight NMAs reported results for PFS (BICR) and all showed an advantage for lorlatinib over alectinib (which was statistically significant in two NMAs [35, 38] and in the CS NMA) and over brigatinib (which was statistically significant in four NMAs[35, 36, 38, 39] and in the CS NMA). PFS (BICR) effect estimates for lorlatinib compared to alectinib and brigatinib were generally quite similar across the previous NMAs and compared to the CS NMA results; minor differences in the NMA results may be due to differing data inputs (i.e. different included studies and different data cut-offs from those studies), or differences in the modelling approach (i.e. fixed effect or random effect).

None of the NMAs included in the Ou *et al.* (2024) review reported results for PFS (INV). Therefore, no comparison to the PFS (INV) results from the CS NMA is available.

Time to intracranial/CNS progression (IC-TTP)

Two NMAs[35, 41] reported numerically improved IC-TTP for lorlatinib compared to alectinib (which not statistically significant in either NMA but was statistically significant in the CS NMA) and brigatinib (which was statistically significant in one of the NMAs[35] and in the CS NMA). Both NMAs did not specify if IC-TTP was INV-assessed or BIRC-assessed, thus limiting the comparison of these results to the results from the CS NMA.

Grade ≥ 3 AEs

Five NMAs[36, 37, 39, 41, 42] reported Grade ≥ 3 adverse events and one NMA[35] reported Grade 3/4 AEs. All NMAs found that lorlatinib was associated with a numerically increased risk of experiencing ≥ Grade 3 adverse events when compared with alectinib and brigatinib. The increased risk was statistically significant when compared with alectinib, but not against brigatinib. This is consistent with the CS Grade 3/4 AEs NMA result.

Adverse events leading to discontinuation (AEDC)

Two NMAs [35, 39] reported AEDC. Lorlatinib had a numerically lower risk of discontinuation following adverse events compared to alectinib and brigatinib in both NMAs. However, the reduced risks are statistically non-significant. These results are broadly consistent with the CS AEDC NMA result, except that alectinib showed a numerical lower risk of discontinuation following adverse events, though the reduced risk is statistically non-significant.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Due to the exclusion of ALEX in the additional NMA carried out by the company in their response to clarification question A17 to explore the impact of treatment crossover in the ALTA-1L trial (see Section 3.4.4.1), the EAG conducted an additional analysis to further evaluate the relative OS effect of lorlatinib versus alectinib and lorlatinib versus brigatinib including MSM (marginal structural models) and IPCW adjusted OS estimates extracted from the Camidge *et al* 2021[29] publication of the ALTA-1L trial with unadjusted OS data from the latest data-cut offs of the CROWN, ALEX and ALESIA trials.

The EAG used the same approach as the company NMAs, applying Bayesian fixed-effect model code, presented in the CS Appendix N.5 and in response to clarification question A14, which is in line with approaches recommended in Decision Support Unit Technical Support Document (DSU TSD) 2.[43] A summary of the EAG NMA OS results, with unadjusted and adjusted company OS NMA results for reference, is presented in Table 10.

Table 10: Company and EAG NMA results: OS including unadjusted and crossover-adjusted results from the ALTA-1L trial

Comparison: HR (95% CrI)[1]	Unadjusted OS[2]	Adjusted OS (excluding ALEX)[3]	MSM adjusted OS (including ALEX)[4]	IPCW adjusted OS (including ALEX)[4]
Lorlatinib vs. alectinib	1.12 (0.59, 2.11)	1.20 (0.57, 2.52)	1.18 (0.59, 2.10)	1.18 (0.59, 2.11)
Lorlatinib vs. brigatinib	0.89 (0.44, 1.78)	1.44 (0.65, 3.18)	1.44 (0.61, 2.90)	1.56 (0.65, 3.19)

Abbreviations: CrI: Credible interval; HR: hazard ratio; IPCW inverse probability censoring weighting; MSM marginal structural model; OS overall survival

Footnotes: 1. HR<1 indicates an advantage to the treatment versus the comparator; 2. Unadjusted OS presented in CS Doc B, Table 28; 3. adjusted OS presented in response to clarification question A17; 4. adjusted OS EAG analyses.

Source: CS Document B, Table 28, response to clarification question A17, and EAG analyses including MSM and IPCW adjusted OS values from ALTA-1L and OS data from the latest data-cut offs of the CROWN, ALEX and ALESIA trials.

OS results using the unadjusted OS values from ALTA-1L showed a numerical (non-statistically significant) difference favouring lorlatinib over brigatinib and favouring alectinib over lorlatinib. All analyses using the adjusted OS values from ALTA-1L showed a numerical difference in OS favouring alectinib and brigatinib over lorlatinib that was also not statistically significant. The direction of the OS effect of lorlatinib versus alectinib was unchanged whether analyses included unadjusted or crossover adjusted results from the ALTA-1L trial (as expected due to the lack of closed loops in the company NMA). However, the direction of the OS effect (i.e. the direction of the HR of the point estimate) of lorlatinib versus brigatinib changed considerably. These changes indicate that crossover in the ALTA-1L may have an important impact on the OS relative effectiveness of lorlatinib versus brigatinib. The EAG emphasises that these results should be interpreted as exploratory as this analysis does not adjust for confounding of OS due to other subsequent therapies received by patients' post-progression in any of the trials included in the NMAs.

3.6 Conclusions on clinical effectiveness

In this review of TA909, the CS presents evidence on the efficacy and safety of lorlatinib in ALK-positive treatment-naïve NSCLC is primarily from post-hoc analyses from CROWN RCT 5-year data cut for unblinded investigator-assessed outcomes (PFS, intracranial outcomes, response rates) and safety. No new data cuts were presented for OS (18-months) and HRQL (3-years).

The 5-year PFS rate was 60% (95% CI 51 to 68) for lorlatinib, and 8% (95% CI 3 to 14) for crizotinib, reflecting a statistically significant and clinically significant advantage for lorlatinib compared with crizotinib (HR 0.19; 95% CI 0.13 to 0.27). The probability of being free of intracranial progression at 5 years was 92% (95% CI 85 to 96) with lorlatinib and 21% (95% CI 10 to 33) with crizotinib, which was also statistically and clinically significant (HR 0.06; 95% CI 0.03 to 0.12).

At the 18-months data-cut, the median OS was not estimable in either treatment arm. No statistically significant difference in OS was found between lorlatinib and crizotinib (HR 0.72, 95%: CI 0.41 to 1.25). As the 18-month OS data is still very immature, no conclusions can be drawn from this analysis. At the current available data cut, CROWN provides no evidence that the clinically significant PFS benefits from lorlatinib lead to improved OS compared to crizotinib. A subgroup of 30 treatment-naïve patients from the non-randomised Study 1001 provides very limited additional evidence of long-term OS benefit for lorlatinib.

The company NMA indicates that lorlatinib leads to a statistically and clinically meaningful improvement in PFS and IC-TTP but shows no statistically significant difference in OS when compared with either alectinib or brigatinib. In the absence of sufficiently mature OS data, the EAG considers that the extent to which PFS results observed in the CROWN trial may translate into OS benefits relative to alectinib and brigatinib is uncertain. The validity of OS estimates in the NMA is also limited by confounding due to treatment crossover and use of subsequent therapies following progression, and lack of direct trial evidence between lorlatinib, alectinib and brigatinib, and the violation of the proportional hazard assumption. All trials included in the NMA were randomised comparisons against crizotinib, which is an outdated treatment. The NMA did not include HRQL, therefore it is uncertain whether lorlatinib is associated with improved HRQL compared with alectinib and brigatinib. The company NMA shows that the odds of experiencing a Grade 3-4 TRAE are higher with lorlatinib than with alectinib or brigatinib, although the difference between lorlatinib and brigatinib is not statistically significant; there is no evidence that discontinuation rates due to AE differ significantly between lorlatinib and alectinib or brigatinib. However, the safety NMAs do not include CNS AEs, nor Grade 5 AEs which have been observed with lorlatinib treatment in CROWN. This limits the relevance of the NMAs to the decision problem.

The decision problem includes a comparison of lorlatinib against alectinib or brigatinib in the 1L setting but does not account for subsequent therapies which are likely to impact significantly on OS and other relevant outcomes. The ALK inhibitor treatment sequences used in both arms of the CROWN trial and in comparator trials have very limited applicability to both current NHS practice and to future practice if 1L lorlatinib were to be recommended by NICE. A trial that compares 1L lorlatinib (with eligible patients remaining on lorlatinib after progression) with 1L alectinib (or brigatinib) followed by lorlatinib at 2L would be most applicable to inform NHS practice. However, such a trial is not currently ongoing or planned to the EAG's knowledge.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

The company undertook three SLRs to identify relevant economic evaluations, literature relating to health-related quality of life, and on costs and healthcare resource use for patients with ALK-positive advanced NSCLC. The company provides a detailed report of the methods and results of the SLRs in Appendix G, H, and I of the Company Submission.

4.1.1 Search strategy

The searches were conducted in August 2018 and were updated in November 2019 and were not updated since being undertaken for the TA909 submission. In response to clarification question C2, the company stated that it was unlikely these searches would have yielded additional relevant studies or data. Therefore, the critique of the searches outlined in the TA909 EAG report (pp.52-53) is still applicable, and the EAG is concerned that relevant up-to-date evidence has been missed.

4.1.2 Study selection criteria

The PICOS criteria applied by the company to assess eligibility for inclusion were described in CS Appendix G, Table 21 for the review of cost effectiveness studies, in CS Appendix H, Table 29 for HRQL review, and in CS Appendix I, Table 38 for the cost and resource review. Only studies published over a 10-year period since 2007 in the English language were eligible for inclusion. The population of interest was adult patients with advanced/metastatic ALK-positive NSCLC who were being treated in a 1L setting using interventions listed in CS Appendix G, Table 21 versus any chemotherapy. There were no specific inclusion criteria in terms of interventions and comparators received in the HRQL and cost reviews. Two reviewers independently assessed studies based on title and abstracts against the study selection criteria, with discrepancies checked by a third reviewer. Full-text screening was performed independently by two reviewers. Data were extracted by one reviewer and checked against the original source by a second reviewer.

The EAG considers the selection criteria and the company's methods of assessment against these criteria generally appropriate. However, the limit on language and date (effectively 2007-2019) may be overly restrictive and may have led to relevant, recent studies being omitted from the reviews.

4.1.3 Studies included in the cost effectiveness review

Twenty records were judged to meet the inclusion criteria of the cost effectiveness review from the main searches, with an additional seven records from the searches of international HTA body websites, and three further studies from the searches of conference proceedings. A total of 25 unique studies were extracted from the 30 included records, results of which are presented in CS Appendix G, Table 21. The EAG concurs with the company's conclusion that there were no more relevant

economic models to inform the present decision problem identified in the review. However, the EAG notes that several studies addressing the cost effectiveness of lorlatinib as a 1L in a non-UK setting have been published between November 2021 and the submission date (September 2024).[44-46]

Thirteen articles were included from the main searches of HRQL studies, six from the HTA search, and nine from the bibliography search, yielding 17 unique studies. Thirteen of these studies were economic models, the results of which are presented in CS Appendix H, Table 30.

Twenty-four unique studies were judged to meet the inclusion criteria in the cost and resource review. The results are presented in full in CS Appendix I, Table 39.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 11 summarises the EAG's assessment of whether the company's economic evaluation meets the NICE reference case and other methodological recommendations.

Table 11 NICE reference case checklist

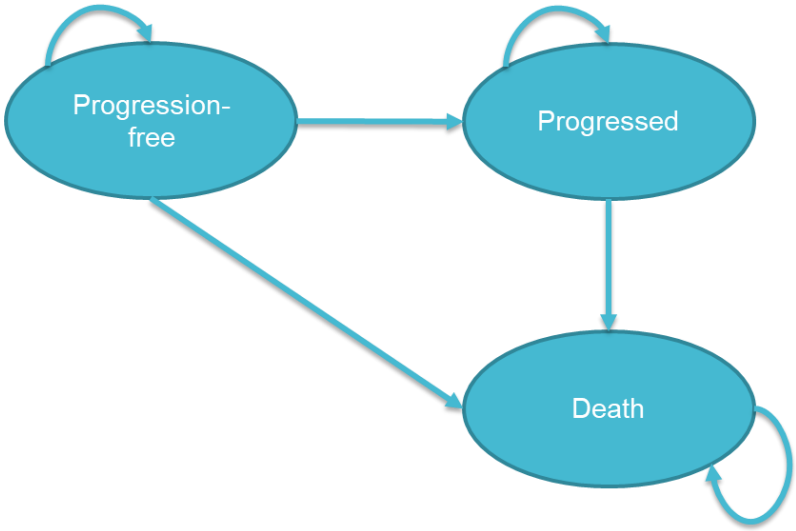
Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALY benefits for treated individuals were considered.
Perspective on costs	NHS and PSS	NHS and PSS costs were considered.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Fully incremental cost-utility analysis was implemented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model uses a 30-year time horizon. In the company's base case analysis this is likely adequately long to capture lifetime costs and benefits though a non-negligible proportion of patients are assumed alive at the end of the model time horizon.
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review to identify relevant data sources.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	EQ-5D-5L data were collected in the CROWN trial. These data were cross-walked to EQ-5D-3L using the Hernández-Alava *et al.*[47] mapping algorithm.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D data was directly obtained from patients in the CROWN trial. Unlikely to adequately represented HRQL in progressed disease.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs based on UK sources including eMIT, BNF and NHS reference costs. Resource use based on previous appraisals and clinical advice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits were discounted at 3.5% per annum.
Abbreviations: BNF, British national formulary; EQ-5D, EuroQol 5-Dimension scale standardised instrument for use as a measure of health outcome; eMIT, electronic market information tool; HRQL, health related quality of life; PSS, personal social services; QALYs, quality-adjusted life years;		

4.2.2 Model structure

The company submitted a three health state model to evaluate the lifetime cost effectiveness of lorlatinib monotherapy for the treatment of ALK-positive NSCLC. The three mutually exclusive health states are comprised of the following: (i) progression-free (PF) health, (ii) progressed disease (PD), and (iii) death, which is an absorbing state (Figure 3).

Figure 3: Three-state model structure



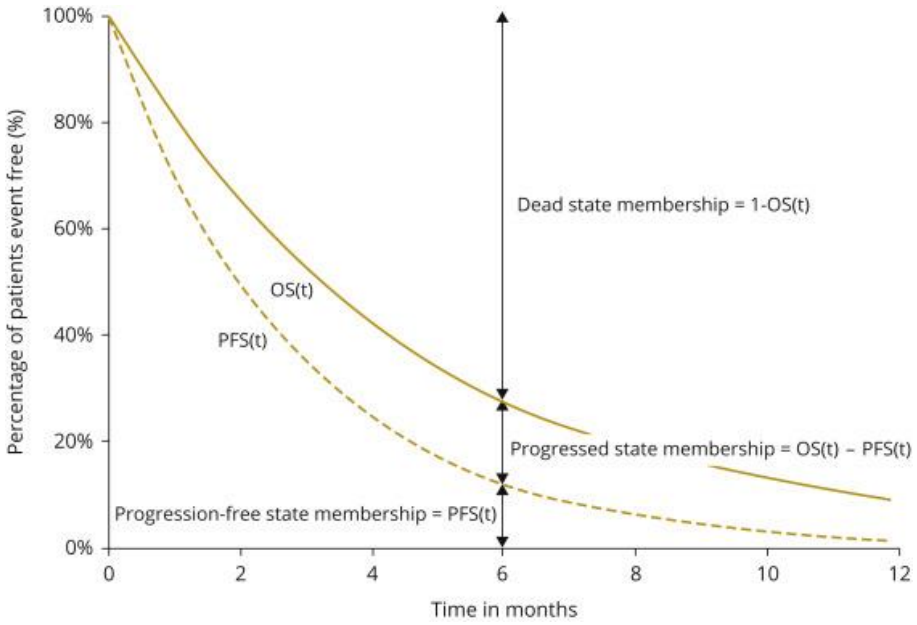
Source: CS, Document B**,** Figure 18

Patients enter the model in the PF state and in each 30-day cycle, patients can remain in this state, progress into PD, or progress to death. Patients cannot return to the PF state once in the PD state. Further to the above, the PF health state is divided into on and off-treatment periods. This allows the modelled patients to discontinue treatment prior to progression and enables the model to capture the HRQL effects of being on treatment. All patients in the model were assumed to be ALK-positive, as testing was assumed to be performed prior to 1L treatment.

Modelled patients were allocated to receive either lorlatinib or one of two comparator treatments: alectinib or brigatinib. Health state occupancy was determined using two alternative approaches depending on the modelled treatment arm.

Firstly, in the lorlatinib arm, a partitioned survival model (PSM) was used in which state occupancy is directly determined by the estimates of survival over time. The proportion of patients in the PF state is based on PFS estimates, while the proportion of patients in the death state is 1 minus the OS estimate. Membership of the PD state is calculated as the difference between the proportion of patients in the PFS state and the death state. A central characteristic of the PSM approach is that OS is determined directly by the model OS curve and independently of progression status. Figure 4 provides a visual illustration of the calculation of model health state occupancy in a PSM model.

Figure 4 Partitioned survival model estimation of health state occupancy



Abbreviations: OS, overall survival; PFS, progression-free survival; (t), time

In the comparator arms (alectinib or brigatinib) state occupancy was determined using a state transition model (STM). Under this approach, transition probabilities between health states are explicitly modelled and define the proportion of patients moving to each health state within a given model cycle. Health state occupancy is therefore the product of three transition probabilities: i) the probability of progression, ii) the probability of death in the PF health state, and iii) the probability of death from the PD health state. In STM, OS is determined by all three transition probabilities and is a function of time spent in the PF and PD health states.

Table 12 summarises the clinical data utilised to inform the economic analysis, including the sources employed in scenario analyses that consider alternative model structures. The EAG highlights the incorporation of supplementary data from PROFILE 1001/1005 and cohorts EXP3B-5 of Study 1001 to inform 2L outcomes. Is unclear how these studies were selected whether any kind review process was undertaken to identify alternative. An overview and critique of these studies are presented in Appendix 2 and 3 (Section 9.2 and 9.3). The EAG also notes that although crizotinib is not a comparator within the model, data from the crizotinib arm of the CROWN trial is used as a reference

to anchor outcomes for the alectinib and brigatinib models. For more detailed information regarding the clinical data used in the economic analysis, refer to Section 4.2.6.

Table 12 Summary of data used to determine health state occupancy

	PSM approach		STM approach	
Health state	**Lorlatinib arm***	**Alectinib/brigatinib arm**	**Lorlatinib arm**	**Alectinib/brigatinib arm***
Progression-free Survival	CROWN Trial - lorlatinib arm	CROWN trial – crizotinib arm and PFS HR (NMA)	CROWN Trial - lorlatinib arm	CROWN trial – crizotinib arm and PFS HR (NMA)
Progressed Disease	OS minus PFS		PROFILE 1001/1005	Study 1001 (EXP3B-5) and PROFILE 1001/1005
Overall survival	Pooled data from CROWN Trial - lorlatinib arm and Study 1001 (EXP1)	CROWN trial – crizotinib arm and OS HR (NMA)	Sum of PFS and PD	

Abbreviations: HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PD, progressive disease;

* Company base case approach

Points for critique

Differential modelling approach

The EAG is concerned with the use of a differential modelling approach in the intervention and comparator model arms. As described above, a PSM and STM approach adopt fundamentally different assumptions and derive OS differently. Except in a limited number of cases (i.e. within-trial analyses or where survival data has been fully observed, which do not apply to this appraisal) a PSM and an STM will produce different results.[48] This is particularly likely in scenarios where survival functions are based on the extrapolation of incomplete observed data or there is uncertainty regarding the relationship between PFS and OS, both of which apply to the current context. Moreover, in the context of the current appraisal, the modelling approach also determines the data used to populate the model, as summarised in Table 12, meaning that the model's predictions depend on the structure adopted.

The company's justification of using a different modelling approach (response to clarification question B1) emphasised scenario analysis presented in the CS in which an STM approach is also used in the lorlatinib arm. However, the company considered this scenario pessimistic as it relies on PROFILE 1001/1005 evidence to inform post-progression survival (PPS) in the lorlatinib arm. Clinical advice highlighted that longer PPS following lorlatinib would be expected than observed in the PROFILE 1001/1005 study, where crizotinib was the 1L treatment (see Section 9.3).

The EAG acknowledges that there are limitations associated with PROFILE 1001/1005 but notes that the lack of generalisability of the CROWN trial to NHS practice necessitates some suboptimal assumptions. Regardless of which modelling approach is adopted (PSM or STM), the EAG considers it inappropriate to use a different modelling approach in each arm as differences in both the underlying assumptions and data used to populate the model will necessarily bias predictions.

PSM vs STM

PSM and STM are widely accepted approaches to oncology modelling, and both have been accepted in previous NICE TAs. In the present context, each approach is associated with specific advantages and disadvantages, and it is necessary to consider these in judging the most appropriate approach.

The primary advantage associated with the PSM approach is that comparisons are based on randomised evidence. As such, modelled relative treatment effects reflect those observed in the relevant trial evidence, namely, CROWN, ALEX, ALESIA, and ALTA-1L. The main disadvantages of the PSM approach relate to the available OS data. As noted in Section 3.2.1.2, CROWN OS data is immature and is likely not reflective of NHS outcomes as the 2L treatments received by patients do not reflect the NHS pathway. Moreover, NMA estimates of relative effectiveness are similarly subject to extensive confounding bias due to differences in the subsequent treatments received within the comparator trials (Section 3.4.1.2). A PSM approach also means there are significant differences between modelled outcomes and modelled costs which may introduce further bias.

The main advantages associated with an STM approach are a greater emphasis on PFS where more mature data are available, which is not subject to the confounding biases from subsequent treatment. An STM approach also allows for alternative data, including non-randomised evidence or real-world evidence, more representative of the NHS treatment pathway, to be incorporated into the model, and can therefore better reflect current NHS practice regarding 2L treatment options. The main disadvantage associated with the STM approach is that modelled OS is no longer based on a randomised comparison and therefore comparisons of OS remain subject to confounding bias due to imbalances in patient characteristics. Further, the evidence available to inform survival in the PD health state is limited and the available studies do not fully reflect the modelled pathway.

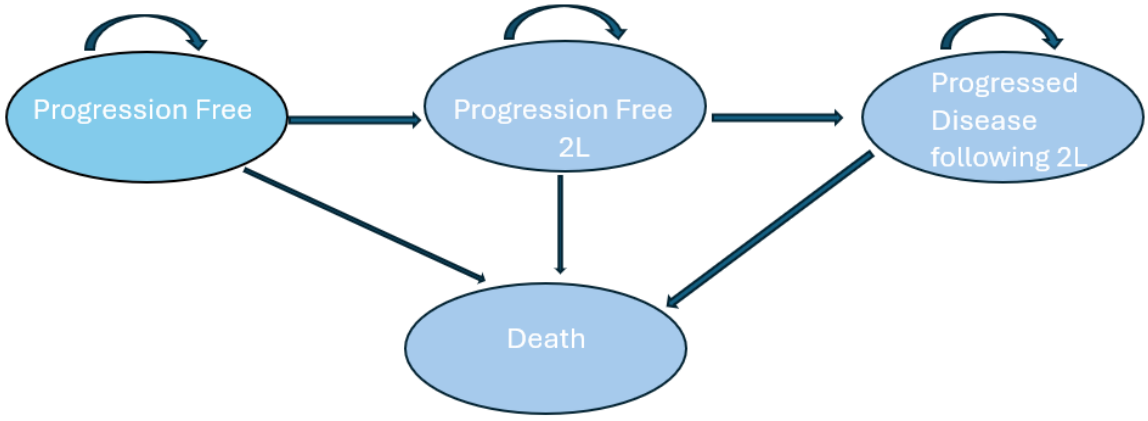
On balance, the EAG considers that the STM approach represents the most appropriate approach because of the substantive issues with the available OS data from CROWN and the NMA, which neither reflects UK practice nor provides reliable estimates of relative effectiveness. The PSM also produces predictions that appear to lack clinical validity. For example, the PSM predicts that patients in the alectinib/ brigatinib model arms spend substantively longer in the PD health state (51.25 months) than they do in the PFS health state (29.57 months). The EAG base case therefore uses an STM approach in both the lorlatinib and comparator arms. EAG scenario analysis is, however, also presented using a PSM approach to explore the impact of these assumptions, see Section 6. The EAG emphasises the considerable uncertainty surrounding both approaches, due to the significant limitations of the data used to inform the model. Cost effectiveness estimates produced by either approach should be considered with caution.

No explicit modelling of 2L outcomes

The economic model is structured around a three-state approach, commonly used in oncology appraisals. However, the EAG considers that the decision problem in this appraisal differs from typical oncology evaluations, as it focuses on comparing treatment sequences, with significant emphasis on the effectiveness and cost effectiveness 2L treatment options, see Section 2.3. The company's base case reliance on a three-state model limits its ability to fully account for the impact of 2L treatments within the catch-all PD health state.

The EAG suggests that adopting a four-state model, which includes a new progression free 2L (PF 2L) state, may be beneficial and improve transparency. This proposed alternative differs from the four-state models considered in TA670 and TA909, which focused on distinguishing between non-CNS and CNS progression within separate health states. The proposed PF 2L state would subdivide the current PD health state into two phases: PFS 2L and PD (following 2L treatment) see Figure 5 EAG proposed four-state model Figure 5.

Figure 5 EAG proposed four-state model



This alternative four-state model would have several advantages over the current model. Firstly, it would allow the model to capture both the health costs and HRQL associated with being on 2L treatment. For instance, we might expect an improved HRQL in patients receiving 2L treatment, especially when receiving a 2L ALK inhibitor such as lorlatinib.

Secondly, it would enable the model to impose structural relationships between the time spent on 2L treatment and health state occupancy. This is particularly important because 2L lorlatinib is significantly more expensive than other options, and in the current model, time on treatment (ToT) is modelled independently of time in the PD state, see Section 4.2.4. This leads to sensitivity in cost effectiveness estimates, as assumptions regarding time spent in the PD state greatly affect model predictions. For example, scenarios using the PSM approach to model outcomes in the alectinib and brigatinib arms increase the time spent in the PD state but do not affect acquisition costs for 2L lorlatinib.

Thirdly, it would allow for a more transparent evaluation of the relative health benefits of 2L treatments that better reflects the NHS treatment pathway. This approach would allow structural relationships to be imposed that make it more explicit where health benefits are being generated i.e. those associated with 1L treatment and those associated with 2L treatment. This would help inform extrapolations of survival data used to inform the current PD health state and may be particularly important due to the limitations associated with data used to inform survival in this health state.

The EAG is unable to implement a revised model structure within the time frame of the appraisal but considers this could be implementable given the current data and would be informative for decision making.

4.2.3 Population

The modelled population is based upon the CROWN phase 3 trial data (n=296) and considers adult patients with ALK-positive advanced NSCLC who had not been previously treated with an ALK inhibitor. This population fully aligns with the marketing authorisation lorlatinib and the NICE scope. The baseline characteristics of the modelled population are presented in Table 13. Age and sex were used to inform general population mortality rates as well to adjust the utility values for HRQL in the model as explained in Section 4.2.7. Patient weight and height were used to inform dosing associated with weight- and body surface area-based therapies.

Table 13 Baseline patient characteristics of the modelled population

Characteristic	**Modelled population**
Age	57.38 years
Sex	59.12% female
Weight	65.36 kg.
Height	164.13 cm
Source: Company model	

Points for critique

Clinical advice to the EAG supported the CROWN trial population being broadly representative of practice. The EAG's clinical advisers raised two minor points. Firstly, the CROWN study excluded patients who had received any prior systemic NSCLC treatment. This is not fully representative of the UK population where a minority of patients will receive chemotherapy while awaiting confirmation of ALK status. Secondly, the population may be older than the patients seen in practice noting that ALK-positive patients tend to be younger than the general NSCLC population. These minor points aside the EAG is satisfied that the modelled population sufficiently aligns with the eligible population in NHS practice and considers the modelled patients characteristics reasonable.

Trials included in the NMA

As highlighted in Section 3.4.1.1, the EAG is concerned about the comparability of the trials included in the NMA and notes differences in the proportion of patients with CNS metastases at baseline.

While the presence of CNS metastases in NSCLC is generally associated with a poor prognosis, it remains uncertain whether CNS metastases are a treatment effect modifier in ALK-positive NSCLC which might impact the relative treatment effects generated by the NMA.

4.2.4 Interventions and comparators

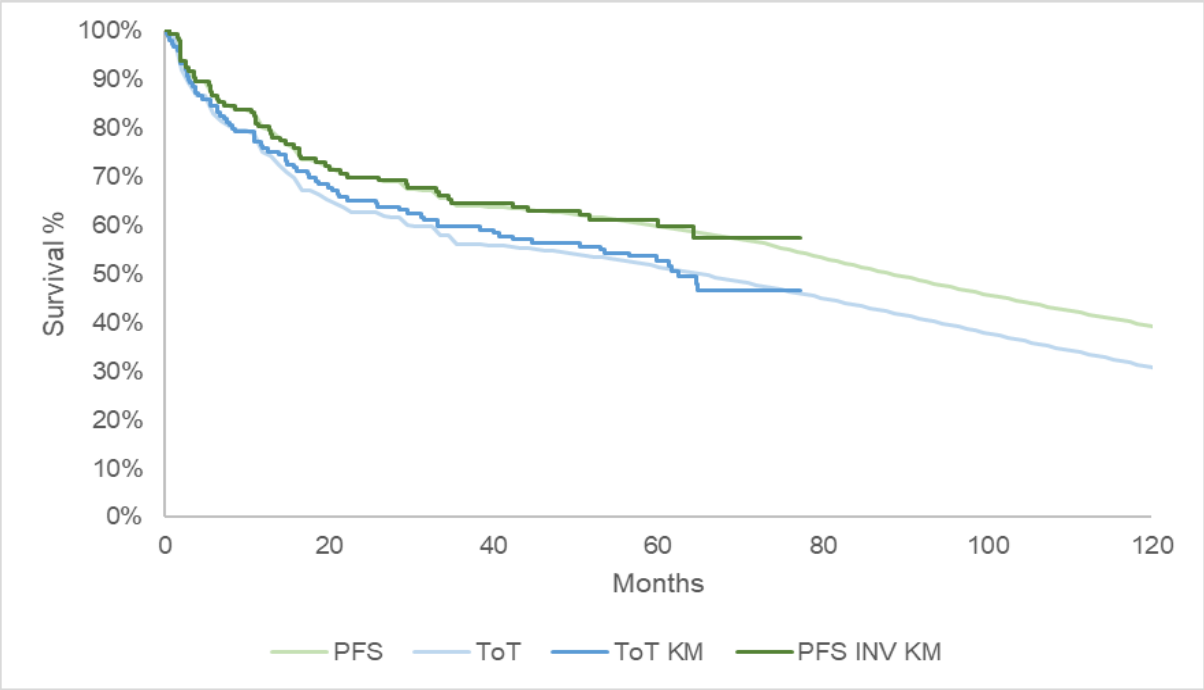
The modelled intervention and comparators aligned with current and anticipated NHS practice should lorlatinib be recommended as 1L treatment option, see Section 2.2, Figure 1. The modelled intervention consists of treatment sequencing comprising lorlatinib 1L followed by chemotherapy with two comparator sequences comprising either alectinib or brigatinib 1L followed by lorlatinib 2L followed by chemotherapy 3L. The modelled decision problem can therefore be surmised as a decision between lorlatinib as 1L treatment compared to lorlatinib as 2L treatment.

4.2.4.1 Lorlatinib

In accordance with the marketing authorisation extension granted on September 23, 2021, the modelled intervention is lorlatinib monotherapy, administered as either 100 mg or 25 mg film-coated tablets, for the treatment of adult patients with ALK-positive advanced NSCLC not been previously treated with an ALK inhibitor.

The modelled ToT for lorlatinib is based on data from the CROWN trial, utilising information on both ToT and PFS (INV). The company employs a Cox regression model to estimate a HR that defines the relationship between ToT and PFS, which is then used in the model to calculate ToT (CS, Section B.3.3.5). The company justifies this approach by noting that observed ToT is consistently shorter than PFS (INV; Figure 6), attributing this shortfall to the longer duration of lorlatinib treatment compared to earlier-generation ALK inhibitors, which the increases the likelihood of discontinuation of lorlatinib. Clinical advice to the company validated this methodology; however, the company also acknowledged dissenting opinion from one clinical expert, who suggested that patients are typically treated with lorlatinib until progression.

Figure 6 Extrapolated PFS INV and ToT vs Kaplan–Meier curves from CROWN



Abbreviations: INV, investigator assessed; KM, Kaplan–Meier; PFS, progression-free survival; ToT, time on treatment.
Source: CS, Document B, Figure 30

Importantly, the model does not allow for treatment beyond progression. The company emphasises that although the CROWN trial protocol and market authorisation permitted treatment beyond progression, the observed ToT data does not support its use in this context. Additionally, the company argues that while treatment beyond progression was observed in Study 1001 in the 2L setting, these findings are not generalisable to the 1L setting, where treatment duration is significantly longer. The company, however, provides functionality in the model to incorporate progressed on-treatment duration. In these scenarios, data from a subgroup of patients in Study 1001 (cohort unknown) who achieved a best overall response of either complete response, partial response, or stable disease were used to assess the duration of treatment beyond progression. Of these patients, 56 out of 74 continued to receive lorlatinib following progression, with a median additional treatment duration of 5.7 months (95% CI: 0.8 to 32.7 months). This scenario aligns broadly with the committee-preferred assumptions in TA909.

Subsequent treatment is assumed to comprise 2L chemotherapy consisting of pemetrexed plus cisplatin for 6.30 weeks based on the median ToT observed in ASCEND-5. Pemetrexed is modelled at a dose of 500 mg/m^2 at a mean body surface area of 1.73m^2 while cisplatin is modelled at a dose of 75 mg/m^2 at a mean body surface area of 1.73m^2 for a maximum of 3 treatment cycles. The chemotherapy duration was obtained from the ASCEND-5 trial of chemotherapy and crizotinib,[49] as described in Section 4.2.4. No 3L treatment options was modelled in the lorlatinib arm.

4.2.4.2 Comparators

The model evaluates comparator regimens in line with the NICE scope consisting of 1L treatment with either alectinib or brigatinib. CS Document B, Table 1 outlines that marketing data indicates that alectinib is the most commonly used 1L treatment comprising approximately 80% of the market and the company therefore considers alectinib to be the main comparator.

Aligning with its marketing authorisation, alectinib was modelled as a BID dose of 600 mg (total daily dose of 1200 mg). Similarly, brigatinib is modelled at a once-daily dose of 180 mg. Contrasting with the approach adopted for lorlatinib, ToT was assumed to be equal to PFS (i.e. HR=1). The company justifies this approach noting that observed PFS from the respective pivotal trials (i.e. ALEX and ALTA-1L) almost perfectly aligns with ToT (CS, Section B.3.3.5).

The CS did not include crizotinib or ceritinib as comparators in the economic analysis as these are no longer in use on the NHS and have been displaced by more effective 2nd generation ALK inhibitors. The crizotinib arm of the CROWN trial is, however, used as reference arm to which relative treatment effects are applied, and the economic model includes functionality to assess include crizotinib as a comparator.

Subsequent treatment modelled following alectinib and brigatinib included both 2L and 3L treatment. Treatment at 2L comprised lorlatinib monotherapy (100 mg per day) for 64.36 weeks with treatment duration based on the mean ToT in Study 1001 (cohort unknown). Treatment at 3L comprised chemotherapy and was modelled as per the lorlatinib arm consisting of pemetrexed plus cisplatin for 6.30 weeks.

Points for critique

Time on treatment

The EAG is concerned by the company's approach to modelling ToT and notes that this deviates the company's approach in TA909 where ToT was assumed to be equal to PFS across all treatment arms in the company's base case, a position that the EAG and committee in TA909 found reasonable.

While the EAG acknowledges that the company's approach is consistent with the clinical data from the CROWN trial used to inform health state occupancy (PFS and OS) and that ToT data undercuts observed PFS, there are several reasons to believe that ToT as observed in CROWN will not reflect NHS practice. The EAG considers that decisions to discontinue treatment reflect clinical experience of managing AEs associated with lorlatinib, knowledge of the efficacy and the availability of 2L treatment options and are context-specific; 50% of progressed patients received an ALK inhibitor as 2L treatment option in CROWN following lorlatinib, see Table 25 of the CS for a breakdown. At the time of the CROWN trial, clinical experience of using lorlatinib would have been very limited unlike at present where lorlatinib is established as 2L treatment option in the NHS, this is likely to mean that clinicians are better at managing AEs which might otherwise lead to discontinuation. Similarly,

clinicians are more aware that lorlatinib is a highly efficacious treatment and are therefore likely to continue lorlatinib treatment for patients who are receiving benefit. The 2L treatment options available to patients in the CROWN trial also differ substantively from those currently available on the NHS and include 2nd generation ALK inhibitors which are not available in the NHS where only chemotherapy is available. These factors all imply that ToT will be longer in NHS practice than observed in the CROWN trial.

Furthermore, the EAG also has more pragmatic concerns with the company's approach. Firstly, if we accept the company's approach of applying a HR to modelled PFS, then the estimation of this HR should use PFS (BICR) rather than PFS (INV). As outlined in the CROWN trial protocol, decisions on discontinuation of treatment were based on progression events evaluated by BICR and not investigators. It is therefore inappropriate to compare the two evaluating any difference between PFS and ToT using PFS (INV). The EAG, however, notes that PFS (BICR) and PFS (INV) are therefore use of PFS BICR is likely to have limited impact on the estimated HR.

Secondly, the company estimation of ToT in the lorlatinib arm only is inconsistent and does not reflect the fact that ToT does not perfectly align with PFS in either ALEX (alectinib), or ALTA-1L (brigatinib). In ALEX, ToT also undercuts PFS, reflecting that a proportion of patients discontinued treatment due to AEs and other tolerability issues. In ALTA-1L, time on treatment exceeds PFS, but this is because ALTA-1L permitted treatment beyond progression, where ALEX did not. The EAG notes that a higher proportion of patients in ALEX and ALTA-1L discontinue treatment due to AEs than in CROWN (11% alectinib and 12.5 % brigatinib vs. 7.4% lorlatinib), i.e., the observed data suggests that more patients are likely to discontinue treatment prior to progression when receiving alectinib and brigatinib compared with lorlatinib.

Thirdly, the company's model predicts a large and potentially clinically implausible difference between the mean ToT and PFS. According to the base case, the mean PFS is estimated at 80.3 cycles (6.51 years), while the mean ToT is 68.5 cycles (5.62 years), suggesting a 12-month gap between when patients stop treatment and disease progression. Additionally, this implies that no patients will continue treatment beyond progression, which as described below, is likely to occur in practice given the wording of the marketing authorisation.

Reflecting these concerns, the EAG preference is to assume ToT is equal to PFS across all treatments. While this is not fully in line with the observed data it is likely to best reflect clinical practice and represents a consistent approach ensuring a fair comparison.

Treatment beyond progression

The company's base case analysis, consistent with the observed ToT in the CROWN trial, assumes that patients are not treated beyond progression. However, this assumption conflicts with the MHRA marketing authorisation for lorlatinib, which states that patients may continue treatment "as long as

they derive clinical benefit without unacceptable toxicity."[50] Furthermore, clinical advice to the EAG indicates that some patients are expected to be treated beyond clinical progression, in line with historical practice for other TKIs used to treat ALK-positive NSCLC. The EAG also highlights that in TA909, clinical advice to the committee suggested that treatment beyond progression was common in NHS practice. Previous TAs for crizotinib, ceritinib, and brigatinib have also all assumed treatment beyond progression.[4, 6, 51]

In response to clarification question B10, the company emphasised that its base case assumptions are consistent with TA536 and TA670, where trial-observed ToT data were used to inform the model. The company also suggested that only a minority of patients would receive treatment beyond progression, citing evidence from an unpublished report.[13] Furthermore, the company argued that this implies an average of only 1.14 months of treatment beyond progression, with a limited impact on cost effectiveness estimates.

The EAG does not consider these justifications appropriate or an accurate reflection of decision making in the previous appraisals. While it is accurate that previous appraisals accepted the use of observed ToT data, this does not capture the full context in which these decisions were made. In TA406 (crizotinib), TA500 (ceritinib), and TA670 (brigatinib), treatment beyond progression was recognised as occurring in clinical practice, and this was modelled using observed ToT data. In all of these cases, the data demonstrated clear evidence of treatment extending beyond progression.

The only appraisal of a 1L ALK inhibitor where treatment beyond progression was not assumed is TA536 (alectinib). In that instance, treatment beyond progression was not allowed in the ALEX trial, and unlike the other agents, the alectinib SmPC does not permit treatment beyond progression.

Additionally, the EAG disagrees that only a minority of patients would receive treatment beyond progression. The calculations presented in the company response to clarification question B10 misrepresent the proportion of patients who received treatment beyond progression in Study 1001 (whole population). According to the Study 1001 CSR (May 2017 data cut), 78% (89 out of 114) of patients, i.e. the majority, who experienced progression received treatment beyond progression.

While the EAG acknowledges that the modelled base case analysis is consistent with observed ToT in CROWN, the clinical advice to the EAG and previous NICE precedent on this issue suggest that it is likely that treatment beyond progression will occur in clinical practice. Given the available evidence, the EAG considers it important to consider the uncertainty associated with the current assumption and therefore, presents additional scenario analysis in Section 6, in which treatment beyond progression is permitted.

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide,[52] the company's base case analysis adopted an NHS and Personal Social Services (PSS) perspective and discounted costs and benefits at a rate of 3.5% per annum. The impact of alternative discount rates was not explored in the analysis.

A lifetime horizon of 30 years was chosen to capture all relevant differences in costs and benefits between comparators. The use of a 30-year lifetime horizon is considered broadly appropriate by the EAG, and necessary to account for the claimed survival gains associated with lorlatinib which are predicted to extend beyond 20 years in the company's base case analysis.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Sources of efficacy data used in the economic model

As described in Section 4.2.2, the company base case model structure is based on three health states progression-free survival, progressed disease, and death. In the lorlatinib arm, transitions are modelled using a PSM approach informed by survival analysis of PFS and OS. In the alectinib and brigatinib model arms, the company base case transitions are modelled using an STM approach and informed by survival analysis of PFS and PPS.

4.2.6.2 Progression-free survival

Survival outcomes for PFS for lorlatinib and crizotinib were based on data from the CROWN trial using PFS (INV) from the October 2023 data cut, extrapolated beyond the 5-year follow-up. PFS on alectinib and brigatinib was calculated by adjusting the crizotinib curve from the CROWN trial using the HR for PFS (INV) between crizotinib and each drug from the NMA, see Table 7. In the alectinib and brigatinib arms only, consistent with the STM approach, a proportion of PFS events were assumed to be death events. This was informed by data from CROWN where 4.35% of PFS events for crizotinib were death events.

The company base case used different approaches to extrapolate PFS in the lorlatinib and comparator arms. This was primarily justified based on distinct hazard trends in the lorlatinib arm and the implausibility of survival predictions using standard parametric approaches. To address these limitations, the company explored a wide range of alternative extrapolation methods. These included mixture cure models, flexible spline models, response-based models, and piecewise extrapolation with cut points at 23 and 36 months (CS, Section B.3.3.2.1). The evaluation of these alternatives was primarily driven by the clinical plausibility of the predictions, leading the company to reject most of these methods. Of these alternatives, the company considered a 36-month piecewise approach to offer the most plausible predictions and utilised this extrapolation approach in its base case.

A piecewise extrapolation approach (as implemented by the company) segments the observed PFS data into two pieces such that a parametric function is fitted to the tail of the observed data following

the cut point; before this point, the observed KM data is used directly. The company explored the standard range of alternative parametric models fitting them to the observed data beyond 36 months and selected a Weibull model in its base case analysis. Selection of the Weibull function was based on clinical advice with the gamma also considered a plausible alternative; other parametric models were considered to provide implausible predictions. The Weibull curve had the 2nd best statistical fit in terms of AIC and BIC, though differences in fit statistics are small. It is also the 2nd most pessimistic extrapolation, resulting in 18.5% of patients remaining progression-free at 30 years.

CS Document B, Table 39, 40 and 41 present landmark analyses of the predictions generated by each parametric model for PFS at time points between 1 and 30 years, considering both standard parametric models and piece-wise models. Figure 7 and Figure 8 provides a graphical comparison of these extrapolations.

Figure 7: PFS (INV) for lorlatinib – standard parametric curves

Abbreviations: INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.
Source: CS, Document B, Figure 19

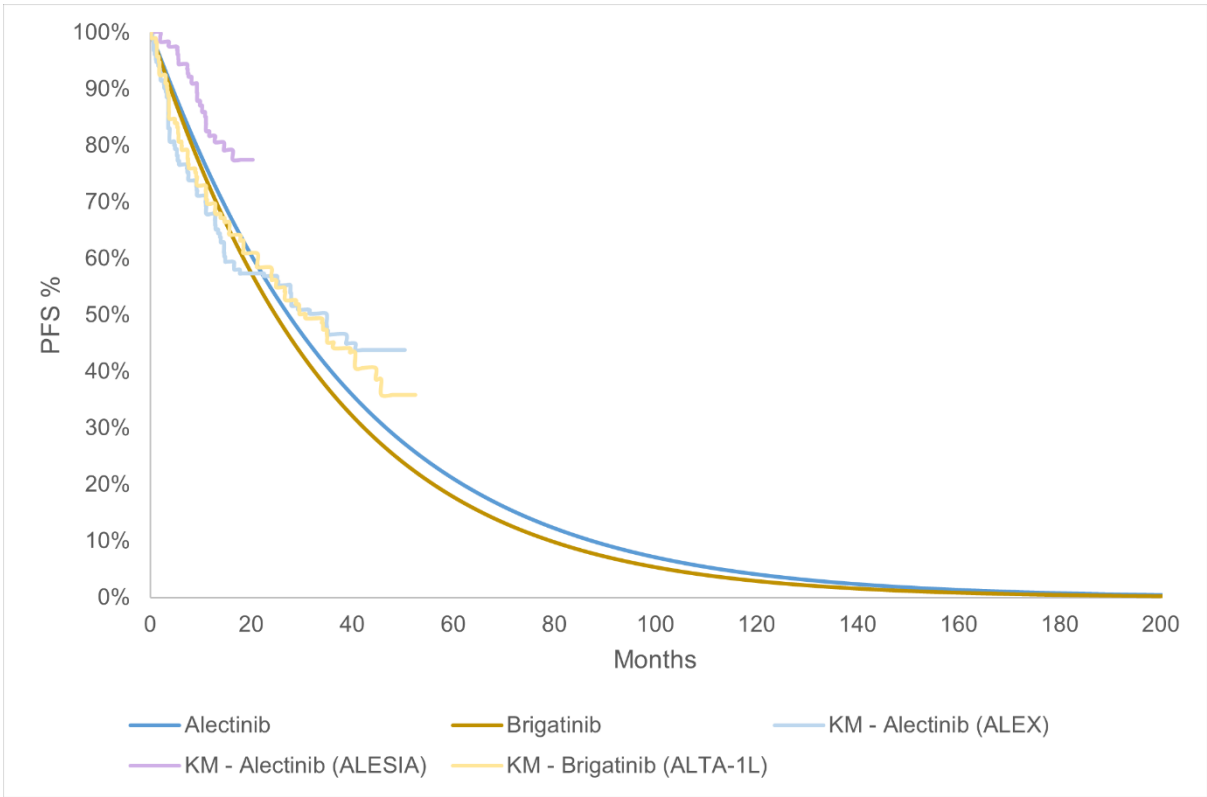
Figure 8: PFS (INV) for lorlatinib – 36 months piecewise

Abbreviations: INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.
Source: CS, Document B, Figure 21

For "consistency" (CS, Document B, p120), a Weibull model was also applied to the crizotinib PFS from CROWN. This was, however, applied as a standard parametric model fitting to the whole KM curve rather than as a piecewise model. The EAG notes that this distribution has a particularly poor statistical fit to the data, ranking last (see CS, Document B, Table 38). Further landmark analysis comparing the proportion of patients remaining progression-free on crizotinib across each of the modelled distributions, shows the Weibull function to be amongst the most pessimistic resulting in no patient remaining progression-free beyond 10 years (CS, Document B, Table 42).

Evaluation of survival predictions for alectinib and brigatinib similarly appear to demonstrate particular pessimistic PFS predictions with predicted PFS significantly undercutting observed data from the ALEX, ALESIA and ALTA 1L trials, see **Error! Reference source not found.**.

Figure 9 Comparison of PFS extrapolations – alectinib and brigatinib



Abbreviations: INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.
Source: Company economic model

Points for critique

Extrapolations of crizotinib and waning

While crizotinib is not a comparator considered in the economic analysis, the PFS survival data for crizotinib from the CROWN trial plays an important role in the economic model as it provides the reference curve from which estimates of PFS for alectinib and brigatinib are derived and it also informs the hazards applied in the post-waning period (10 years) for all treatments. This latter function of the crizotinib curve is extremely important in determining outcomes in the lorlatinib arm of the model. In the absence of waning, most extrapolations of lorlatinib PFS data, including the company's preferred 36-month piecewise Weibull extrapolation, provide very optimistic predictions implying that a substantial number of patients will remain progression-free beyond 10 years (Table 14). The company has therefore implemented waning assumption as an effective correction that ensures PFS projections better align with clinical expectations. The success of this correction is, however, dependent on using a standard Weibull function to extrapolate crizotinib PFS. If alternatives are selected, the correction to model predictions offered by waning largely breaks down and the model generates overly optimistic predictions that do not align with clinical expectations (Table 14).

Table 14 Landmark analysis PFS - lorlatinib, considering alternative extrapolations of crizotinib

Distribution	Modelled landmarks					
	1 year	**5 years**	**10 years**	**15 years**	**20 years**	**30 years**
	12 months	**60 months**	**120 months**	**180 months**	**240 months**	**360 months**
No waning	80.2%	60.5%	40.9%	22.5%	10.6%	1.6%
Exponential	80.2%	60.5%	40.9%	0.9%	0.0%	0.0%
Generalised gamma	80.2%	60.5%	40.9%	18.6%	10.4%	4.4%
Gompertz	80.2%	60.5%	40.9%	33.3%	31.6%	31.0%
Log-logistic	80.2%	60.5%	40.9%	19.4%	11.3%	5.3%
Log-normal	80.2%	60.5%	40.9%	11.3%	4.1%	0.8%
Weibull*	80.2%	60.5%	40.9%	0.6%	0.0%	0.0%
Gamma	80.2%	60.5%	40.9%	0.4%	0.0%	0.0%

Notes: The model cycle length (30 days) is not exactly equal to 1 month (30.44 days); therefore, the nearest value to each landmark is returned. * Company base case
Source: Company economic model

Importantly, it is not obvious that the Weibull function represents the most appropriate extrapolation of crizotinib PFS. The company's motivation for using a Weibull function is primarily based on the fact a Weibull function is used to extrapolate beyond 36 months in the lorlatinib arm. However, unlike in the lorlatinib arm, this is applied as a standard parametric function to the whole survival curve and does not use the piecewise approach adopted in the lorlatinib arm. The EAG does not consider using a piecewise extrapolation approach in one arm and a standard parametric extrapolation approach in another treatment arm to be consistent, nor appropriate as these approaches imply fundamentally different hazard trends across treatment arms. According to DSU guidance,[53] the same type of parametric model should be used across model arms, with any exceptions requiring clear justification which the company do not provide. This ensures that survival trajectories remain consistent and do not assume underlying differences in hazard trends. The Weibull function also represents the worst fitting curve for the crizotinib PFS data, providing poor statistical fit relative to alternatives. Further, it is the most pessimistic curve contributing to the model under predicting PFS for alectinib and brigatinib compared to observed survival data from ALEX and ALTA 1L.

To address this issue, the EAG proposes using the lorlatinib arm as the reference arm to which relative treatment effects are applied. In response to clarification question A4, the company acknowledged that scenarios using the lorlatinib arm as the reference arm were also plausible, noting the similar shape of smoothed hazard plots between alectinib and lorlatinib. This resolves the inconsistency issue, as the same underlying extrapolation approach is applied in both arms. The EAG also suggests revising waning assumptions so that hazards are waned to the alectinib arm because this

avoids the need to use the crizotinib arm in the model entirely and therefore resolves uncertainty regards the appropriate extrapolation. See Section 4.2.6.5 for further discussion of the waning assumptions applied in the model.

Extrapolations of lorlatinib

CS Section B.3.3.3 outlines an exhaustive approach to extrapolating PFS, and the EAG considers that the company has explored all relevant alternatives. However, the EAG is concerned that, despite this thorough approach, most of the survival projections generated by these alternatives lead to clinically implausible long-term predictions for PFS. This includes the company's preferred 36-month piecewise Weibull model, which predicts that more than 10% of patients will remain progression-free at 20 years. Clinical advice to the EAG suggests that 10-year survival with lorlatinib is more likely to be around 10%, based on known relapse mechanisms with TKI treatment, though they acknowledged that the impressive PFS observed in the CROWN trial is redefining clinical expectations.

The company acknowledges the uncertainty in longer-term PFS estimates and applies waning assumptions to address potential overestimation in long-term predictions. However, this correction depends on selecting a standard Weibull function to model crizotinib PFS, which the EAG finds difficult to justify. Most alternative models do not provide the same "correction," and the EAG considers it inappropriate to rely heavily on waning assumptions to adjust to clinically implausible survival projections. The EAG believes that the primary function of waning should be to reflect uncertainty regarding the durability of the treatment effect, not as a correction to otherwise clinically implausible parametric extrapolations.

Among the parametric survival curves fitted by the company, only two, the standard exponential curve and the 36-month piecewise Gompertz model, produce predictions that the EAG considers clinically plausible. However, the standard exponential curve has a poor visual fit to observed data, overestimating the proportion of patients who remain progression-free throughout much of the observed period, and it has the worst statistical fit of all models (CS Document B, Table 35). This leaves the 36-month piecewise Gompertz model as the EAG's preferred extrapolation. While the EAG acknowledges that this model provides the most conservative predictions among the alternatives, given the high uncertainty surrounding long-term projections, it considers this conservative approach the most reasonable.

4.2.6.3 OS – lorlatinib

As described in Section 3.2.1.2, the company were unable to provide OS data the CROWN trial which aligned with the most recent October 2023 data cut for PFS. The available OS data for lorlatinib are therefore immature, with median follow-up of 18 months. To overcome this limitation, OS in the lorlatinib arm was informed by a pooled analysis of data from the CROWN trial (n=149) and data from cohort EXP1 of Study 1001 (n =30). This cohort included *ALK*-positive, treatment-naive

patients and was considered by the company to be broadly representative of the patients recruited to the CROWN trial with similar baseline characteristics. Follow-up in Study 1001 (EXP1) is considerably longer than that of the CROWN trial with a max follow-up of 90 months.

Extrapolation of OS was undertaken by fitting standard parametric survival curves to both the CROWN trial alone and pooled data from CROWN and Study 1001 (CS, Section B.3.3.4). The company also explored fitting piecewise models to OS (consistent with PFS) but considered that this approach did not add anything over standard parametric approaches and did not address the issue of limited follow-up. The selection of parametric distribution for lorlatinib was primarily based on the clinical plausibility of long-term predictions and consistency. Statistical and visual fit were also considered but were less relevant to curve choice given the relative immaturity of the available data (CS, Document B, Table 44 and Table 45).

The company's base case analysis adopted a Weibull curve to extrapolate OS fitted to pooled data from (CROWN + Study 1001). The Weibull curve had the 2nd worst statistical fit in terms of AIC and BIC, though differences in fit statistics are small (CS, Document B, Table 45) It is also the 2nd most pessimistic extrapolation, resulting in 6.5% of patients remaining alive at 30 years (Table 15).

Table 15: Landmark analysis of OS - lorlatinib using Pooled CROWN + Study 1001 EXP1 (adjusted for background mortality)

Distribution	Modelled landmarks					
	1 year	**5 years**	**10 years**	**15 years**	**20 years**	**30 years**
	12 months	**60 months**	**120 months**	**180 months**	**240 months**	**360 months**
Exponential	90.4%	61.5%	37.7%	23.1%	14.1%	5.3%
Generalised gamma	87.8%	74.2%	68.6%	63.5%	56.0%	29.5%
Gompertz	90.1%	71.7%	64.7%	59.9%	52.8%	27.8%
Log-logistic	90.2%	64.6%	47.0%	36.9%	30.3%	15.9%
Log-normal	90.0%	67.1%	52.9%	44.2%	38.1%	20.0%
Weibull*	90.3%	62.3%	39.4%	25.1%	16.1%	6.5%
Gamma	90.5%	61.9%	38.4%	23.8%	14.8%	5.6%

*Company base case
Source: CS Document B, Table 48

Points for critique

As discussed in Section 4.2.2, the EAG prefers using an STM model to evaluate all model arms, this implies that OS is not required in the economic analysis. The following critique is therefore only relevant to scenarios where a PSM is used to determine transitions.

Extrapolations of OS

The EAG considers the company's general approach to extrapolation reasonable and agrees with prioritising alignment with modelled PFS and clinical plausibility when selecting the most appropriate

survival curve. Although the preferred Weibull function ranks among the lowest in terms of statistical fit, the EAG does not consider statistical fit an essential criterion in this case due to the immature OS data and minimal differences among fit statistics.

The EAG views the pooling of Study 1001 EXP1 data with CROWN data as broadly appropriate in the context of the immature OS data available from CROWN. One justification for pooling is that it produces more optimistic predictions that better align with the company's preferred PFS extrapolation i.e. PFS and OS curves do not cross. This issue, however, could be addressed by selecting a more conservative Gompertz curve to extrapolate PFS. Nevertheless, the EAG finds the use of the Gompertz curve inconsistent with all OS extrapolations, as it results in an unrealistically prolonged PPS that lacks clinical validity due to the limited treatment options available after disease progression.

In light of these factors, the EAG considers the company's Weibull extrapolation of pooled CROWN and Study 1001 EXP1 data reasonable but underscores the high level of uncertainty associated with predictions and emphasises the limitations of the OS data not only in terms of maturity but also relevance to the NHS clinical pathway.

4.2.6.4 Post-progression survival – alectinib and brigatinib

In line with the STM approach, the company base case model explicitly models post-progression survival in the alectinib and brigatinib arms. This approach allows data on the effectiveness of 2L treatments to be incorporated into the model and overcomes limitations in the OS data from CROWN which is both immature and confounded by the use of 2L treatments that do not reflect NHS practice. Within the economic model, it assumed that all patients progressing on either alectinib or brigatinib move to 2L treatment consisting of either lorlatinib (86.4%) or chemotherapy (13.6%). Survival outcomes for patients receiving lorlatinib 2L were modelled using data from cohorts EXP3B-5 of Study 1001, while outcomes for chemotherapy patients were modelled using data from the PROFILE 1001/1005 studies (Table 12).

Extrapolation of PPS was undertaken using an exponential curve assuming constant hazard throughout the model time horizon and was applied such that time in the state was independent of when a patient entered the progressed disease health state (CS, Section B.3.3.4.1). In response to clarification question B3, the company provided alternative extrapolation approaches using other parametric functions. Table 16 presents the mean PPS predicted for post-progression survival for 2L lorlatinib, i.e. following progression on alectinib and brigatinib. The exponential curve selected in the company's base case has the best statistical fit and is the 3rd most, resulting in 13.98% of patients remaining alive at 5 years.

Table 16 Models applied to Study 1001 PPS data (2L lorlatinib)

Model	AIC	BIC	Median (months)	Mean (months)	Proportion alive at each landmark value (%)				
					1 year	5 years	10 years	15 years	20 years
Exponential*	890.34	893.27	26.61	39.87	74.1%	22.3%	4.9%	1.1%	0.2%
Generalized gamma	892.00	897.87	21.68	51.03	67.9%	25.4%	13.1%	8.4%	6.0%
Gompertz	882.15	890.95	23.66	54.14	68.7%	25.3%	13.9%	10.8%	9.7%
Log-logistic	886.44	892.31	22.67	48.36	69.7%	23.7%	11.5%	7.2%	5.1%
Log-normal	883.13	889.00	22.67	48.34	69.0%	24.6%	11.5%	6.7%	4.3%
Weibull	880.64	886.51	25.63	41.43	71.8%	23.5%	6.4%	1.8%	0.5%
Gamma	891.20	897.07	26.61	40.52	73.0%	23.0%	5.5%	1.3%	0.3%

***Company base case
Source: Company response to clarification question B3, Table 7 and Table 8

Points for critique

Extrapolation of PPS

The company's selection of exponential extrapolation is based primarily on the need to model a constant hazard and avoid introducing a tunnel state to account for time-dependent hazards in the PD health state (CS, Document B, p133). In response to clarification question B3, the company argues that this simplification has minimal impact on the model's outcomes. However, the EAG finds this reasoning unsatisfactory and notes that the choice of extrapolation curve does affect model outcomes. The EAG highlights the Gompertz curve as a superior alternative with a significantly better statistical fit to the data, predicting a longer PPS than the company's base case (51.14 months compared to 39.87 months). Indeed, the exponential function is not only the most pessimistic choice but also demonstrates a substantively poorer fit (both visual and statistical) to the observed data than several other alternatives.

Despite these concerns, the EAG agrees that the exponential extrapolation is ultimately the most appropriate choice because it provides the most conservative estimate. As discussed in Section 3.2.2 and Appendix 1 (Section 9.1), Study 1001 does not reflect NHS practice, as patients in the study received subsequent treatments unavailable in the NHS. Consequently, Study 1001 is likely to overestimate PPS, justifying a more conservative extrapolation.

4.2.6.5 Treatment effect waning

The company base case applies treatment effect waning to extrapolated PFS and OS curves from 10 years; waning is not applied to PPS. Treatment effect waning is applied using an instantaneous approach and hazards across all model arms and assumes that to revert to those of crizotinib i.e. hazards for extrapolated PFS and OS curves for crizotinib. The company justify the use of treatment effect waning due to the uncertainty in long-term treatment effects and for consistency with previous NICE TAs including TA909. Waning is assumed to occur at 10 years as the company. The impact of

waning on the company's preferred extrapolations of PFS and OS is illustrated in Figure 10 and Figure 11.

Figure 10: PFS (INV) extrapolations for all treatments

Abbreviations: INV, investigator; KM, Kaplan–Meier curve; PFS, progression-free survival.
Source: CS, Document B, Figure 23

Figure 11: OS extrapolations for all treatments

Abbreviations: OS, overall survival.
Notes: The per cycle probability of death is capped at the age- and sex-matched general population.
Source: CS, Document B, Figure 28

Points for critique

Appropriateness of waning assumptions

The EAG considers the application of treatment waning to both PFS and OS data to be broadly reasonable, noting that it aligns with committee preferences from TA909. This approach is also consistent with prior assumptions accepted in TA536 and TA670, where treatment waning was

applied similarly. However, the EAG is concerned that waning is being applied to correct extrapolations of PFS that are otherwise clinically implausible. The EAG does not consider this approach appropriate, as it believes that waning assumptions should primarily address uncertainties regarding the durability of the treatment effect.

Reflecting this position the EAG considers that the implementation of waning assumptions should wane relative treatment effects to survival estimates which are reflective of either the alectinib or brigatinib arm, not the crizotinib arm. This ensures that waning addresses uncertainties about the durability of relative treatment effects rather than serving as a correction for extrapolations that may lack clinical plausibility. Regarding the timing of treatment waning, the EAG considers a 10-year period reasonable, given the 5 years of PFS INV follow-up data in the CROWN study, and notes that this timing aligns with preferences expressed in TA909.

These assumptions, however, are subject to considerable uncertainty. As such, it remains difficult to rule out scenarios where waning might be applied at earlier or later time points, or even more optimistic scenarios in which waning may not be necessary at all.

4.2.6.6 Adverse events

The model included Grade 3+ AEs that were observed in at least 5% of patients in either of the CROWN treatment arms, the alectinib arm of ALEX, or the brigatinib arm of ALTA-1L. Further, AEs of special interest (hypertriglyceridemia, hypercholesterolemia, peripheral neuropathy, cognitive effects and mood effects), regardless of Grade, were also modelled in the lorlatinib arm. Data on the proportion of patients experiencing each event was combined with data on AE duration from CROWN (lorlatinib arm) assuming the same event duration across all arms (Table 17). This was used to estimate a one-off disutility and costs applied in the first model cycle. See Section 4.2.7.3 for a summary of AE disutilities applied and Section4.2.8.5 for a summary of management costs applied.

Points for critique

The EAG considers the company's approach to modelling AE appropriate and to align with the available safety data from the CROWN trial.

Table 17 Incidence and rate of AE by treatment arm

Adverse Event	Lorlatinib (CROWN)		Alectinib (ALEX)		Brigatinib (ALTA-1L)	
	Proportion	Duration (days)	Proportion	Duration (days)	Proportion	Duration (days)
Hypertriglyceridemia*	66.44%	714	0.00%	714	0.00%	714
Weight increased	22.82%	778	0.00%	778	0.00%	778
Increased lipase level	6.04%	30	0.00%	30	12.50%	30
Hypercholesterolemia*	72.48%	770.5	0.00%	770.5	0.00%	770.5

Aspartate aminotransferase increased	2.01%	30	5.26%	30	2.21%	30
Gamma-glutamyltransferase increased	6.04%	30	0.00%	30	0.74%	30
Hypertension	12.08%	30	0.00%	30	7.35%	30
Anaemia	4.03%	30	5.92%	30	1.47%	30
Amylase increased	0.00%	30	0.00%	30	5.88%	30
Neutropenia	0.67%	30	0.00%	30	0.00%	30
Blood creatine phosphokinase increased	2.68%	30	3.29%	30	23.53%	30
Neutrophil count decreased	0.00%	30	0.00%	30	0.00%	30
Peripheral neuropathy*	43.62%	380	0.00%	380	0.00%	380
Cognitive effects*	27.52%	221	0.00%	221	0.00%	221
Mood effects*	20.81%	218	0.00%	218	0.00%	218
Notes: * includes all AEs of special interest regardless of grading. **Source:** adapted from CS, Document B, Table 53 and the company's executable model						

4.2.7 Health related quality of life (HRQL)

The CS considers HRQL relating to the i) health states PF and PD, ii) disutility associated with CNS metastasis iii) disutilities to account for AEs. In the PF health state utility values are treatment-specific with different values applied to lorlatinib, alectinib and brigatinib. In the lorlatinib arm only the company also applies different utility values in accordance with whether patients are on/off treatment. An age- and gender-related utility adjustment is applied to all health-state utilities over the model time horizon to reflect decreases in HRQL in the general population.

4.2.7.1 Collection of utility data in CROWN

HRQL data was collected in the CROWN trial up to the September 2021 data cut using the EQ-5D-5L questionnaire and were mapped to EQ-5D-3L using the algorithm derived in Hernández-Alava *et al*[47] for use in the economic model.

Using the mixed-effects utility model, CROWN utility values had the functionality to be stratified by health state, treatment status (on or off) and treatment arm (joint or separate). The company response to clarification question B7 presents the HRQL regression model with the addition of CNS metastases as a covariate.[54]The reported results show a 0.10 difference in EQ-5D baseline utility value in patients with brain metastases (0.709) and those without (0.797) exists. The company state that no differences in EQ-5D-5L index scores between treatment arms were observed in patients with (lorlatinib 0.75; crizotinib 0.80); and without brain metastases (lorlatinib 0.85; crizotinib 0.82); however, there were absolute differences between those with and without brain metastases in the lorlatinib arm (0.75 vs. 0.85).

4.2.7.2 Health state utilities

The utility values applied in the company's base case are summarised in Table #. Utility values of lorlatinib in the PF health state were derived from the CROWN study and were generated using a

mixed-effects regression model. Utility values for comparator treatments in the PF health state were informed by reported values in TA536 and TA670 and were derived from respective pivotal trials ALEX and ALTA-1. Utility values in the PD health state were informed by values from TA670 aligning with EAG and committee preferences in TA909.

To account for the impact of brain metastasis on HRQL the company applied an externally derived multiplier to the trial-derived utilities to account for the impact of CNS progression. Following the method adopted in TA670, the company used a study evaluating brain metastases' impact on HRQL in patients with Stage IV NSCLC.[55] This study included 29 patients with brain metastases (utility 0.52) and 111 patients with contralateral lung metastases (utility 0.69). The company therefore applied the proportional relationship of 75.36% between these two values (i.e. 0.52/0.69) to the utility for progressive disease to each treatment option to quantify the impact of CNS-metastases in the model for a duration of 24 months based on Li et al., 2023 meta-analysis paper. [56]

Table 18 Summary of utility values for cost effectiveness analysis

	State	Utility value: mean
Utility values	**Progression-free (on treatment)**	
	Lorlatinib	0.845
	Brigatinib	0.793
	Alectinib	0.814
	Progression-free (off treatment)	
	Lorlatinib	0.768
	Brigatinib	0.793
	Alectinib	0.814
	Progressed (on and off treatment)	
	Lorlatinib	0.624
	Brigatinib	0.624
	Alectinib	0.624
One-off utility for CNS progression (based on 24 months duration)	Lorlatinib	0.416
	Brigatinib	0.401
	Alectinib	0.391
Source: adapted from CS, Document B, Table 61		

4.2.7.3 Adverse effects utility decrements

Utility decrements and durations are presented in CS, Document B, Tables 59 and 60. The loss of QALYs per AE was calculated as the product of the utility decrement and the duration of the AE. Within the model, the company calculated a one-off AE disutility for each treatment as: lorlatinib (-0.1907); alectinib (-0.0004); brigatinib (-0.0016).

Points for critique

Division of utilities by treatment

In the PF health state, utility values differ by treatment. This differential contradicts clinical advice provided to the EAG and is inconsistent with the precedents set in TA536, TA670, and TA909. In

response to clarification question B9, the company indicated that separate PFS utilities, adjusted for trial-specific AE decrements, were considered to better reflect patient experiences on each ALK inhibitor. The company also conceded that the PF utility values derived from the CROWN trial are likely too similar to general population norms (0.836 for a 57-year-old) and expressed willingness to consider alternative sources that offer a plausible range of PF utility values. The EAG does not consider them to be sufficient evidence or clinical rationale to justify differential utilities in the PF health state. The EAG agrees with the company the PF utilities from CROWN appear too high compared population norms and prefers to use values from TA670 as this is consistent with the values used in the PD health state.

Division of utilities by treatment status (on/off)

The EAG disagrees conceptually with the division of utility in the PF state into on- and off-treatment categories, noting the absence of precedent for such an approach in prior appraisals[3-5]. Nonetheless, the EAG in TA909 acknowledged that applying on/off treatment utilities is appropriate for patients with progressed disease, consistent with past appraisals. However, the company applied a single utility value in the PD health state regardless of on- or off-treatment status.

The EAG believes it is plausible that patients on- and off-treatment in the CROWN trial would have different utility values. Typically, patients off-treatment while in the PF state would be due to treatment interruptions to manage significant TRAEs. This implies that patients off-treatment in the PF state would likely experience lower health-related quality of life (HRQL) because of ongoing AEs, contributing to the lower off-treatment utility observed in the company's regression model. However, it is problematic to separate these patients statistically while s also applying disutilities to account for AE's. This approach is also inconsistent across treatment arms as the same approach is not applied in the alectinib and brigatinib arms.

PD utility

The company does not use CROWN trial data to inform the utility value applied to the PD health state and instead uses external from TA670. The company justify this approach noting that the data available from CROWN is limited with most values obtained close to the date of progression. The company therefore considered that utility values obtained from the CROWN trial therefore unlikely to capture the deterioration in HRQL associated with progressive disease. The EAG broadly agrees with the company's use of alternative external data and recognises the limitations of the CROWN trial data. The EAG further highlights that this approach is consistent with TA909.

The EAG is, however, concerned that this approach fails to reflect the HRQL benefits associated with receiving a 2L ALK inhibitor. As outlined in Section #, treatment options following progression are limited to chemotherapy and do not include ALK inhibitors. This contrasts with the comparator arms, where lorlatinib is available as a 2L treatment option. As highlighted in TA628 (lorlatinib 2L),

patients receiving chemotherapy are likely to experience poorer HRQL compared to those on ALK inhibitors, which was accounted for in TA628 by applying treatment-specific utility values. The EAG considers it appropriate to adopt a similar approach by applying an on-treatment utility for patients receiving a 2L ALK inhibitor. Scenario analyses exploring this approach are presented in Section 6.

Use of Roughley et al. multiplier for CNS PD

The company notes the use of this multiplier derived from this study is consistent with TA670 (also TA536) and acknowledges the limitation that only a small number of patients with brain metastases were included (n=29), and that co-morbidities, age, and treatment-related AEs were not reported in these patients. In TA909, the company's economic model used a four-state approach, which separately captured CNS progression from non-CNS progression. In the context of this model, the decrement associated with CNS progression was a significant driver of the cost effectiveness model and contributed significantly to incremental QALYs. The company has, however, revised its approach for this appraisal and the QALY gain associated with the CNS progression multiplier is now small relative to total incremental QALYS and is not a key driver of the decision. Therefore, the EAG considers the use of Roughley et al.[55] to be reasonable despite the limitations of the evidence and does not explore this issue further.

Effect of adverse events on HRQL

The EAG highlights the extended duration of adverse events (AEs) experienced by patients on lorlatinib. Considering the AE profiles, it is surprising that the treatment-specific progression-free utility values for lorlatinib are higher than those for comparators. While a one-off disutility is a conventional method for capturing the impact of AEs on health-related quality of life (HRQL) in the model, the EAG questions whether this approach accurately reflects patient experience. Nonetheless, the EAG is willing to accept this method in the absence of a better alternative.

4.2.8 Resources and costs

The CS provided a description of resource use and costs applied in the model. This included drug acquisition and administration costs, costs associated with the management of adverse events, monitoring costs, the cost associated with subsequent treatments, and resource use associated with end-of-life care of patients with ALK-positive advanced NSCLC.

As described in Section 4.1, the company extracted and synthesised data from 24 unique studies from included 33 publications from the SLR of resource use and cost data. The cost values for the resources identified were extracted from monthly index of medical specialities (MIMS) online database, British National Formulary, NHS reference costs (2021 -202) and Personal Social Services Research Unit (PSSRU) 2023-unit costs report.

4.2.8.1 Drug acquisition costs

Acquisition costs for lorlatinib in the model were based on its MHRA marketing authorisation, i.e. a 100mg or 25mg tablet. The drug costs were calculated for lorlatinib, alectinib and brigatinib as the 1L therapies. The drug costs were calculated based on each drug's unit cost per package, which was derived from the Monthly Index of Medical Specialities (MIMS).[57] Acquisition costs applied for lorlatinib were inclusive of a differential PAS discount of [redacted] on the list price in 1L and [redacted] for 2L. The company also applied a simple discount of [redacted] to simulate the commercial arrangements available for alectinib and brigatinib. On the advice of the NICE technical team, this discount has been removed. All analyses presented in the EAG report therefore use the list price for alectinib and brigatinib. Pemetrexed, and cisplatin are also subject to confidential commercial arrangements not included in the company's analysis or replicated in this report. Analysis inclusive of all confidential pricing arrangements is included in a confidential appendix to the EAG Report.

Dosing schedules and costs modelled for the intervention drug lorlatinib and comparators drugs alectinib and brigatinib are summarised in 4.2.4 and were informed by the SmPCs for alectinib and brigatinib[58, 59] and the CROWN trial for lorlatinib.[11]

Lorlatinib is available in three pack sizes: 120x tablets 25mg, 90x tablets 25 mg, or 30x tablets 100 mg. The acquisition costs associated with lorlatinib are dose-dependent and do not scale on a pro rata basis. Although the acquisition cost for the 90 tablet 25mg pack and the 30 tablet 100mg pack are the same, the 30 tablet 100mg pack has 750mg more per pack compared to the 90 tablet 25mg pack. In the base case economic analysis only the 30 tablet 100mg packs were used to estimate costs.

Given that lorlatinib, alectinib, and brigatinib are all orally administered, the CS assumed that the only administration cost required would be a pharmacist's time to dispense the medications. An administration cost of £10.40 was applied per pack, sourced from the Personal Social Services Research Unit (PSSRU) 2023 as the cost for 12 minutes of work for a Band 6 community-based scientific and professional staff member (£52 per hour).[60]

Drug and administration costs are incurred at the beginning of each cycle and so differences between pack size (drug cycle) and model cycle length produce drug 'wastage' which is included in modelling. For lorlatinib the pack size (30) aligns with cycle length but for alectinib and brigatinib the pack size is equivalent to 28 days and so any pill wastage is costed. The relative dose intensity (RDI) was applied in the model to reflect treatment costs more accurately, by adjusting per-cycle costs to account for dose interruptions, reductions or non-compliance.

Table 19 Drug unit costs, doses, and dose intensity

Treatment	Cost per pack, £	Pack size	Dose, mg	Dosing schedule	Mean RDI (%)	Drug cost per month (cycle), £
Lorlatinib	7,044.00 with PAS discount: [redacted]	120	25	100 mg orally once daily	92.3	[redacted]
	5,283.00 with PAS discount: [redacted]	90	25			
		30	100			
Alectinib	5,032.00	224 capsules	600	600 mg orally twice a day	95.6	5,154.21
Brigatinib	4,900.00	28 tablets	180	180 mg orally once daily	85.5	4,869.28

Abbreviations: RDI, relative dose intensity; PAS, patient access scheme
Source: adapted from CS, Document B, Table 54 - 58 and company economic model (drugs cost worksheet)

Points for critique

The EAG accepts the calculations of the drug costs per month which are consistent with previous precedent and has no concerns with the calculations and derivations of the unit costs. The EAG notes several uncertainties regarding to wastage and differences in how dose reductions were accounted for.

Wastage and dose reductions

The EAG considers the RDI approach to modelling wastage to be broadly appropriate and has been previously accepted by NICE Committees. There is provision for both adjusting drug costs using RDI and including drug wastage based on differences between model cycle and the treatment cycle in the model. There does not appear to be any specific mention of accounting for dose reductions in the CS or provision in the model. It was reported in the CROWN trial that at least one dose reduction occurred in 49/149 (33%) lorlatinib patients and this was not accounted for in the model. The EAG stance is that this is likely to be consumed as part of the RDI calculation though this is not explicitly expressed in the CS.

4.2.8.2 Health state unit costs and resource use

A micro-costing approach was used in line with the brigatinib (TA670) and alectinib (TA536) appraisals, whereby the frequencies of individual resources were broken down depending on the health state.[4, 5] Medical resources for monitoring patients with NSCLC based on the progression-free and post-progression health states. Frequencies are based on NICE TA670 and TA536. National Institute for Health and Care Excellence, 2018 #49;National Institute for Health and Care Excellence, 2021 #19} All monitoring costs are derived from the latest NHS Reference costs (2021/22) and from the PSSRU 2023.[60, 61]

Following the same approach as for the one-off disutility in Section 4.2.7, a one-off cost is applied for intercurrent CNS progressions. The additional costs associated with CNS progression are sourced from Le *et al*. 2023[62]The study compares the average costs for patients without CNS metastases with patients with CNS metastases during the first and subsequent years after CNS progression. The cost difference associated with CNS metastases is estimated and applied in the model as one-off costs. As

the costs provided in the study are annual costs, the cost difference is adjusted to fit the assumed 24-month duration of CNS intercurrent events (duration discussed in Section 4.2.7 above).

AE costs were informed by NHS Reference Costs and the brigatinib appraisal (TA670).[4] AE unit costs were applied to the yearly patient AE rate to calculate annual AE costs, before these were combined with life years in each cycle of the model.

Points for critique

The EAG has no concerns with the health state unit costs included in the model. The costs applied are consistent with previous appraisals and appear to include all relevant costs incurred.

4.2.8.3 Subsequent treatments

Subsequent treatments following progression and cessation of initial treatment are included in the model and are applied once at the point of progression as a simplifying assumption.

The proportion of patients incurring the cost of subsequent treatments in each cycle was estimated as the proportion of patients who transitioned out of the on-treatment health state in each model cycle without dying. This was estimated using the proportion of PFS (INV) events that were deaths from the October 2023 data cut-off of the CROWN trial for lorlatinib (16.36%) and crizotinib (4.35%), assumed to be constant over time and assuming the same proportion as crizotinib for alectinib and brigatinib.[12] The inverse of this proportion was applied to the proportion of patients leaving the on-treatment health state in each cycle to estimate the proportion of patients whose ToT events were discontinuation. This approach was consistent with that used in the 2L lorlatinib appraisal (TA628) and was a simplifying assumption to enable an estimation of the proportion of patients in each cycle who are discontinuing treatment and are entering the progressed health state and hence are eligible for subsequent treatment.[2]

Subsequent treatment distributions following 1L treatment with alectinib or brigatinib were estimated using UK market share data for 2L and 3L treatment and were also further validated in one-to-one sessions with the company's clinicians, see Table 20.[63]

Table 20 Re-weighted subsequent treatment distributions in clinical practice

Subsequent treatments	Lorlatinib	Alectinib	Brigatinib
Alectinib	0.00%	0.00%	0.00%
Crizotinib	0.00%	0.00%	0.00%
Ceritinib	0.00%	0.00%	0.00%
Brigatinib	0.00%	0.00%	0.00%
Lorlatinib	0.00%	86.80%	86.80%
Chemotherapy	86.80%	54.00%	54.00%
Immunotherapy	0.00%	0.00%	0.00%
VEGF-R	0.00%	0.00%	0.00%

Abbreviations: VEGF-R, vascular endothelial growth factor-receptor.
Source: CS, Document B, Table 71

The mean duration for which patients were on lorlatinib as a 2L treatment was 64.36 weeks as sourced from TA628[2] where lorlatinib was evaluated as a 2L treatment for ALK-positive NSCLC. The mean duration over which patients were on chemotherapy as either 2L or 3L treatment was 6.3 weeks as sourced from ASCEND-5 trial.[49] The total costs for subsequent treatment for patients on lorlatinib with chemotherapy (pemetrexed and cisplatin) was £3,172.24 while the total costs for subsequent treatments for patients on alectinib or brigatinib with lorlatinib 2L (inclusive of cPAS) was estimated to be [redacted].

Table 21 presents the breakdown of total costs by subsequent treatment received. A month is assumed to be 30.4 days (calculated as 365.25 divided by 12).

Table 21 One-off subsequent treatment costs applied in in the model

Subsequent treatment	Drug cost (per admin)	Admin cost (per admin)	Admins (per month)	Total cost (per month)	Treatment duration (weeks)	Treatment duration (months)	Total cost
Pemetrexed	£1,380.87	£287.00	1.45	£2,417.42	6.30	1.45	£3,502.52
Cisplatin	£72.44	£0.00	1.45	£105.00	6.30	1.45	£152.13
Lorlatinib	[redacted]	£10.40	1.01	[redacted]	64.36	14.80	[redacted]
Source: CS, Document B, Tables 72 -75 of the CS							

Points for critique

Proportion of patients receiving systemic 2L treatment

Evidence from CROWN indicates that 86.8% of patients received systemic treatment following progression. Clinical advice to the EAG supports the figures observed in CROWN suggesting that > 80% of patients would receive subsequent treatment beyond progression and that the use of lorlatinib in a 2L setting is universal, subject to patients' fitness to receive treatment; patients with rapidly progressing disease are often not fit enough to receive further systemic treatment and would receive only palliative care. The EAG considers it reasonable to assume that the proportion of patients receiving 2L treatment will be the same regardless of the 1L TKI received.

Duration of chemotherapy treatment

The company utilises data from the ASCEND-5 trial to inform the duration of chemotherapy treatment. The EAG has concerns about using this data source and notes several generalisability and inconsistency issues. ASCEND-5 was a randomised trial of ceritinib vs chemotherapy in patients who had previously received crizotinib and one to two lines of chemotherapy (including platinum doublet therapy).[49] The ASCEND-5 population, therefore, does not match the population modelled as receiving chemotherapy (2L or 3L chemotherapy following one or two previous TKIs).

The chemotherapy regimens modelled (doublet treatment; pemetrexed in combination with cisplatin) also do not reflect those received by patients in ASCEND-5. Patients in ASCEND-5 received single-agent therapy consisting of either pemetrexed or docetaxel. Further, the use of ASCEND-5 does not match the clinical data used to inform post-progression survival which was based on PROFILE 1001/1005. This creates an inconsistency between modelled health benefits and costs. The duration of chemotherapy of 6.3 weeks is substantially less than the 5.9 months used in TA909. Using CROWN (non-ALK-TKIs) as source, 34.92 weeks (~8 months) increases the company base case ICER to £20,645 vs. alectinib). Notwithstanding the issues raised above, the EAG considers the use of ASCEND-5 pessimistic and would expect a longer duration of chemotherapy treatment similar to the CROWN trial. This is explored in Section 6 as part of the EAG base case.

4.2.8.4 Health state costs

Healthcare resource use in the model was specific to each health state, the health states being progression-free, progressed disease and death. Resource use and costs for each health state was based on NHS reference costs (21/22). [60] A micro-costing approach was used with resource use assumed to be equal to that reported in the brigatinib (TA670) and alectinib (TA536) appraisals.[4, 5] In the PF and PD health states, costs were applied on a per-cycle basis (where each cycle is 30 days long) while the death state costs were applied as a one-off cost upon progression as explained in Section 4.2.8.8.

In the second and all subsequent cycles, per cycle progression-free (on-treatment) health state costs were estimated to be £465.31 while in the first cycle it was estimated to be £363.04 as shown in Table 22. The per cycle of progressed health costs was estimated to be £686.57 as shown in Table 23.

Table 22 Progression-free health state cycle costs

Resource	Unit cost, £	Frequency of use	Cost per cycle, £
Progression-free health state - first cycle			
Healthcare provider visits			
Oncology outpatient (first visit)	£363.83 per visit	100% of patients (1 visit per month)	£358.60
Tests and procedures			
Full blood test	£2.96 per test	100% of patients (1 set of tests per month)	£2.92
Biochemistry	£1.55 per test	100% of patients (1 set of tests per month)	£1.52
Total cost for the first progression-free (on-treatment) cycle			***£363.04***
Progression-free health state – second and subsequent cycles			
Healthcare provider visits			
Oncology outpatient (subsequent visit)	£221.48 per visit	100% of patients (0.75 visit per month)	£163.72
GP visit	£55.00 per visit	10% of patients (1 visit per month)	£5.42
Cancer nurse	£119.00 per visit	50% of patients (1 visit per month)	£58.65
Tests and procedures			
Full blood test	£2.96 per test	100% of patients (1 set of tests per month)	£2.92
Biochemistry	£1.55 per test	100% of patients (1 set of tests per month)	£1.52
CT scan	£123.49 per scan	100% of patients (0.5 scans per month)	£60.86
MRI	£346.43 per scan	50% of patients (0.2 scans per month)	£34.14
X-ray	£38.28 per X-ray	50% of patients (0.3 scans per month)	£5.66
ECG	£134.35 per scan	100% of patients (1 scan per month)	£132.42
Total cost per cycle for the second and subsequent progression-free (on-treatment) cycles			***£465.31***

Abbreviations: CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; MRI: magnetic resonance imaging.
Source: adapted from CS, Document B, Table 66 and company economic model (resource use costs worksheet)

Table 23 Progressed (off-treatment) health state cycle costs

Resource	Unit cost, £	Frequency of use	Cost per cycle, £
Progressed (off-treatment) health state cycle cost			
Healthcare provider visits			
Oncology outpatient (subsequent visit)	£221.48 per visit	100% of patients (1.25 visit per month)	£272.87
GP visit	£55.00 per visit	50% of patients (1 visit per month)	£27.10
Cancer nurse	£119.00 per visit	80% of patients (1.5 visits per month)	£140.75
Tests and procedures			
Full blood test	£2.96 per test	100% of patients (1.5 set of tests per month)	£4.38
Biochemistry	£1.55 per test	100% of patients (1.5 set of tests per month)	£2.29
CT scan	£123.49 per scan	100% of patients (0.75 scans per month)	£91.28
MRI	£346.43 per scan	80% of patients (0.5 scans per month)	£136.58
X-ray	£38.28 per X-ray	60% of patients (0.5 scans per month)	£11.32
Total cost per cycle for the non-CNS progressed health state			***£686.57***

Abbreviations: CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; MRI: magnetic resonance imaging.
Source: adapted from CS, Document B, Table 67 and company economic model (resource use costs worksheet)

In addition, a one-off management cost of £18,373.64 based on 24 months duration was applied to those with CNS progression to reflect the resource-intensive nature of this site of progression and the additional (incremental) resource use compared to those without CNS progression. The inputs are obtained from Le *et al*. 2023[62] and presented in Table 24. All monitoring costs for NSCLC patients with and without CNS progression were derived from the NHS reference costs (2021/22) and from the PSSRU. [60, 61]

Table 24 CNS progression management costs

Resource	Patients without CNS metastases (First and subsequent years)	Patients with CNS metastases (First year)	Patients with CNS metastases (Subsequent years)
Breakdown of unit costs applied			
Specific procedures for the treatment of metastases	£0.00	£5,715.86	£2,393.70
Hospitalisations	£370.41	£1,062.09	£2,070.73
Medical visits	£2,817.43	£5,068.47	£5,068.47
Laboratory tests	£99.91	£99.91	£99.91
Imaging techniques	£1,039.23	£2,724.23	£2,724.23
Total	**£4,326.98**	**£14,670.55**	**£12,357.04**
Summary of costs applied			
Months	24		
Costs during first year (incremental)	£10,343.58		
Cost during subsequent year (incremental)	£8,030.06		
Total one-off	**£18,373.64**		

Abbreviations: CNS, central nervous system; HCRU, healthcare resource utilisation.
Source: adapted from CS, Document B, Table 69 and company economic model (resource use costs worksheet)

The 24-month assumption incorporates CNS metastases specific procedures – i.e. holocranial radiotherapy, radiosurgery (or stereotactic radiotherapy) and surgical resection – which in practice require at least 1 year for these procedures to take place as validated in the one-to-one clinical validations. [63]

Points for critique

The EAG has no major concerns with the health state costs included in the model. The costs are in line with previous submissions (TA670) and appear to include the relevant costs which would be incurred in this health state. The addition of the Le *et al*. 2023[62] study on CNS treatment costs is welcomed and responds to the previous uncertainties regards the appropriate CNS management costs in TA670. The progressed-disease health state costs were also reviewed by the EAG's clinical advisers, who considered them reasonable.

4.2.8.5 Adverse reaction unit costs and resource use

The model includes Grade 3+ all-cause AEs observed in at least 5% of patients in the lorlatinib or crizotinib arms of CROWN, as well as the following AEs of special interest: hypertriglyceridemia, hypercholesterolemia, peripheral neuropathy, cognitive effects and mood effects. See CS Document B, Table 53 for a summary of the Grade 3/4 AEs proportions for each relevant ALK TKI

Le *et al.* 2023 conducted interviews with UK clinical experts to assess the HCRU associated with CNS progression.[62] During the interviews, experts agreed that most of the adverse effects would require two blood tests and two medical oncology outpatient visits, aligned with NICE TA628 and TA670.[2, 4] However, experts also flagged that managing the AEs will not require additional resources as it will be considered during the regular visits and tests. These are nevertheless costed in this submission, which is a conservative approach.

AE unit costs were derived from NHS Reference Costs 2021/22 and other recent appraisals of brigatinib.[4, 61] The AE costs, resource assumptions, and the sources cited by the company in their submission are summarised in Table 70 of the CS AE unit costs were applied to the yearly patient AE rate to calculate annual AE costs, before these were combined with life years in each cycle of the model. The average annual AE costs per patient on lorlatinib was [redacted]; alectinib was [redacted] and brigatinib was [redacted]

Points for critique

The EAG's clinical advisers agreed that the consideration of only Grade 3+ AEs is reasonable. The EAG notes that in the earlier appraisals TA536 and TA670, AEs were based on Grade 3+ events occurring in more than 3% of patients (rather than 5%) but does not consider this an important difference.

4.2.8.6 End of life costs

The CS model calculated a one-off cost to account for terminal care sourced from Round *et al*.[64] and uprated to 2022/2023 using the PSSRU.[60] An end-of-life cost of £5,334.20 is used in the model. Upon entering the death health state, patients incur this terminal care cost. The cost estimated for lung cancer in Round *et al.*[64] assumed to be generalisable to ALK-positive NSCLC in the company model. This method of including the end-of-life costs in the brigatinib (TA670)[4] appraisal was provided as an alternative approach in the model with a lower cost of £1,958.00.

Points for critique

The EAG notes that the end-of-life (EoL) cost applied in the model are than those applied in the brigatinib appraisal (TA670). However, the ICER is not sensitive to this input and the EAG considers the sources used broadly reasonable. The EAG notes that the model ICER results is not sensitive to this parameter, therefore, any uncertainty around this parameter is not explored further.

4.2.8.7 Confidential pricing arrangements

As noted in Section 4.2.8.1, the acquisition costs applied for lorlatinib were inclusive of a differential PAS discount of [redacted] on the list price in 1L and [redacted] for 2L. The lower PAS discount applied in the 2L setting reflects existing commercial arrangements for lorlatinib, while the higher PAS applied to lorlatinib 1L reflects an updated commercial arrangement offered by the company and is conditional on NICE recommending lorlatinib as a 1L treatment option. The EAG, however, notes that updated

commercial arrangements are indication agnostic and will apply to both 1L and 2L use should a positive recommendation be made.

Table 25 presents details of which comparator and subsequent treatments have confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 20/09/2024.

Table 25 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Lorlatinib 1st line	Simple PAS/commercial access agreement
Lorlatinib 2nd line	Simple PAS/commercial access agreement
Alectinib	Simple PAS/commercial access agreement
Brigatinib	Simple PAS/commercial access agreement
Pemetrexed	MPSC, medicines procurement supply chain (two preparation available; six different options)
Cisplatin	eMIT price (two preparations available)

Points for critique

Implementation of the PAS

The EAG is concerned with the implementation of the PAS for lorlatinib by the company and does not view the conditional status of the PAS as a relevant factor in how it is applied within the economic model. After raising this issue with NICE, the technical team responded with the following guidance:

Because of the conditions attached to the proposed updated PAS for lorlatinib (the proposed PAS is conditional on a positive recommendation in this appraisal), the NICE technical team advises the EAG to use the newly proposed PAS for the intervention arm, and the existing PAS for the comparator arm, for the base case in this appraisal. This approach reflects the decision problem for the committee and the economic implications of introducing lorlatinib in this indication.

The EAG's disagrees with the advice from the NICE technical team as does not consider it appropriate to use a differential PAS in which the acquisition costs for lorlatinib differ in the comparator and intervention arms.

The main argument for adopting a differential PAS is that it reflects a comparison of two states of the world: one where lorlatinib is recommended as a 1L treatment option and another where it is not, effectively a "before" versus "after" scenario. However, presenting the decision in this manner inaccurately frames the committee's decision, presenting both practical and methodological issues, introducing a temporal aspect to the decision. The EAG considers it inappropriate to frame the

committee decision as a "before and after" comparison. Instead, decisions should reflect a single point in time to ensure consistency and fairness in decision making. This approach aligns with NICE's established procedures, which generally do not consider hypothetical future scenarios.

Further, framing the decision this way does not accurately reflect the clinical landscape should a positive recommendation made. NICE guidance recommending lorlatinib as a 1L option does not invalidate the existing guidance for its 2L use. Therefore, a positive recommendation would establish a world where lorlatinib remains available as both a 1L and 2L treatment. The EAG argues that the committee should evaluate the decision within this context; failure to do so could lead to a scenario in which NICE guidance is self-invalidating. Since the enhanced PAS would extend to 2L use as well, the cost effectiveness of the current standard of care (alectinib/brigatinib followed by lorlatinib) would be significantly altered, potentially undermining the validity of the recommendation. The EAG, considers issuing guidance that is self-invalidating to be highly undesirable as it breaks the incremental nature of decision making which is fundamental feature of the NICE TA process.

More broadly, the EAG raises practical concerns. This appraisal is being conducted within the context of a single technology appraisal (STA), but it's unclear how a differential PAS approach could be applied in a multiple technology appraisal (MTA) when multiple alternatives are being considered simultaneously. It seems unreasonable for the PAS implementation to depend on whether the technology is appraised within an STA or MTA. A similar issue may also arise if lorlatinib 1L does not displace lorlatinib as a 2L option. This would necessitate comparisons to lorlatinib 1L as well existing standard of care (alectinib/brigatinib followed by lorlatinib). Evaluation of a new intervention in this context would be highly problematic as the cost effectiveness of the comparator would be radically different.

Finally, the EAG is gravely concerned that using a differential PAS discount intuitive sense. The EAG advises the NICE committee to adopt an approach that applies the PAS for lorlatinib consistently across all lines of treatment.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's updated base case analysis. The results presented in the following sections are inclusive only of the PAS discounts for lorlatinib, with differential PAS discounts as per line of treatment. Results including commercial arrangements available for alectinib, brigatinib, and chemotherapy (pemetrexed and cisplatin) are provided in a confidential appendix to the EAG Report.

5.1.1 Deterministic Results

The company presents a fully incremental analysis including all relevant comparators as described in Section #. The incremental cost effectiveness ratio is the ratio of expected additional total costs to those of expected additional QALYs compared with alternative technologies) at a willingness-to-pay threshold of £30,000 per QALY gained.

The results of the company's cost effectiveness pairwise analysis after the application of the differential lorlatinib PAS discount are summarised in Table 26. Including only the lorlatinib PAS discount, in the company base case, [redacted]

Table 26 Company base case results: deterministic pairwise analysis (lorlatinib PAS only)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Lorlatinib vs brigatinib							
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib vs alectinib							
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years							

5.1.2 Probabilistic Results

The company performed a probabilistic sensitivity analysis (PSA), running 2,000 iterations for each pairwise comparison. The PSA results were relatively stable at this point, but more iterations could have increased the certainty in the results. The mean probabilistic ICER for lorlatinib compared to each of the comparators is presented in Table 27. With the differential lorlatinib PAS discount, in the comparison with alectinib, lorlatinib had a [redacted] probability of being cost-effective at a threshold of £20,000 per QALY). In the comparison with brigatinib, lorlatinib had a [redacted] probability of being the most cost-effective option at a £20,000 per QALY willingness-to-pay threshold.

Table 27 Company base case results: probabilistic pairwise analysis (lorlatinib PAS only)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Lorlatinib vs brigatinib							
Brigatinib	[redacted]	[redacted]	[redacted]				

Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib vs alectinib							
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years							

5.2 Company's additional analyses

These scenarios were presented in pairwise fashion against alectinib. The results of these pairwise analysis are presented in Table 28

Table 28 Company's additional scenario analysis (deterministic): lorlatinib vs alectinib (inclusive of lorlatinib PAS)

#	Parameter varied	Incremental costs	Incremental QALYs	ICER
	Lorlatinib vs Alectinib			
	Base case	[redacted]	[redacted]	[redacted]
1	TA670 EOL cost source	[redacted]	[redacted]	[redacted]
2	Criztotinib PFS BICR estimates (full follow-up)	[redacted]	[redacted]	[redacted]
3	Criztotinib PFS BICR estimates (after month 16)	[redacted]	[redacted]	[redacted]
4	Lorlatinib semi-PSM approach for lorlatinib	[redacted]	[redacted]	[redacted]
5	OS/PFS waning at 12 years	[redacted]	[redacted]	[redacted]
6	OS/PFS waning at 15 years	[redacted]	[redacted]	[redacted]
7	Lorlatinib PFS utility from TA536 (ALEX)	[redacted]	[redacted]	[redacted]
8	PFS utility from TA670 (ALTA 1L)	[redacted]	[redacted]	[redacted]
9	Lorlatinib OS/PFS - Exponential	[redacted]	[redacted]	[redacted]
10	Crizotinib PFS (best AIC/BIC) - Log logistic	[redacted]	[redacted]	[redacted]
11	Standard PSM approach for comparators - Crizotinib OS/PFS Weibull	[redacted]	[redacted]	[redacted]
12	Crizotinib PFS - Exponential	[redacted]	[redacted]	[redacted]
13	Roughley et al. (2014) - decrement approach	[redacted]	[redacted]	[redacted]
14	CNS progression utility decrement based on Liu et al.(2022)	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion, BICR, Blinded independent central review; CNS, central nervous system; EOL, End of life; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life-years; PFS, Progression-free survival; PSM, Partition survival model; OS, Overall survival.				

5.3 Model validation and face validity check

The CS stated that model inputs such as CNS progression HCRU, subsequent treatment distributions and survival extrapolation outputs were validated in one-on-one interviews. The face validity of model predictions was assessed by comparing the model's predicted incremental life years for alectinib and brigatinib with those reported in a TA536 and TA670 respectively. These comparisons suggest some disparity in results with the company's base case model predicting life year gains lower than predicted in the TA536 and TA670.

5.3.1 Validation undertaken by the EAG

As part of the EAG assessment of the economic analysis, the EAG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing.

Overall, the model was well-coded and very clearly presented. The EAG, however, identified a small number of minor coding errors which are documented in Table 29. All identified errors were corrected by the EAG, and a revised model was supplied to the company with altered cells highlighted to aid verification. These corrections do not affect the company base case results and only impact selected scenarios. Revised results are presented in Section 6.

Table 29 Summary of Calculation errors

#	Description of error	Proposed change
1	Scenario analysis exploring the use of PSM in the lorlatinib arm assumes treatment beyond progression in the lorlatinib arm.	While this is not a calculation error *per se* the EAG prefers to separate assumptions relating to model structure and treatment beyond progression. Update Sheet 'ToT', cell AO11 to read = IF (Controls!N15=1, p_lorla_trt_beyond_prog, 0)
2	Treatment beyond progression scenario assumes a median of 5.7 cycles of treatment beyond progression rather than 5.7 months	Update Sheet 'ToT', cell AO11 to read =p_lorla_trt_beyond_prog/(365.25/12)*con_CL
3	The calculation of occupancy of the Progress on treatment substate is incorrect and underestimates time on treatment in the progressed disease health state.	Update Sheets "Engine (1)', column AL to read =IFERROR(AL16*(1+@INDEX(ToT!$AP$11:$AP$15,$H$8,1))+(Y16-Y17)*(1-(IF($H$8=1,p_con_prop_PFS_death_lorla,p_con_prop_PFS_death_comp))),0)

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the company's cost effectiveness analysis. These issues are identified and critiqued in Section 4.2. The EAG presents several alternative scenarios where an alternative approach was considered more appropriate, or where it was considered important to explore the impact of uncertainty. In response to the EAG's clarification questions, the company provided several scenario analyses, a few of which are amended in the EAG exploratory analyses. The EAG includes several further scenarios in the following section to demonstrate the impact of alternative assumptions on the EAG base case.

Descriptions of the exploratory analyses are presented in Section 6.1 and the impact of these analyses on the revised company's base case are presented in Section 6.2 and Section 6.3, along with the EAG's preferred base case.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The following deterministic exploratory analyses were conducted by the EAG following corrections to the company's base case as described in Section 5, including removing PAS for comparators and making calculation corrections (Section 5.3.1). This calculation correction does not affect the company base case and is only relevant with a specific scenario (see Scenario 3 below).

Each of the following analyses are based on the company's revised/updated (at clarification) and 'corrected' base case model.

1. Model Structure

As described in Section 4.2, the EAG highlights issues with the company's approach to the model structure with a PSM for the lorlatinib arm and STM for the comparators. The company's approach is inconsistent. The EAG considers that this limits the model's ability to accurately reflect outcomes. The EAG proposed an alternative base case approach of using STM in both arms to ensure consistency in the assumptions applied across treatment arms(Scenario 1a). The EAG also provides a scenario where both arms are based on a PSM model structure (Scenario 1b).

2. Time on Treatment - lorlatinib

As discussed in Section 4.2.4 , the EAG is concerned by the company's approach to modelling ToT for lorlatinib. The EAG, therefore, explores a scenario in which the ToT for lorlatinib is equal to PFS. This approach is consistent with the assumptions made in the alectinib and brigatinib arms of the model.

3. Lorlatinib treatment beyond progression

As discussed in Section 4.2.4, it is expected that a proportion of lorlatinib patients will go on to receive lorlatinib even after progression as there will be no alternative treatment except chemotherapy in the NHS. This scenario assumes that 75.6% of patients continued to receive lorlatinib following progression for 5.7 months. Both values are informed by Study 1001 and align with committee preferred assumption in TA909.

4. Extrapolations of crizotinib in PFS

In Section 4.2.6.2, the EAG outlined concerns regarding the extrapolation of crizotinib data which is used as the reference arm for the modelled comparators alectinib and brigatinib and informs waning assumptions applied to all arms. The company base case uses a Weibull function. The log-logistic, log normal and generalised gamma functions all offer substantially improved statistical fit and more optimistic projections than the Weibull function. Amongst these, the EAG prefers the log-logistic as it offers the best statistical fit and represents a middle ground between the three alternatives in terms of survival projections. Scenario 4 therefore explores the use of the log-logistic function to extrapolate crizotinib PFS.

5. Using Lorlatinib arm as the reference arm to model PFS and OS outcomes

In response to clarification question B2c – the executable model allows the reference arm to be switched to lorlatinib. Scenario 5a explores using the lorlatinib arm as the reference curve to which relative treatment effects are applied. Scenario 5b extends this scenario to use a 36-month piecewise Gompertz extrapolation. As discussed in Section 4.2.6.2. the Gompertz extrapolation provides more conservative predictions which EAG consider to better align with clinical expectations.

6. Appropriateness of waning assumptions

As discussed in sections 4.2.6.5, the EAG considers the 10-year waning scenario included in the company's base case to be reasonable, though subject to uncertainty. The EAG believes it would be more appropriate to apply waning to the hazards in the alectinib arm rather than the crizotinib arm. This approach ensures that the waning assumptions address uncertainties regarding the durability of the treatment effect and are not used to correct clinically implausible extrapolations of PFS. Scenario 6 includes four alternatives and incorporates scenario 5b.

6a. Scenario 5b plus no waning
6b. Scenario 5b plus 7-years waning to the alectinib arm
6c. Scenario 5b plus 10-years waning to the alectinib arm
6d. Scenario 5b plus 15-years waning to the alectinib arm

7. Post-progression survival – alectinib and brigatinib (Weibull for PPS)

Extrapolation of PPS was undertaken using an exponential curve assuming constant hazard throughout the model time horizon and was applied such that time in the state was independent of when a patient entered the progressed disease health state. The company did not explore the use of alternative extrapolation approaches using other parametric functions in its submission. In response to clarification question B3, the company provided alternative extrapolations. This scenario explores the use of the Weibull function which provides more optimistic predictions to extrapolate PPS (6.4% of patients remaining alive at 10 years vs. 4.9% alive using the exponential function) and offer improved statistical fit.

8. Alternative utility values

In Section 4.2.7 the EAG discussed the HRQL utility alternatives. For the PF state, the EAG rejects treatment-specific values and prefers the value of 0.793 used in ALTA-1L for brigatinib, as using this value would be inconsistent with those used in the PD health state (Scenario 8a). Additionally, the EAG explores a scenario to better account for the HRQL benefits of lorlatinib in the post-progression setting (either treatment beyond progression or as 2L treatment). In this scenario, the EAG applies a utility value of 0.725 (midpoint between the PF and PD utilities) to patients receiving lorlatinib post-progression (Scenario 8b). A final scenario (8c) combines scenarios 8a and 8b.

9. Duration of chemotherapy

The duration of chemotherapy of 6.3 weeks (1.45 months) from the ASCEND-5 trial is short relative to time alive in the PD health state (22.2 months in the company base case) and is substantially less than the 5.9 months used in TA909. It is also substantively less than the 8.04 months observed in CROWN. Scenario 9a therefore explores increasing the duration of chemotherapy to 5.9 months and scenario 9b to 8.04 months.

10. Differential PAS for Lorlatinib

As discussed in Section 4.2.8.7, the company only applies this updated PAS for lorlatinib to the 1L setting. The EAG does not consider this appropriate as the PAS is indication agnostic and will also apply to the 2L setting should Lorlatinib be recommended in this indication. Scenario 10 therefore explores the implications of applying the updated PAS consistently across both 1L and 2L.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the scenario analyses described in Section 6.1 inclusive of the differential PAS discount for lorlatinib 1L and 2L. The exploratory scenarios presented in Table 30 are conducted on the EAG-corrected company base case analysis. Results inclusive of all available PAS discounts and other commercial arrangements are provided in the confidential appendix to this report.

Table 30 EAG Exploratory fully incremental scenario analyses (deterministic)

Scenario		Technology	Total		Incremental		Fully incremental ICER
			Costs	QALYs	Costs	QALYs	
Company base case		Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1a	**Model Structure (STM)**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1b	**Model Structure (PSM)**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	**ToT = PFS (Both arms)**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	**Treatment beyond progression**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	**Log-logistic extrapolation for crizotinib PFS**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5a	**Using lorlatinib as reference arm in PFS**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5b	**5a+ Gompertz extrapolation +no waning**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6a	**5b+ no waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6b	**5b+7-yr waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6c	**5b+ 10-yr waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6d	**5b+15-year waning to alectinib**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	**Weibull for PPS**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8a	**ALTA-1L pre-progression utilities**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8b	**Using a utility score half-way between**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	pre-and post-progression for time on lorlatinib 2L and beyond progression	Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8c	**8a + 8b**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9a	**Increase duration of chemotherapy to 5.9 months**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9b	**Increase duration of chemotherapy to 8.0 months**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	**Lorlatinib PAS same for 1L & 2L**	Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line; 2L, second line, Ext., extended; HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; PSM, partitioned survival model; PPS, post-progression survival; QALY, quality-adjusted life-year; STM, state transition model; ToT, time on treatment.

6.3 EAG's preferred assumptions

The cumulative impact of the EAG's preferred assumptions is presented in Table 31 below. The EAG's preferred base case is primarily driven by consistency in model structure and ToT assumptions. Given the high of level uncertainty around a number of the key efficacy parameters in the model, the EAG's preferred base case represents a plausible but reasonably optimistic set of assumptions.

The EAG base case adopts the following scenarios described in Section 6.1:

- Scenario 1a: STM in both arms
- Scenario 2: PFS = ToT for lorlatinib
- Scenario 3: Treatment beyond progression TA909 assumptions
- Scenario 5b: Lorlatinib arm, Gompertz extrapolation and 10-yr waning assumption
- Scenario 8c: 8a (Utility value of PFS from ALTA-1L) + 8b (EAG preferred utility values for PD health states)
- Scenario 10: Same PAS for lorlatinib 1L and 2L

Table 31 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

Probabilistic results for the EAG's alternative base case are presented in Table 32. The model was set to the EAG's preferred assumptions and run with 2,000 iterations. Lorlatinib remained [redacted] in the probabilistic EAG base case, with a [redacted] probability of being the most cost-effective option at a willingness-to-pay threshold of £30,000.

Table 32 EAG's base case analysis results (probabilistic)

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					

6.3.1 Additional scenario analysis on the EAG base case

Table 33 presents the EAG preferred base case without scenario 10 applied i.e. with a differential PAS discount for Lorlatinib.

Table 33 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					

6.4 Conclusions of the Cost Effectiveness Section

The company submitted a *de novo* economic analysis to assess the cost effectiveness of lorlatinib in a fully incremental comparison with alectinib and brigatinib for the treatment of untreated ALK-positive advanced NSCLC. The company's model comprised three health states (progression free, progressed disease) in the form of a hybrid PSM / STM model. The company's base case analysis suggested that lorlatinib is less costly and more effective than both alectinib and brigatinib. Lorlatinib dominated both comparators in the deterministic base case analysis with QALY gains of [redacted] and [redacted] versus brigatinib and alectinib respectively.

In the company's probabilistic base case analysis, lorlatinib continued to dominate both comparators, with a [redacted] probability of cost effectiveness at a willingness-to-pay threshold of £20,000 per QALY gained. Note that these results are based on the net price of lorlatinib inclusive of a patient access scheme and an assumed confidential discount for alectinib and brigatinib.

6.4.1 Conclusions of the EAG's critique

The EAG considers the company's economic analysis to reflect the decision problem and meets the requirements of the NICE reference case. It is important to emphasise the decision problem includes the comparison or alternative treatment sequences and is fully reflected by the NICE scope which

focuses only on 1L treatment The EAG's review of the CS identified two key areas of uncertainty which the EAG has sought to characterise in its critique and address where possible in the revised base case and scenario analyses.

The first key uncertainty concerns the clinical data. As elaborated in Sections 3 and 4, the trial data supporting the evidence base, not only from the CROWN study of lorlatinib but also the comparator trials ALEX and ALESIA (alectinib) and ALTA-1L (brigatinib), does not reflect the clinical pathway in NHS practice. Additionally, concerns surrounding the immaturity of CROWN OS data, and the plausibility of the PH assumption mean this evidence cannot provide meaningful estimates of relative OS benefits.

These limitations in clinical data are central to many of the issues highlighted by the EAG. Specifically, the limitations of the available OS data necessitate reliance on external sources to populate the model, reflecting the EAG's preference for using a STM to incorporate such evidence. This approach, however, does not fully overcome these issues as the external data used for modelling 2L treatment benefits does not fully represent the clinical pathway in the NHS. Moreover, it implies that modelled OS is no longer based on randomised comparisons.

This approach also emphasises PFS as the principal driver of cost effectiveness. While the EAG is less concerned about the reliability of relative treatment effects for PFS, substantive uncertainty remains regards long-term projections. The EAG has refined the company's extrapolation approach to ensure greater methodological consistency, but the plausibility of extrapolations relies principally on clinical judgment. It is therefore important to acknowledge the significant uncertainties associated with these projections in decision making.

The second major area of uncertainty pertains to ToT and treatment beyond progression, both of which have a significant impact on lorlatinib's drug acquisition costs and subsequent cost effectiveness estimates. The company's approach utilises the observed ToT from the CROWN trial to model lorlatinib and assumes no treatment beyond progression. While the EAG acknowledges that this approach aligns with the data informing health benefits, it is important to recognise the limitations inherent in the CROWN data. This approach implies a substantial off-treatment period, and it is not clear to the EAG that this is clinically plausible. Moreover, there are several reasons to believe that CROWN ToT may not reflect NHS practice. The availability of ALK inhibitors as a subsequent treatment option in the trial is particularly likely to have impacted observed ToT.

Regarding treatment beyond progression, the company's approach diverges from both the marketing authorisation and prevailing clinical opinion, which suggests that treatment beyond progression will occur in NHS practice. The EAG's base case and scenario analyses have sought to better align with likely NHS practice in terms of ToT and treatment beyond progression; however, it is important to note that these adjustments do not modify the modelled health benefits. Therefore, it is necessary to

balance the uncertainty in cost effectiveness estimates that arises from aligning with NHS practice against the benefits of an approach that adheres more closely to current trial evidence.

Reflecting on TA909 and the updated analysis provided by the company, the EAG observes that the provision of updated PFS data has not substantially addressed the challenges identified in that appraisal. Consequently, cost effectiveness estimates remain highly uncertain. As the committee concluded in TA909, it is difficult to envision how further follow-up can mitigate these fundamental uncertainties, as the trial evidence itself does not reflect NHS practice.

7 SEVERITY MODIFIER

The company did not provide a severity modifier QALY shortfall analysis in their original submission and is not seeking a severity modifier weighting. In response to clarification question B11, the company provided a written response indicating that they used the York (online) shortfall calculator to calculate general population QALYs.

The expected total QALYs for the general population were based on the 2019-20 National life tables for England and Wales from the ONS.[65]The population EQ-5D-3L data adjusted by age and sex were derived from the Health Survey from England (HSE) 2014, as recommended by the NICE DSU.[66]

The expected total QALYs for the general population was 13.58. The company's QALY shortfall analysis is presented in Table 34, along with the values generated in the EAG preferred base case.

The results of incorporating the expected total QALYs for the general population from the DSU calculator imply that the absolute QALY shortfall is below 12 and no severity weight when using alectinib/brigatinib as the comparator. The EAG feels that a severity modifier of 1 is applicable.

Table 34 Summary of QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY Shortfall
Company base case				
Lorlatinib				
Alectinib	13.58	[redacted]	[redacted]	[redacted]
Brigatinib	13.58	[redacted]	[redacted]	[redacted]
EAG base case				
Lorlatinib				
Alectinib	13.58	[redacted]	[redacted]	[redacted]
Brigatinib	13.58	[redacted]	[redacted]	[redacted]

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9 APPENDICES

9.1 Appendix 1 - Study 1001: cohorts EXP3B-5

9.1.1 Methods and participants

A critique of the Study 1001 design and methods is presented in Section 3.2.2.1. A description of these cohorts is presented in Clarification Response Appendix 2, with further details and results provided in an unpublished manuscript.[13]

EXP3B included ALK-positive patients with disease progression following a 2nd generation ALK TKI with or without chemotherapy, EXP4-5 included ALK positive with disease progression following ≥2 ALK TKIs with or without chemotherapy. EXP3B-5 combined ALK positive with disease progression following ≥1 2nd generation ALK TKI with or without chemotherapy.

9.1.2 Risk of bias and applicability to NHS setting

The company's quality assessment of Study 1001 is presented in Clarification Response Appendix 2, Table 5, and discussed in Section 3.2.2.1. Overall, the EAG believes that the company's quality assessment was not appropriate, and that Study 1001 is significantly limited by the lack of randomised control arm. No formal appraisal of applicability (or external validity) was presented.

None of the trial sites were based in the UK. The EXP 3B-5 cohort definition falls within the previously treated population lorlatinib was recommended for as per TA628: ALK-positive NSCLC patients whose disease has progressed after alectinib or ceritinib as the first ALK TKI, or crizotinib and at least 1 other ALK tyrosine kinase inhibitor.[2] However, the EAG clinical advisers indicated that most patients in practice currently receive alectinib 1L, followed by lorlatinib 2L, and that crizotinib is no longer used in practice (see Section 2.2). Therefore, the applicability of cohorts EXP 4-5 to NHS practice is limited.

9.1.3 Baseline characteristics

Baseline characteristics of EXP3B-5 patients are presented Table 35. The EAG clinical advisers considered that the EXP3B-5 cohort was broadly representative of patients receiving lorlatinib following prior TKI therapy for ALK-positive NSCLC. Although the proportion of white people was lower than in NHS clinical practice, EAG clinical advisers do not believe that ethnicity is a treatment effect modifier.

Table 35 Baseline characteristics of Study 1001 cohorts EXP 3B and EXP 4-5

Characteristic	Previous non-crizotinib ALK TKI with or without chemotherapy EXP3B; n=28	≥2 previous ALK TKIs* with or without chemotherapy EXP4–5; n=111
Age		

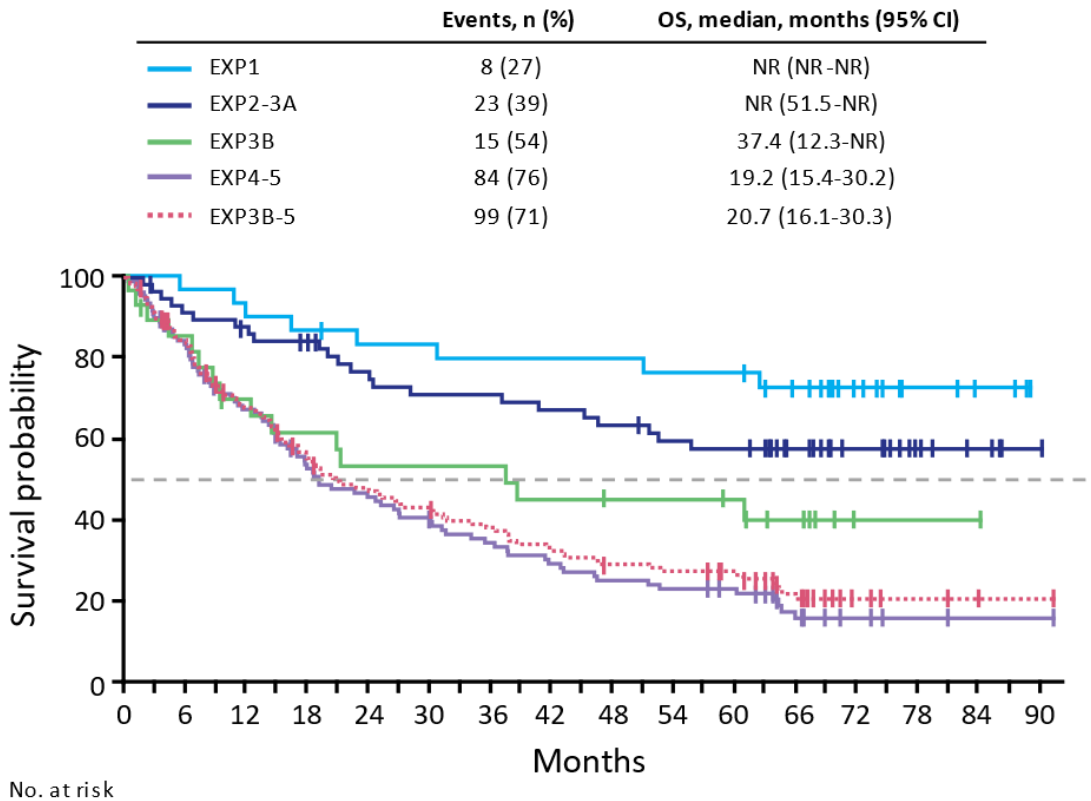
Characteristic	Previous non-crizotinib ALK TKI with or without chemotherapy EXP3B; n=28	≥2 previous ALK TKIs* with or without chemotherapy EXP4–5; n=111
Mean, years (SD)	55·0 (11·6)	51·9 (11·5)
Median	54·0	51·0
Interquartile range	46·5–64·0	43·0–59·0
Sex		
Female, n (%)	16 (57%)	62 (56%)
Male, n (%)	12 (43%)	49 (44%)
Race or ethnic group[b]		
White, n (%)	7 (25%)	59 (53%)
Asian, n (%)	1 (4%)	0
Black, n (%)	16 (57%)	37 (33%)
Missing, n (%)	3 (11%)	10 (9%)
ECOG PS score[c]		
0, n (%)	15 (54%)	46 (41%)
1, n (%)	13 (46%)	59 (53%)
2, n (%)	0	6 (5%)
Number of previous ALK or *ROS1* TKI regimens		
1	28 (100%)	0
2	0	65 (59%)
3	0	42 (38%)
≥4	0	4 (4%)
Number of previous chemotherapy regimens		
0	15 (54%)	26 (23%)
1	10 (36%)	43 (39%)
2	2 (7%)	26 (23%)
3	1 (4%)	8 (7%)
≥4	0	8 (7%)
Brain metastases at baseline		
n (%)	13 (46%)	83 (75%)

Abbreviations: ALK, anaplastic lymphoma kinase, ECOG PS, Eastern Cooperative Oncology Group Performance Status, TKI, tyrosine kinase inhibitor
Notes: [a] Percentages may not total 100 because of rounding. [b] Race or ethnic group was reported by the investigator. [c] ECOG PS scores range from 0 to 5, with higher scores indicating greater disability.
Source: Solomon 2018[67]

9.1.4 Overall survival results

OS results were presented in an unpublished manuscript.[13] Figure 12 presents KM OS curves for all ALK-positive cohorts of Study 1001.

Figure 12 Kaplan-Meier OS curve in ALK-positive patients: cohorts of Study 1001



No. at risk (censored)

EXP1	30	30	29	29	27	27	26	25	24	24	24	23	23	23	23	23	23	23	22	22	22	19	18	16	11	8	6	6	4	4	0	
EXP2-3A	59	56	53	52	50	48	46	42	41	39	38	38	38	37	36	36	34	33	31	30	30	28	22	19	16	13	8	6	5	1	1	0
EXP3B	28	24	22	19	17	15	15	14	13	13	13	13	13	11	11	11	10	10	10	10	9	6	6	3	1	1	1	1	0			
EXP4-5	111	99	89	76	70	63	54	47	45	42	39	35	33	30	28	26	24	24	22	22	20	18	10	5	4	2	2	1	1	1	1	0
EXP3B-5	139	123	111	95	87	78	69	61	58	55	52	48	46	41	39	37	34	34	32	32	29	24	16	8	5	3	3	2	1	1	1	0

Source: Unpublished manuscript (2024)[13]

Abbreviations: ALK, anaplastic lymphoma kinase, CI, confidence interval; OS, overall survival

Notes: EXP1: Treatment naïve (n=30)

EXP2-3A: Previous crizotinib with or without chemotherapy (n=59)

EXP3B: Previous non-crizotinib ALK TKI with or without chemotherapy (n=28)

EXP4-5: ≥ 2 previous ALK TKIs with or without chemotherapy (n=111); if the same TKI was given twice, it was counted as two previous lines of treatment

EXP3B-5: EXP3B and EXP 4-5 combined (n=139)

The median follow-up was 66.7 months for cohorts EXP3B and EXP4-5. The median OS was 37.4 months (95% CI, 12.3 to NR) in EXP3B, 19.2 months (95% CI, 15.4 to 30.2) in EXP4-5, and 20.7 months (95% CI, 16.1 to 30.3) in EXP3B-5; 5-year OS probabilities were 45%, 23%, and 27%, respectively. At least 1 type of subsequent anticancer therapy was received by 14 (50%) in EXP3B, 70 (63%) in EXP4-5, and 84 (60%) in EXP3B-5. Results for EXP3B-5 are driven by the results of the EXP4-5 cohort, who make up 80% of the cohort; results of EXP3B are limited by the small size of this cohort (n=28). OS outcomes are likely to be confounded by the impact of the high proportion of subsequent therapies in EXP3B and EXP4-5. As discussed in Section 9.1.2, the results of EXP4-5 (and by extension, of EXP3B-5) have limited applicability to NHS practice.

9.2 Appendix 2 – Comparison with published NMAs

Table 36: Summary of NMA results from Ou *et al.* (2024) review compared to CS NMA

	CS NMA	Ou 2024	Ando 2021[42]	Chuang 2021[36]	Zhao 2021[40]	Ma 2021[37]	Peng 2021[41]	Wang 2021[38]	Wen 2022[39]
Date of search	**February 2024**	**April 2021**	**May 2021**	**December 2020**	**April 2021**	**September 2021**	**June 2021**	**January 2021**	**April 2022**
Number of RCTs included	4	10	8	6	11	9	9	5	9
J-ALEX included (separate or merged node)	No	Yes (separate node)	Yes (merged node)	Yes (separate node)	Yes (merged node)	Yes (separate node)	Yes (merged node)	Yes (merged node)	Yes (merged node)
NMA method	Bayesian	Bayesian	Bayesian	Frequentist[1]	Bayesian	Bayesian	Bayesian	Bayesian	Bayesian
Meta-analysis model	Fixed effect	Fixed effect	NR	Fixed effect	Random effect	Random effect	Fixed effect	Fixed effect	Fixed effect
OS, HR (95% CrI)[2]									
Lorlatinib vs. alectinib	1.12 (0.59, 2.11)	NR	1.18 (0.59, 2.35)	NR	1.43 (0.17, 18.25)	1.07 (0.42, 2.73)	1.08 (0.25, 5.55)	NR	1.23 (0.64, 2.38)[3]
Lorlatinib vs. brigatinib	0.89 (0.44, 1.78)	NR	0.74 (0.31, 1.76)	NR	0.63 (0.04, 9.09)	0.78 (0.29, 2.08)	0.79 (0.12, 5.15)	NR	0.89 (0.44, 1.79)[3]
PFS (BICR), HR (95% CrI)									
Lorlatinib vs. alectinib	0.59 (0.37, 0.95)	0.61 (0.39, 0.97)	0.74 (0.47, 1.18)	0.68 (0.42, 1.08)	0.53 (0.21, 1.35)	0.68 (0.23, 2.12)	0.82 (0.26, 2.98)	0.59 (0.39, 0.94)	0.66 (0.41, 1.04)
Lorlatinib vs. brigatinib	0.56 (0.34, 0.93)	0.57 (0.35, 0.93)	0.57 (0.33, 1.00)	0.57 (0.32, 0.92)	0.44 (0.15, 1.35)	0.57 (0.16, 2.05)	0.57 (0.13, 2.58)	0.54 (0.31, 0.94)	0.58 (0.35, 0.96)
Time to intracranial/CNS progression, HR (95 % CrI)									
Lorlatinib vs. alectinib	0.39 (0.17, 0.89)	0.56 (0.24, 1.29)	NR	NR	NR	NR	0.35 (0.09, 1.82)	NR	NR
Lorlatinib vs. brigatinib	0.20 (0.07, 0.54)	0.29 (0.10, 0.78)	NR	NR	NR	NR	0.20 (0.03, 1.34)	NR	NR
Grade ≥ 3 or 3/4 AEs, OR (95 % CrI)									
Lorlatinib vs. alectinib	3.90 (2.14, 7.15)	2.95 (1.58, 5.47)	1.92 (1.49, 2.48)[4]	1.62 (0.24, 2.12)[4]	NR	3.46 (0.35, 38.24)	4.26 (1.22, 15.53)	NR	3.39 (1.84, 6.30)
Lorlatinib vs. brigatinib	1.74 (0.87, 3.50)	1.31 (0.65, 2.65)	1.18 (0.90, 1.55)[4]	1.07 (0.84, 1.37)[4]	NR	1.67 (0.12, 24.25)	1.69 (0.36, 9.91)	NR	1.24 (0.62, 3.26)
AEDC, OR (95% CrI)									
Lorlatinib vs. alectinib	1.05 (0.33, 3.37)	0.81 (0.30, 2.20)	NR	NR	NR	NR	NR	NR	0.77 (0.27, 2.13)
Lorlatinib vs. brigatinib	0.59 (0.16, 2.16)	0.45 (0.14, 1.43)	NR	NR	NR	NR	NR	NR	0.44 (0.13, 1.41)

Abbreviations: BICR, blinded independent central review; BID, twice a day; Crl, credible interval; CNS, central nervous system; CS, company submission; HR, hazard ratio; INV, investigator; NMA network meta-analysis; NR, not reported; OR odd ratio; OS overall survival; PFS progression free survival; RR relative risk
Footnotes: HR, OR or RR <1 favours lorlatinib vs. comparator; [1]Estimates from Chuang et al, 2021[36] is in confidence intervals not credible intervals; [2]Not reported in Ou *et al.* (2024), an EAG reviewer extracted the data from the NMA reports, data were checked by EAG reviewer, [3]HR and 95% Crl was inverted; [4]RR;
Source: adapted from CS, Section B.2.6; Ou *et al.* (2024)[35]

9.3 Appendix 3 – PROFILE 1001 and PROFILE 1005 studies

A pooled analysis of the PROFILE 1001 and PROFILE 1005 study cohorts informed post-progression outcomes in the company model (see Section 4.2.2, Table 12)

9.3.1 Methods and participants

PROFILE 1001[68] is an expanded cohort (n=153) of a dose-escalation phase 1 study of crizotinib for ALK-positive NSCLC, and PROFILE 1005[69] is a phase 2 trial of crizotinib which recruited 261 patients after failure of ≥ 1 line of systemic treatment for locally advanced/metastatic disease. Both studies administered 250mg crizotinib BID. PROFILE 1001 and PROFILE 1005 are both single-arm trials and had similar inclusion criteria, except for patients in PROFILE 1005 must have failed at least one line of treatment, while patients in PROFILE 1001 could have been treatment-naïve.

Ou *et al.* (2014)[70] is a retrospective analysis combining the results from patients who experienced disease progression from the PROFILE 1001 and PROFILE 1005 studies. The combined analyses aimed to compare the baseline and post-progression characteristics, sites of progressive disease (PD) and OS, measured from the time of initial crizotinib treatment and from PD, between patients who continued crizotinib beyond disease progression and patients who discontinued crizotinib.

The retrospective analysis included 194 patients; 120 who continued crizotinib following disease progression and 74 who discontinued crizotinib following disease progression and used a Cox PH regression model adjusting for multiple covariates including age, sex, ethnicity, ECOG performance status, smoking history, and prior line of therapy.

9.3.2 Risk of bias and applicability to NHS setting

The company's do not provide a quality assessment of the PROFILE 1001 and PROFILE 1005 studies or the pooled analysis. Overall, the EAG believes that PROFILE 1001 and PROFILE 1005 studies and the pooled analysis are at high risk of bias due to the lack of randomised control arms within the studies, and the retrospective nature of the pooling of the analyses. No formal appraisal of applicability (or external validity) was presented.

None of the trial sites were based in the UK. The majority of the patients included in the pooled analysis of PROFILE 1001 / 1005 had failed at least one line of systemic therapy and were therefore receiving crizotinib 2L. The majority of these patients continued with crizotinib following disease progression, while a minority of these patients discontinued crizotinib and then received subsequent systemic therapy, including chemotherapy 3L. The applicability of the populations recruited into these studies to NHS practice is limited, and the sequences of treatments received 1L, 2L and 3L in these studies is not representative of current NHS practice.

9.3.3 Results

The baseline- and post- progression characteristics showed that there was a statistically significant difference in the ECOG performance status of 0/1 at PD between those who continued crizotinib beyond disease progression compared to those who discontinued, but no other differences between the groups.

Patients who continued crizotinib had longer median OS from time of PD (16.4 months [95% CI 14.5 to not reached]) compared to those who discontinued crizotinib (3.9 months [95% CI 2.7 to 5.1]), and this difference was statistically significant (HR 0.27 [95% CI: 0.17 to 0.42], $p<0.0001$). Furthermore, patients who continued crizotinib had significantly longer OS from time of start of initial crizotinib compared to those who discontinued (median OS 29.6 months [95% CI 23.1 to not reached] compared to 10.8 months [95% CI 8.9 to 14.7]; HR 0.30 [95% CI 0.19 to 0.46].

Within the group of patients who discontinued crizotinib but received subsequent systemic therapies (n=37), median OS was longer compared to those who discontinued crizotinib and did not receive subsequent systemic therapies (n=37); median OS 5.4 months (95% CI of 3.8 to 12.3) compared to median OS 2.2 months (95% CI of 1.1 to 3.8).

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 26 November 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 CROWN trial/protocol issue and others relating to ToT and additional cycles (4 issues altogether)

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Sentences relating to the CROWN trial stating that treatment beyond progression was not allowed in CROWN and factually incorrect. This has been explained in B.3.3.5, which reflects the CROWN protocol (and license wording). This has also been verified by conversations with global/core medical and statistical functions at Pfizer that are involved in trial and data management who verified this is the	These lines should be deleted and replaced or rewritten to correct that the CROWN trial did allow treatment beyond progression. There was not “stopping rule” in the CROWN trial.	Misrepresents CROWN trial protocol and should be corrected.	The EAG has edited page 68 to state that only the ALEX trial did not permit treatment beyond progression. The EAG has edited page 69 to clarify that the model is consistent with the observed ToT data.

case (and that there are no protocol amendments that have adjusted the original protocol in this respect). In particular the statements (both p68 and 69): • "In ALTA-1L, time on treatment exceeds PFS, but this is because ALTA-1L permitted treatment beyond progression, where CROWN and ALEX did not." • "While the EAG acknowledges			

that the modelled base case analysis is consistent with stopping rules implemented in CROWN…"			
Pfizer would like the following sentence adjusted (p69): "The calculations presented in the company response to clarification question B10 misrepresent the proportion of patients who received treatment beyond progression in Study 1001 (whole population). According to the Study 1001 CSR (May 2017 data cut), 78% (89 out of 114) of patients, i.e. the majority, who	Pfizer believe that the response to B10 has been slightly misunderstood and so there is no misrepresentation. Pfizer suggest that the word "misrepresent" should be removed and sentence rephrased to reflect the response provided to B10. That part of the response to B10 was to ascertain where the 5.7 month/cycle figure was sourced from and it appears it was from the Ou et al (2022) publication which is about treatment beyond progression in Study 1001 (Table 2): https://www.sciencedirect.com/science/article/pii/S1556086421034171 The 5.7 figure reflects patients from Study 1001 EXP3B-5 cohort (i.e. cohort reflecting 2L lorlatinib population) who had a BOR of complete or partial response or stable disease and who also had lorlatinb past IV defined progression for more	Does not reflect the response to B10 response accurately.	Not a factual error. The response to B10 suggests that only 20.1% of patients receive treatment beyond progression in Study 1001. This does not reflect the figures in the CSR.

experienced progression received treatment beyond progression."	than 3 weeks. Therefore, the overall mean of cycles/months would be lower by weighting in patients who had less than 3 weeks of lorlatinib treatment past progression (18 patients who had average of 0.3 months) and further the rest of EXP3B-5 cohort who were not responding and so unlikely to have treatment past progression (or very little).		
Pfizer acknowledge the EAG point that 2L options perhaps available/known in CROWN centres are different from NHS practice, however statements about 2L options, such as those below, should be further contextualised by giving the low proportions of patients who received 2L TKIs in the lorlatinb arm of CROWN. In particular statements such as	Add a sentence giving proportions of 2L TKI use from the CROWN trial (lorlatinb arm) as reported in Table 25 of Document B for extra context (i.e. 2L TKI use available to clinicians in many centres but most progressed lorlatinib patients did not get a TKI and in particular not a 2nd generation TKI). As the EAG notes as well, "systemic treatment" included chemotherapy which would be given post lorlatinib 1L in the NHS.	Add further context to point that 2L environments following lorlatinib differ, but that most patients in the lorlatinib arm of CROWN did not receive 2L TKIs anyway.	We have added additional text noting the proportions receiving 2L ALK inhibitors and referred to Table 25 of the CS.

the following could be further contextualised (p67 and p68): • "The EAG considers that decisions to discontinue treatment reflect clinical experience of managing AEs associated with lorlatinib, knowledge of efficacy and the **availability of 2L treatment options and are context-specific**" • "The 2L treatment options available to patients in the CROWN trial also differ			

substantively from those currently available on the NHS and include 2nd generation ALK inhibitors which are not available in the NHS where only chemotherapy is available”			
Pfizer believe a statement should be added (or figure referenced) showing that PFS INV and BICR are in practice very similar for lorlatinib from CROWN (e.g. see figure 24 in B3): “Furthermore, the EAG also has more pragmatic concerns with the company’s	Add an additional sentence saying that fitting a cox model derived HR versus BICR and applying this would make very little difference (and maybe referencing a figure comparing KMs), for example: “However, given that the observed BICR and IA PFS were similar in CROWN deriving and applying a HR based on BICR may not make a great deal of difference.”	Useful to contextualise usefulness of this approach and if it would make much difference.	Not a factual, but we agree that the additional context is relevant and have edited in line with the suggested text.

approach. Firstly, if we accept the company's approach of applying a HR to modelled PFS, then the estimation of this HR should use PFS (BICR) rather than PFS (INV). As outlined in the CROWN trial protocol, decisions on discontinuation of treatment were based on progression events evaluated by BICR and not investigators. It is therefore inappropriate to compare the two evaluating any difference between PFS and ToT using PFS (INV)."			

Issue 2 2L lorlatinib PAS that currently exists

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Pfizer believe this is out of the NICE process and is not consistent with all previous precedents in NICE appraisals. The model is comparing a world where lorlatinib displaces comparator treatments (i.e. lorlatinib arm of the model) versus a world in which it does not (i.e. 2L PAS continues to be maintained with 2L lorlatinib use) and this reflects the correct decision problem for the committee. If there was any 2L lorlatinib use in a world with 1L lorlatinib approved Pfizer would have used the “live” PAS everywhere in the	Remove as technical issue given that it is a process issue.	Not consistent with NICE process and will confuse the committee.	Not a Factual error. We have spoken with the NICE team and agreed that the EAG’s concerns should be outlined in the EAR to ensure transparency in decision making. The EAG disagrees that this is process issue as it relates to the technical specification of the model and the interpretation of the decision problem.

lorlatinb model arm, but this is not the case. This should be removed as a technical issue in line with NICE process and the view of the NICE technical team (as acknowledged in the report).			

Issue 3 PSM vs STM description clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
This is a minor point but the model structure description (p60) is described as an STM (i.e. as in the company base-case settings for lorlatinib), but the model PFS is not determined in this way (i.e. it is determined in the same way as the partitioned survival model, PSM). This is why it is often referred to as “pseudo state transition approach” because only the PPS is modelled in the same way as in a STM.	Adjust description and consider wording from submission – PFS is always determined in the same way as a PSM.	Minor clarification.	Not a factual error. While the EAG acknowledges the point being made, there isn’t a meaningful difference between a full STM and the pseudo version implemented by the company. We feel making this distinction within the text isn’t particularly helpful and isn’t relevant to the issues we discuss in the EAR.

Issue 4 Clarity on how the flatiron RWE reduces decision risk for committee

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pfizer suggest that a statement should be made about how the RWE analysis reduces decision risk for the committee with regard to sequencing and impact on efficacy. This could be added as commentary to issue 1 and 2, the section on the RWE analysis and broad conclusion at the end of the EAG report.	As stated, to the left the KMs and fitted curves of the RWE analysis (adjusted) are very similar to the modelled PFS (i.e. HR applied to lorlatinib PFS) and OS (i.e. PPS based on weighted Study 1001 efficacy). This should reduce decision risk concerning sequencing for the committee, particularly because the RWE analysis does not give very much higher OS for alectinib.	To clarify effect of RWE flatiron analysis on decision risk of committee.	Not a factual inaccuracy.

Issue 5 Minor corrections

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
This is a minor point that Pfizer believe should be deleted or adjusted (p33) because the reason follows from the reason given for PFS updates: "The company did not provide justification for the reporting of unplanned post-hoc analyses for other outcomes presented in the CS."	The reason for having additional post-hoc updates of other secondary endpoints is the same reason as for the updates to PFS (IA): these secondary endpoints are considered primary at the point of primary PFS analysis and so having additional analyses (i.e. 3 and 5 years) does not break trial reporting conventions. These conditions have not been met for the OS endpoint.	Redundant sentence, consider deleting or adjusting.	Not a factual inaccuracy, but the sentence was removed for the sake of concision.
The following statement (and similar) does not reflect that external validity was discussed in section "B.2.12.2.2. External validity of CROWN" of the company submission.	Delete or adjust sentence	External validity was discussed in the submission and included validation from the ad-board etc.	We have removed this sentence.

Rephrase or delete the line and similar (p38): "No formal appraisal of applicability (or external validity) was presented"			
Minor correction in values on p44 and p51: "All-cause CNS AEs were reported in 42% of patients in the lorlatinib group; of those, **88%** were Grade 1 or 2 and **12%** were Grade 3." "In ALESIA, the median PFS (INV) was reached at 41.6 months for alectinib versus 11.1 months for crizotinib, and the 5-year OS rate was **66.4** for alectinib versus 56.0% for crizotinib"	Values should be: "All-cause CNS AEs were reported in 42% of patients in the lorlatinib group; of those, **86%** were Grade 1 or 2 and **13%** were Grade 3." Add % sign to 66.4	Minor reporting errors	Corrected.