Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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**

2. **Clarification questions and company responses**
   a. A&C response
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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. **External Assessment Report** prepared by prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

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6. **Technical engagement response from company**
   a. Initial response
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7. **Technical engagement responses and statements from experts:**
   a. Ai Choo Bennett, Patient Expert – nominated by ALK Positive UK
   b. Dr Alastair Greystoke, Senior Lecturer and Honorary Consultant in Medical Oncology, Clinical Expert – nominated by Pfizer
   c. Debra Montague, Chair of ALK Positive UK, Patient Expert – nominated by ALK Positive UK
   d. Dr Shobhit Baijal, Consultant Medical Oncologist, Clinical Expert – nominated by British Thoracic Oncology Group (BTOG)

8. **Technical engagement response from stakeholders:**
   a. Takeda

9. External Assessment Group critique of company response to technical engagement prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Document B

Company evidence submission

May 2022

File name	Version	Contains confidential information	Date
ID3896_Lorlatinib DocumentB_12May22_Fully Redacted	**FINAL**	**No**	**12th May 2022**

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Abbreviations

Abbreviations	Definition
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDx	Companion diagnostic
CI	Confidence interval
CNS	Central nervous system
CNS-PFS	Intracranial progression-free survival
CPK	Creatinine phosphokinase
CR	Complete response
CrI	Credible interval
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYPX	Cytochrome X
DCO	Data cut-off
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
E-DMC	External Data Monitoring Committee
EGFR	Epidermal growth factor
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EML4	Echinoderm microtubule associated protein-like 4
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-XL	EuroQol 5 dimensions X levels
EQ-VAS	EuroQol 5 dimensions Visual Analogue Scale
ESMO	European Society for Medical Oncology

FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridisation
GP	General practitioner
H_0	Null hypothesis
H_A	Alternative hypothesis
HR	Hazard ratio
HRQoL	Health-related quality of life
IAX	Interim analysis X
IC	Intracranial
IC-CR	Intracranial complete response
IC-DOR	Intracranial duration of response
IC-OR	Intracranial objective response
IC-TTP	Intracranial time to progression
IC-TTR	Intracranial time to tumour response
IQR	Interquartile range
IRR	Independent radiological review
IRT	Interactive response technology
ITT	Intention-to-treat
KM	Kaplan–Meier
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRI	Magnetic resonance imaging
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival; odds ratio
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcome

PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
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
RPFST	Rank-preserving structural failure time
RTK	Receptor tyrosine kinase
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Standard deviation; stable disease
SE	Standard error
SF-36	36-Item Short Form Health Survey
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SRS	Stereotactic radiotherapy
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TPR	Translocated promotor region
TTD	Time to deterioration
TTR	Time to tumour response
VEGF-R	Vascular endothelial growth factor receptor
WBRT	Whole brain radiotherapy

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

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication. The company submission differs from the final NICE scope to align with the marketing authorisation wording and the evidence base for lorlatinib.

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

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated ALK-positive advanced NSCLC	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	The population is aligned with the marketing authorisation for lorlatinib of 'adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor'
Intervention	Lorlatinib	Lorlatinib	NA – in line with the final NICE scope
Comparator(s)	• Alectinib • Brigatinib • Ceritinib • Crizotinib	• Alectinib • Brigatinib	• Alectinib and brigatinib represent the two most effective treatments currently available for patients with previously untreated ALK-positive NSCLC and the most commonly used therapies in this indication in the UK. • During the NICE evaluation of brigatinib as first-line therapy for ALK-positive advanced NSCLC (TA670), ceritinib was excluded from the evaluations as it was agreed by the ERG and clinical experts that ceritinib is rarely used (1–2%) in untreated ALK patients. It was concluded that patients with ALK-positive advanced NSCLC who have not had an ALK inhibitor before are usually offered alectinib.[1] • Since receiving positive NICE guidance in 2016, crizotinib usage in this indication has predominantly been replaced by more effective second-generation ALK inhibitors. Crizotinib is therefore not considered to be a relevant comparator to lorlatinib in this evaluation; this again follows the precedent

			from TA670.[1] • Following brigatinib's approval by NICE, which drew upon indirect comparative evidence that it is as effective as alectinib, the vast majority of patients in this setting are anticipated to receive either alectinib or brigatinib only. As such, these two therapies represent the most relevant comparators for this evaluation.
Outcomes	• OS • PFS • Response rates • Adverse effects of treatment • HRQoL	• OS • PFS • Response rates • Intracranial outcomes • Adverse effects of treatment • HRQoL	All outcomes listed are relevant in this patient population. However, OS comparisons remain immature at this time with only 18 months of follow-up data available for lorlatinib. Comparisons of OS at similar stages of trial evolution are included in this submission. Interim and final data cut-offs for OS are planned for [redacted] and [redacted].

Abbreviations: ALK: anaplastic lymphoma kinase; HRQoL: health-related quality of life; MHRA: Medicines and Healthcare products Regulatory Agency; NA: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival.
Source: NICE 2021.[2]

B.1.2 *Description of the technology being evaluated*

A description of the technology being appraised (lorlatinib [Lorviqua®]) is provided in Table 2. A link to the Summary of Product Characteristics (SmPC) for lorlatinib is provided in Appendix C.

Table 2: Technology being appraised

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.[3] 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.[4] 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,[5] and play an essential role in the regulation of tumour cell survival, growth and metastasis.[6] Lorlatinib has shown potent growth-inhibitory activity and induced cell death in vitro.[7] In vivo, lorlatinib has demonstrated a marked reduction in the number of ALK or ROS1 fusion variant tumour cells in mice. In addition, lorlatinib was specifically designed to cross the blood-brain barrier through the introduction of a macrocyclic ring, and has demonstrated CNS penetration in animal models.[7]
Marketing authorisation/CE mark status	MHRA marketing authorisation for lorlatinib in this indication was granted on 23rd September 2021.[7]
Indications and any restriction(s) as described in the SmPC	*Of relevance to this submission, lorlatinib holds an MHRA marketing authorisation for the following indication:* • 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:*[7, 8] • 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.[7] 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.[9]
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.[10]

Patient access scheme (if applicable)	A confidential PAS of [redacted] has been previously agreed for lorlatinib, providing lorlatinib at a net price of [redacted] and [redacted] tablets.

Abbreviations: ALK: anaplastic lymphoma kinase; CNS: central nervous system; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; NSCLC: non-small-cell lung cancer; PAS: patient access scheme; PASLU: Patient Access Scheme Liaison Unit; ROS1: ROS proto-oncogene 1; RTK: receptor tyrosine kinase; SmPC: Summary of Product Characteristics; TKI: tyrosine kinase inhibitor; UK: United Kingdom.

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

In the UK, 80–85% of lung cancers are classified as non-small cell lung cancer (NSCLC),[11] with ALK gene translocations presenting in 3–7% of NSCLC tumours.[12] ALK-positive advanced NSCLC imposes a substantial clinical, humanistic, and economic burden on patients, their carers and the NHS.

- Patients with NSCLC often have no or light smoking history and are typically diagnosed with advanced disease and at a relatively young age compared with the overall lung cancer population[13, 14]
- ALK is a receptor tyrosine kinase (RTK) that plays an important role in cellular proliferation, differentiation, and apoptosis.[15] Alongside, epidermal growth factor (EGFR) and ROS proto-oncogene 1 (ROS1) mutations, ALK gene translocations represent a key driver of NSCLC.[16] In the UK, NICE recommends that ALK status testing should be conducted for all patients with non-squamous NSCLC at diagnosis[17]
- Brain metastases are highly prevalent in patients with ALK-positive NSCLC; real-world data indicates that 22–30% of patients with ALK-positive NSCLC have brain metastases at diagnosis.[18, 19] Brain metastases are associated with substantial mortality and morbidity, causing patients to experience confusion, drowsiness, weakness in the limbs and severe headaches[20, 21]
- Brain metastases and the symptoms of lung cancer, including a persistent cough, fatigue, pain, weight loss and shortness of breath,[22] have a considerable negative impact on both patients' and their caregivers' quality of life (QoL), well-being and social functioning[23-25]Brain metastases and the symptoms of lung cancer, including a persistent cough, fatigue, pain, weight loss and shortness of breath,[22] have a considerable negative impact on both patients' and their caregivers' quality of life (QoL), well-being and social functioning[23-25]
- The hospitalisation, medical treatment and high incidence of brain metastases in patients with ALK-positive advanced NSCLC is associated with substantial economic burden and healthcare resource use[26, 27]

There remains a substantial unmet need for first-line ALK-positive advanced NSCLC treatments that can penetrate the blood-brain barrier more effectively than currently available therapies and that have low susceptibility to ALK resistance mutations.

- Following diagnosis of ALK-positive advanced NSCLC, a number of first and second-generation ALK inhibitors currently hold a NICE recommendation for use: crizotinib (TA406), ceritinib (TA500), alectinib (TA536) and brigatinib (TA670)[28, 29, 30, #6]
- Alectinib and brigatinib, both second-generation ALK inhibitors, represent the two most effective and most commonly used treatments currently available for patients with previously untreated ALK-positive NSCLC in the UK. As such, these two therapies represent the most relevant comparators to lorlatinib in this evaluation
- Alectinib and brigatinib have improved the prognosis for patients with NSCLC. However, the efficacy and safety of these treatments are limited by the development of resistance mutations and clinically relevant adverse events (AEs) such as constipation, myalgia, hypertension and bradycardia[31, 32,33, 34]
- Lorlatinib is a selective small molecule inhibitor of ALK and ROS1 RTKs, that is capable of crossing the blood-brain barrier,[3] and offers patients with untreated ALK-positive advanced

NSCLC a new, effective treatment option, with a tolerable and manageable safety profile.

- Lorlatinib can overcome some of the limitations associated with currently available therapies in this indication and provide improved outcomes for patients in the first-line setting[35]

B.1.3.1 Overview of the disease

Disease area

Lung cancer is the fourth most common cancer in the United Kingdom (UK),[36] with 31,371 cases diagnosed in England in 2020 and 2,240 cases diagnosed in Wales in 2019.[37] Between 2016–2018, lung cancer caused over 35,137 deaths in the UK;[38] between 2013–2017, only 40.6% of patients survived for more than one year following diagnosis, and 16.2% and 9.5% of patients survived for more than five and ten years, respectively.[39]

Lung cancer refers to tumours that form in tissues of the lung, usually in the cells lining air passages, and consists of two major types, small cell lung cancer (SCLC) and NSCLC. In the UK, 90.3% of lung cancers are classified as NSCLC,[37] which can be further categorised according to histologic subtype (squamous-cell carcinoma, adenocarcinoma and large cell carcinoma) and pathologic stage of disease.

Advances in the understanding of tumour biology have led to the identification of many of the key molecular pathways that drive tumour growth in NSCLC. Growth factors play important roles in affecting cellular proliferation, differentiation, and apoptosis by binding to specific receptors on the surface of cells that convey regulatory signals through associated intracellular receptor tyrosine kinases (RTKs). Dysregulation of RTK activity and escape from normal control of these cellular processes has been found in many types of cancer.[15] Key driver mutations in NSCLC include the RTK ALK, epidermal growth factor (EGFR) and ROS proto-oncogene 1 (ROS1) rearrangements.[16]

ALK gene translocations are present in 3–7% of NSCLC tumours,[12] with the highest prevalence in those of adenocarcinoma histology.[40] At least 28 different ALK rearrangements have been identified to date, of which echinoderm microtubule associated protein-like 4 (EML4)-ALK is the predominant isoform, having been identified in 63.5% of ALK-rearranged cases.[41] Other ALK fusion variants present in NSCLC include kinesin family member 5B-ALK, kinesin light chain 1-ALK and translocated promotor region (TPR)-ALK.[13]

In the UK, NICE recommends that ALK status testing should be conducted for all patients with non-squamous NSCLC at diagnosis. ALK status testing is performed using fluorescence in situ hybridisation (FISH), immunohistochemistry, chromogenic in situ hybridisation and reverse transcription polymerase chain reaction (RT-PCR).[17]

Clinical burden of disease

Patients with NSCLC often have no or light smoking history and are typically diagnosed at a relatively young age compared with the overall lung cancer population.[13] As lung cancer progresses, the associated symptom burden is high, with patients often experiencing a persistent cough, fatigue, pain, weight loss and shortness of breath.[22] However, due to the usually asymptomatic nature of lung cancer in the early stages,[42] and the lack of smoking history, patients often have advanced disease at the time of diagnosis.[14]

In the UK, approximately 49% of patients with lung cancer present with metastatic stage IV disease and 12% present with locally advanced, stage IIIB/C.[43] Common metastatic sites in patients with ALK-positive NSCLC include the central nervous system (CNS), liver, pleura and bone.[18] Brain metastases are highly prevalent in patients with ALK-positive NSCLC; real-world data indicates that 22–30% of patients with ALK-positive NSCLC have brain metastases at diagnosis.[18, 19] Brain metastases are also associated with substantial morbidity, causing patients to experience confusion, drowsiness, weakness in the limbs and severe headaches.[20]

Humanistic burden of disease

Whilst a substantial burden of lung cancer is related to mortality, its symptoms can have a considerably negative impact on both patients' and their caregivers' quality of life (QoL), well-being and social functioning.[23, 24] Increasing symptom severity and the number of symptoms experienced are both negatively correlated with QoL.[44] Health-related QoL (HRQoL) has been shown to be associated with survival, with the global QoL and physical functioning scores of the disease-specific European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) shown to be predictive of survival among 1,194 patients with NSCLC, most of whom (55%) were diagnosed with stage IV disease. For every 10-point improvement in global QoL or physical functioning scores, there was a 9% and 10% increase in survival ($p<0.001$), respectively.[45] In addition, improved 36-Item Short Form Health Survey (SF-36) general health and QLQ-C30 global QoL scores are associated with a lower risk of death among patients with NSCLC who have undergone initial therapy.[46]

Moreover, the high incidence of brain metastases in ALK-positive NSCLC is likely to have a further negative impact on QoL.[25] A United States (US)-based observational study found a greater decline over time in 18 of 20 evaluated HRQoL measures in patients with brain metastases than in patients without.[47]

Economic burden of disease

In addition to the high clinical and humanistic burden of disease, the hospitalisation and medical treatment in patients with ALK-positive advanced NSCLC is associated with substantial economic burden and healthcare resource use.[27] Moreover, the high incidence of brain metastases in this population is likely to increase the economic burden further due to the frequent hospital visits and inpatient stays, increased medical treatment, imaging and radiotherapy.[26]

Indirect medical costs are also high in patients with NSCLC.[48] ALK-positive patients are more likely to be of working age, have dependents, or be carers, than those with ALK-negative disease.[13] Therefore, the impact of reduced QoL and functioning may lead to higher productivity loss in this population. The economic burden of NSCLC on carers is also substantial, and has been shown to increase over time with disease progression.[49] On average, caregivers of patients with advanced NSCLC are estimated to provide 29.5 hours of support each week.[50]

B.1.3.2 Clinical pathway of care

Current treatment pathway

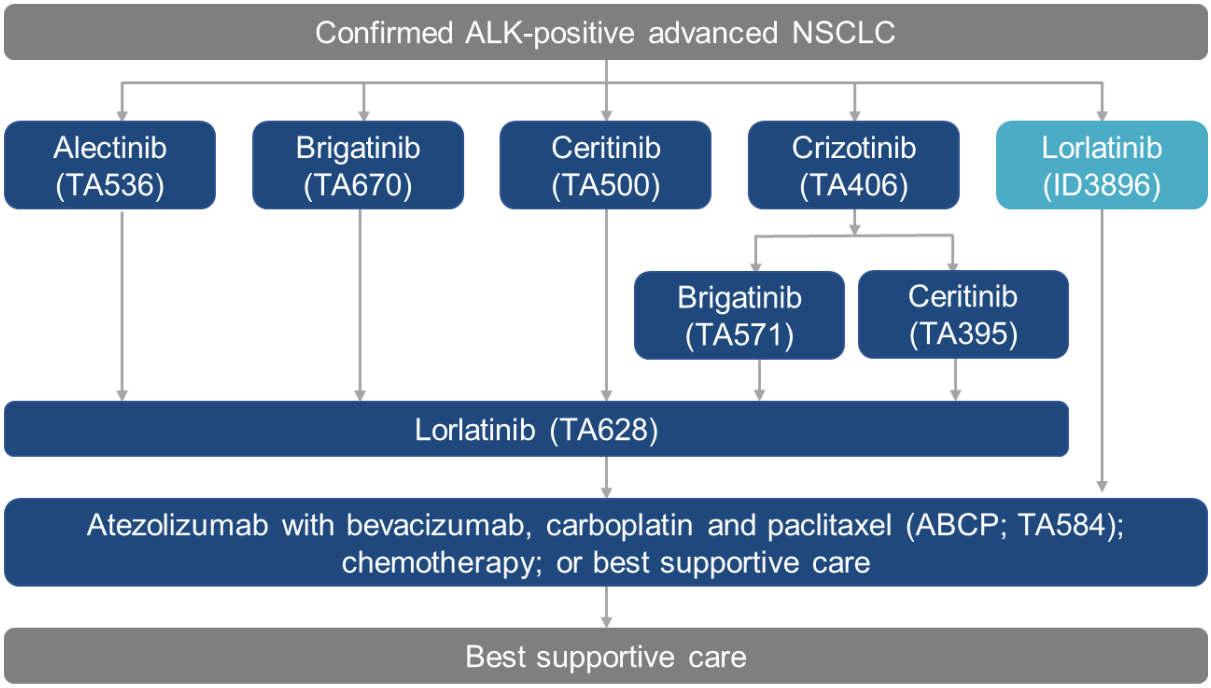
Prior to 2011, patients with ALK-positive advanced NSCLC had few effective treatment options available and a relatively poor prognosis. The standard of care comprised treatment with traditional chemotherapy including docetaxel, gemcitabine, paclitaxel or vinorelbine plus a

platinum-based drug (carboplatin or cisplatin) for advanced NSCLC. However, the identification of the ALK driver mutation has led to a major shift in the treatment of this cancer as targeted therapies can now be utilised in the clinical management of patients with ALK-positive advanced NSCLC.

NICE and European Society for Medical Oncology (ESMO) guidelines in lung cancer recommend that ALK status testing should be undertaken for all patients with non-squamous NSCLC at diagnosis, as the mutation is more common in this subgroup.[51]

Following diagnosis of ALK-positive advanced NSCLC, a number of first and second-generation ALK inhibitors currently hold a NICE recommendation for use: crizotinib (TA406), ceritinib (TA500), alectinib (TA536) and brigatinib (TA670) (see Figure 1).[1, 28, 29, 37]

Figure 1: Anticipated positioning of lorlatinib relative to the current treatment pathway for patients with ALK-positive advanced NSCLC



Lorlatinib in the first-line position (ID3896) is the subject of this evaluation.
Abbreviations: ALK: anaplastic lymphoma kinase; NSCLC: non-small-cell-lung cancer.
Source: NICE Pathways (advanced non-squamous [stages IIIB and IV] NSCLC: ALK-positive).[52]

Crizotinib

Crizotinib is a first-generation ALK inhibitor and was the first ALK inhibitor to be granted European Medicines Agency (EMA) approval in ALK-positive advanced NSCLC in October 2012, and later in 2016 received a positive NICE recommendation for both untreated ALK-positive advanced NSCLC (TA406) and for ALK-positive advanced NSCLC previously treated with chemotherapy (TA422).[28, 53] While the superiority of crizotinib to traditional chemotherapy has been well documented,[54-56] other studies have shown that patients treated with crizotinib often develop treatment resistance and may relapse due to ALK dependent and independent mechanisms.[57] Disease progression generally occurs within one year from the start of treatment with crizotinib, with the CNS often being the first and most common site of progression due to the known low CNS penetration of crizotinib.[54, 55, 57, 58] Consequently, in the UK, crizotinib usage has

predominantly been replaced by more effective second-generation ALK inhibitors and crizotinib is therefore not considered to be a relevant comparator to lorlatinib in this evaluation.

Ceritinib

In 2016, the second-generation ALK inhibitor ceritinib received a positive NICE recommendation for patients with ALK-positive advanced NSCLC who had previously been treated with crizotinib (TA395) and later in 2018 received a positive recommendation in the first-line advanced setting (TA500).[29, 59] However, the use of ceritinib as a first-line therapy is extremely limited, with clinical experts during the NICE appraisal for brigatinib (TA670; recommended in 2021) suggesting that only 1–2% of patients with ALK-positive advanced NSCLC currently receive ceritinib in UK NHS practice.[1] This low usage is thought to be due to its limited efficacy against CNS metastases and concerns about its tolerability profile.[1] For example, diarrhoea, nausea and vomiting were commonly reported adverse events (AEs) in the randomised-controlled trial (RCT) of ceritinib versus platinum-based chemotherapy (ASCEND-4).[60] Based on this lack of use in clinical practice, the NICE Committee agreed to exclude ceritinib as a relevant comparator in the brigatinib appraisal (TA670).[1] Similarly, ceritinib is therefore not considered to be a relevant comparator to lorlatinib in this evaluation.

Alectinib and brigatinib

In 2018, alectinib received a positive NICE recommendation for untreated ALK-positive advanced NSCLC (TA536).[30] Alectinib demonstrated systemic and CNS superiority over crizotinib in the randomised head-to-head ALEX trial,[61, 62] and has a more favourable safety profile compared with ceritinib.[57, 63] Consequently, clinical experts during the NICE appraisal for brigatinib (TA670; recommended in 2021) suggested that at least 90% of patients with advanced NSCLC who have confirmed ALK status at diagnosis receive alectinib.[1] Similarly, brigatinib demonstrated superiority over crizotinib in untreated patients with ALK-positive advanced NSCLC in the randomised head-to-head ALTA1-1L trial.[54] While no head-to-head data exist for alectinib and brigatinib, clinical experts and the Committee agreed during the NICE appraisal for brigatinib (TA670; recommended in 2021) that it is plausible OS with brigatinib could be expected to be similar to alectinib due to their biological and pharmacological similarities.[1] Considering the similar efficacy of alectinib and brigatinib, and the high use of alectinib prior to brigatinib's approval, the vast majority of patients with ALK-positive advanced NSCLC who have not previously received an ALK inhibitor are most likely to receive alectinib or brigatinib in current clinical practice. As such, these two therapies represent the most relevant comparators to lorlatinib in this evaluation. In 2018, alectinib received a positive NICE recommendation for untreated ALK-positive advanced NSCLC (TA536).[30] Alectinib demonstrated systemic and CNS superiority over crizotinib in the randomised head-to-head ALEX trial,[61, 62] and has a more favourable safety profile compared with ceritinib.[57, 63] Consequently, clinical experts during the NICE appraisal for brigatinib (TA670; recommended in 2021) suggested that at least 90% of patients with advanced NSCLC who have confirmed ALK status at diagnosis receive alectinib.[1] Similarly, brigatinib demonstrated superiority over crizotinib in untreated patients with ALK-positive advanced NSCLC in the randomised head-to-head ALTA1-1L trial.[54] While no head-to-head data exist for alectinib and brigatinib, clinical experts and the Committee agreed during the NICE appraisal for brigatinib (TA670; recommended in 2021) that it is plausible OS with brigatinib could be expected to be similar to alectinib due to their biological and pharmacological similarities.[1] Considering the similar efficacy of alectinib and brigatinib, and the high use of alectinib prior to brigatinib's approval, the vast majority of patients with ALK-positive advanced NSCLC who have not previously received an ALK inhibitor are most likely to receive alectinib or

brigatinib in current clinical practice. As such, these two therapies represent the most relevant comparators to lorlatinib in this evaluation.

While alectinib and brigatinib, both second-generation ALK inhibitors, have improved the prognosis for patients with NSCLC, limitations still exist with these treatments. ALK-resistance mutations, most of which are difficult to treat, are common after treatment with currently available ALK inhibitors, and are more common with second-generation ALK inhibitors.[31, 32] Moreover, it has been shown that resistance mutations to alectinib may rapidly develop within as little as three months of treatment initiation.[31] In addition to the limitations related to resistance, alectinib and brigatinib are also associated with clinically relevant AEs such as constipation, myalgia, hypertension, bradycardia, respectively.[33, 34] [31, 32] Moreover, it has been shown that resistance mutations to alectinib may rapidly develop within as little as three months of treatment initiation.[31] In addition to the limitations related to resistance, alectinib and brigatinib are also associated with clinically relevant AEs such as constipation, myalgia, hypertension, bradycardia, respectively.[33, 34]

Unmet need

There remains a substantial unmet need for treatments that can penetrate the blood-brain barrier more effectively than currently available therapies and that have low susceptibility to ALK resistance mutations. Whilst a number of ALK inhibitors are currently available, there are relevant differences between them in terms of chemical and molecular structure, binding specificities to the ALK kinase, and kinase inhibition potency. These characteristics are reflected in the individual limitations of each treatment, including variable safety profiles, varying efficacy in the presence of ALK mutations, and varying ability to penetrate the blood-brain barrier and thereby, target CNS metastases.[64, 65]

Brain metastases in patients with ALK-positive NSCLC are associated with a generally poor survival outcome, low quality of life and high economic burden.[25,47] A large pooled retrospective analysis conducted in patients with ALK-positive NSCLC pre-treated with chemotherapy identified CNS as the main site of progression on crizotinib in patients with brain metastases at baseline after first-line treatment found that survival probability and overall objective response were lower for patients with brain metastases at baseline compared to patients without.[58]

Consequently, the burden of ALK-positive advanced NSCLC remains high and there is a need for a broader range of treatment options in this population, particularly in the first-line setting.

Positioning of lorlatinib in the treatment pathway

Lorlatinib is a third-generation ALK inhibitor that offers patients with untreated ALK-positive advanced NSCLC a new, effective treatment option, with a tolerable and manageable safety profile, that can overcome some of the limitations associated with currently available therapies in this indication and provide improved outcomes for patients in the first-line setting.

Lorlatinib has previously been recommended by NICE in May 2020 for patients with previously treated ALK-positive advanced NSCLC (TA628). An updated marketing authorisation has been issued by the Medicines and Healthcare products Regulatory Agency (MHRA) for lorlatinib for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.[8] Lorlatinib is proposed to be positioned for use in UK clinical practice in a broader population for adult patients with untreated ALK-positive advanced NSCLC as shown in Figure 1,

which is aligned to the patient population in the pivotal CROWN study and the marketing authorisation.

B.1.4 *Equality considerations*

It is not expected that this evaluation will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this evaluation will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

The phase 3 randomised-controlled trial (RCT), CROWN, represents the pivotal source of clinical evidence for lorlatinib in previously untreated advanced anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC)[35, 66]

- CROWN is an ongoing phase 3, multinational, multicentre, randomised, open-label, parallel, two-arm study in which patients with previously untreated advanced ALK-positive NSCLC were randomised 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy[35]
- The outcomes of the interim analyses (IAs) of the CROWN trial presented in this submission (data cut-offs in March 2020 and September 2021) are well aligned with the decision problem for this evaluation and are directly relevant to treatment in NHS clinical practice

The CROWN study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in BICR-assessed PFS in the lorlatinib arm compared with the crizotinib arm[35, 67]

- At the September 2021 data cut-off (DCO), the percentage of patients who were alive without disease progression at 36 months was [redacted]% (95% confidence interval [CI]: [redacted]) in the lorlatinib group and [redacted]% (95% CI: [redacted]) in the crizotinib group (hazard ratio [HR] = [redacted] [95% CI: [redacted]; [redacted]])[66]
- The majority of patients in both treatment arms at the March 2020 DCO were still alive. Lorlatinib demonstrated a 28% reduction in the risk of death compared with crizotinib (HR=0.72 [95% CI: 0.41, 1.25]), however due to the immaturity of the data, no robust conclusions can yet be drawn for OS[35, 67]
- As of the September 2021 DCO, the objective response rate (ORR) was significantly higher in the lorlatinib arm compared with the crizotinib arm ([redacted]% [95% CI: [redacted]] versus [redacted]% [95% CI: [redacted]], 1-sided p[redacted]). Among those with measurable brain metastases, [redacted]% (95% CI: [redacted]) in the lorlatinib arm and [redacted]% (95% CI: [redacted]) in the crizotinib arm had an intracranial objective response (IC-OR), and [redacted]% of the patients who received lorlatinib had an intracranial complete response (CR)[66]
- Intracranial time to progression (IC-TTP) from the September 2021 DCO was significantly longer in the lorlatinib arm compared with the crizotinib arm, with a HR of [redacted] (95% CI: [redacted]; p[redacted]) corresponding to a [redacted]% reduction in the risk of IC-progression[66]
- Patients in the lorlatinib arm had a significantly greater overall improvement from baseline in global QoL than those who received crizotinib (September 2021 DCO: estimated mean difference = [redacted] [95% CI: [redacted]], although the difference was [redacted])[66]
- Overall, the results of the CROWN trial clearly demonstrate the superior clinical efficacy of lorlatinib compared with crizotinib in patients with previously untreated advanced ALK-positive NSCLC, with meaningful improvements in PFS and response rates, including for those patients with measurable brain metastases

In a network meta-analysis (NMA), lorlatinib showed a statistically significant reduction in the risk of progression or death, reducing the risk of progression or death by [redacted]% and [redacted]% compared with alectinib and brigatinib, respectively

- In the NMA, lorlatinib showed a [redacted] improvement in PFS using data from the September 2021 DCO, with a HR of [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) compared with alectinib and brigatinib, respectively
- Using OS data from the March 2020 DCO for lorlatinib, there were [redacted] in OS, with a HR of [redacted] and [redacted] compared with alectinib and brigatinib, respectively. However, OS data are still immature. Further OS data cuts are planned for [redacted] and [redacted].

The results from the CROWN trial demonstrate lorlatinib to be tolerable, with an acceptable, and manageable adverse event (AE) profile[35, 67]

- At the September 2021 DCO, almost all patients had experienced at least one AE, with [redacted]% and [redacted]% of patients experiencing a serious adverse event (SAE) in the lorlatinib and crizotinib arms,

respectively. The most common AEs with lorlatinib in the CROWN trial were [redacted][66]

- Grade 3 or 4 AEs occurred in [redacted]% of patients who received lorlatinib and [redacted]% of those who received crizotinib, and permanent discontinuation due to AEs was low in both treatment arms, occurring in [redacted]% and [redacted]% of patients receiving lorlatinib and crizotinib, respectively[66]

Lorlatinib has been recognised as an innovative therapy by the Medicines and Healthcare products Regulatory Agency (MHRA), having been granted ORBIS designation, and represents a novel, third-generation inhibitor that is at least as effective as its key comparators, alectinib and brigatinib, for patients with previously untreated ALK-positive advanced NSCLC

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. 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. In total, the SLR identified 100 records reporting on ten unique RCTs and 139 records reporting on 79 unique non-RCTs. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

As identified in the clinical SLR, the pivotal trial for lorlatinib in this indication is the open-label, phase 3 RCT (CROWN) investigating the efficacy and safety of lorlatinib versus crizotinib in patients with previously untreated advanced ALK-positive NSCLC.

The results of the CROWN trial are presented in this submission from the publication from Shaw et al. 2020 and supplemented by the interim CSR, both of which present data from the interim analysis 1 (IA1) for the first data-cut in March 2020.[35, 67] Longer-term results from the second interim analysis (IA2) based on the September 2021 data-cut are presented in Document B where available,[66] with data from the March 2020 data-cut being presented in Appendix M. Where data from the September 2021 data-cut were not available, data from the March 2020 data-cut are presented in Document B.

Table 3: Clinical effectiveness evidence

Study	CROWN (NCT03052608),[67] Shaw et al. 2020.[35]
Study design	Multinational, multicentre, randomised, open-label, parallel, two-arm phase 3 trial.
Population	Patients with advanced ALK-positive NSCLC who had received no previous systemic treatment for metastatic disease.
Intervention(s)	Lorlatinib 100 mg, oral once daily.
Comparator(s)	Crizotinib 250 mg, oral twice daily.
Rationale for use/non-use in the model	CROWN is the pivotal phase 3 trial for lorlatinib in patients with previously untreated advanced ALK-positive 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.
Reported outcomes specified in the decision problem	*Primary outcome* • **PFS based on BICR assessment (RECIST v1.1)** *Secondary outcomes*

	• PFS based on investigator's assessment (RECIST v1.1)
	• **OS**
	• Response rates
	  ○ ORR based on BICR and on investigator's assessment (RECIST v1.1)
	  ○ DOR based on BICR (RECIST v1.1)
	  ○ TTR based on BICR assessment (RECIST v1.1)
	• IC outcomes
	  ○ IC-TTP based on BICR assessment (modified RECIST v1.1)
	  ○ IC-OR based on BICR assessment (modified RECIST v1.1)
	  ○ IC-DOR based on BICR assessment (modified RECIST v1.1)
	  ○ IC-TTR based on BICR assessment (modified RECIST v1.1)
	• Adverse effects of treatment
	  ○ AEs
	  ○ Treatment discontinuation due to AEs
	  ○ Deaths
	  ○ SAEs
	  ○ AEs of special interest
	• HRQoL as assessed by EORTC QLQ-C30, EORTC QLQ-LC13, **EQ-5D-5L**

All other reported outcomes	• **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

Abbreviations: AE: adverse event; ALK: anaplastic lymphoma kinase; BICR: blinded independent central review; CNS: central nervous system; DOR: duration of response; 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; HRQoL: 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; 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: Pfizer Ltd Data on File (Interim Clinical Study Report) 2020.[67]

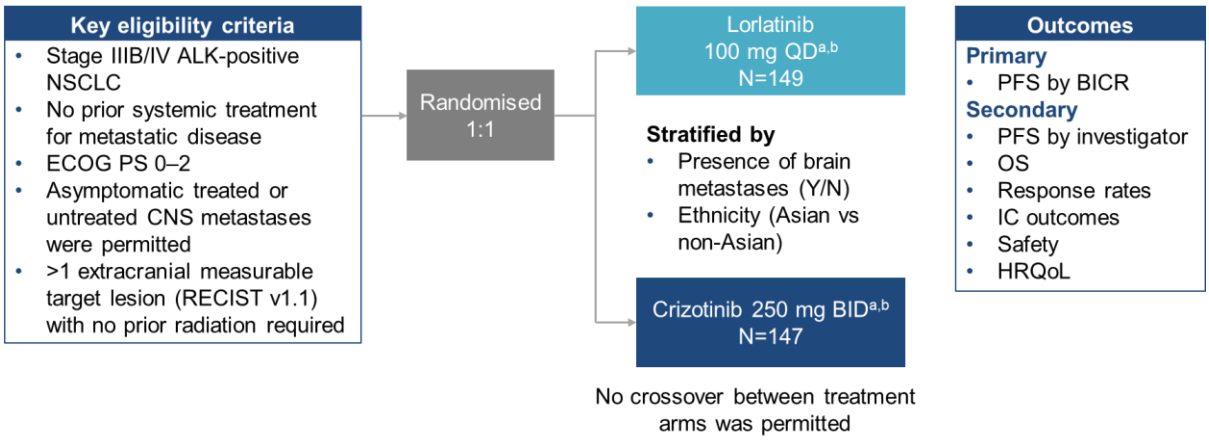
B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Summary of trial design and methodology

CROWN is an ongoing phase 3, multinational, multicentre, randomised, open-label, parallel, two-arm study in which patients with previously untreated advanced ALK-positive NSCLC were randomised 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy.[35]

Summaries of the CROWN study design and methodology are presented in Figure 2 and Table 4.

Figure 2: CROWN study design



[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.
Abbreviations: ALK: anaplastic lymphoma kinase; BICR: blinded independent central review; BID: twice daily; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HRQoL: 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.
Source: Pfizer Ltd Data on File (Interim Clinical Study Report) 2020.[67]

Table 4: 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]; Czech Republic [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 3, multinational, multicentre, randomised, open-label, parallel two-arm study
Duration of study and follow-up	• Study treatment may continue until confirmed disease progression assessed by BICR, patient refusal, patient lost to follow-up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first • 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 2 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/anticancer drugs, including anticancer systemic chemotherapy or biological therapy • Select vitamin or herbal supplements, including herbal remedies with anticancer 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
	  ○ 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 investigator's assessment (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 investigator's assessment (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 (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 assessment (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 assessment (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 assessment (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 death due to any cause in the subset of patients with an IC-DOR of CR or PR ○ **IC-TTR based on BICR assessment (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 • **HRQoL:** 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).

[a] Tumour assessments included all known or suspected disease sites. Imaging included chest, abdomen, brain and pelvis CT or MRI scans.
Abbreviations: 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; HRQoL: 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; 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.
Source: Pfizer Ltd Data on File (Clinical Study Protocol) 2020;[35] Pfizer Ltd Data on File (Clinical Study Report) 2020.[67]

Eligibility criteria

A summary of the key eligibility criteria for CROWN is presented in Table 5. Please refer to Appendix M for the full eligibility criteria.

Table 5: 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 prior to 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 prior to 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
  - Liver

Exclusion criteria

- Major surgery within four weeks prior to 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 prior to randomisation, including stereotactic or partial brain irradiation. Patients who complete whole brain irradiation within four weeks prior to randomisation or palliative radiation therapy outside of the CNS within 48 hours prior to 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 (please refer to Appendix M for full details)

Abbreviations: 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 Tumor version 1.1.
Source: Pfizer Ltd Data on File (Clinical Study Protocol) 2020.[35]

B.2.3.2 Baseline characteristics

A summary of the baseline characteristic of patients in the CROWN trial is shown in Table 6. The baseline patient demographics were well-balanced between treatment arms, with no major differences with respect to gender, race or clinically important characteristics. The median age of patients enrolled in CROWN across both treatment arms was 57.38 years, with 40.88% male patients enrolled across both treatment arms. There were numerically slightly fewer female patients in the lorlatinib arm compared with the crizotinib arm. Although there were some slight imbalances in gender and ethnicity, demographics were generally similar to that expected of patients with ALK-positive NSCLC in the UK.

Table 6: 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]		
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 anticancer 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)

[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 anticancer 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.
Abbreviations: AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITT: intention-to-treat; SD: standard deviation.
Source: Shaw et al. 2020.[35]

Additional details of patient baseline characteristics can be found in Appendix M.

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

B.2.4.1 Analysis sets in CROWN

The analysis sets defined in the CROWN trial are presented in Table 7.

Table 7: Analysis sets in CROWN

Analysis set	Description	Applicable endpoint
FAS (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.
SAS (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.
PRO analysis set (N=285)	Defined as patients from the FAS who completed a baseline (last PRO assessment prior to 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.

Abbreviations: FAS: full analysis set; PRO: patient-reported outcome; SAS: safety analysis set; TTD: time to deterioration.
Source: Pfizer Ltd Data on File (Interim Clinical Study Report) 2020 (Table 4).[67]

B.2.4.2 Patient disposition

Between 11 May 2017 and 28 February 2019, 296 patients were randomised in the CROWN trial, 149 to the lorlatinib arm and 147 to the crizotinib arm (including five patients who were not treated).[35, 67] Patient disposition as of the September 2021 DCO is presented in Table 8**Error! Reference source not found.**.

At the September 2021 DCO, 149 and 142 patients were treated with lorlatinib and crizotinib, respectively. Of these patients, [redacted] and [redacted] of patients in the lorlatinib and crizotinib

arms, respectively, permanently discontinued treatment; this was mostly due to PD, followed by AEs (see Section B.2.10).[66]

A total of [redacted] and [redacted] patients in the lorlatinib and crizotinib arms, respectively, were still ongoing in the treatment phase as of the data cut-off date.

Table 8. Patient disposition (data cut-off: 20 September 2021)

Event	Lorlatinib	Crizotinib
Randomised, n (%)	149 (100)	147 (100)
Treated, n (%)	149 (100)	142 (97)
Not treated, n (%)	0	5 (3)
Event	**Lorlatinib (N=149)**	**Crizotinib (N=142)**
Discontinued		
Total discontinued, n (%)	[redacted]	[redacted]
AE, n (%)	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]
PD, n (%)	[redacted]	[redacted]
Withdrawal by patient, n (%)	[redacted]	[redacted]
Global deterioration of health status, n (%)	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ongoing		
n (%)	[redacted]	[redacted]

Footnotes: The number of treated patients was the denominator to the calculation of percentages.
Abbreviations: AE: adverse event; PD: progressive disease.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

A CONSORT diagram for the CROWN trial is presented in Appendix D.

B.2.4.3 Statistical analysis

A summary of the statistical analyses of the CROWN trial are provided in Table 9.

Table 9: Summary of statistical analyses

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: $HR_{PFS} \geq 1$ versus 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 (prior to any new anticancer treatment) for patients who did not have an event (PD or death), for patients who started new

	anticancer treatment prior to 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 one 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* • IA1 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 futility 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 • IA1 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 IA1, 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 are planned when 70% and 100% (final OS analysis) of the 198 OS events have occured. A Lan-DeMets (O'Brien-Fleming) α-spending function would be used • IA2 was not pre-specified, but was performed after 141 PFS events based on BICR assessments (80% of the 177 events for the final analysis) had occurred (data cut-off 20 September 2021). This data cut was introduced to provide a median follow-up of approximately 36 months, which was deemed to be clinically relevant and at the same level of other ALK TKI trials
Sample size, power calculation	296 patients were randomised in the CROWN trial. 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). 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 IA. 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 IAs 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.

Abbreviations: 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; H_0: null hypothesis; H_A: alternative hypothesis; HR: hazard ratio; IA: interim analysis; 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 Ltd Data on File (Clinical Study Protocol) 2020.[35]

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

A quality assessment of the CROWN trial, based on the CROWN protocol, CSR and Shaw et al. 2020 publication, using the risk of bias checklist recommended by NICE is provided in Table 10. CROWN was methodologically robust, well-reported and considered to be at low risk of bias.[35, 67]

Table 10: 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

Question	CROWN trial
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

B.2.6 *Clinical effectiveness results of the relevant studies*

The CROWN study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in BICR-assessed PFS in the lorlatinib arm compared with the crizotinib arm[35, 67]

- At the September 2021 data cut-off (DCO), the percentage of patients who were alive without disease progression at 36 months was [redacted]% (95% confidence interval [CI]: [redacted]) in the lorlatinib group and [redacted]% (95% CI: [redacted]) in the crizotinib group (hazard ratio [HR] = [redacted] [95% CI: [redacted]; [redacted]])[66]
- The majority of patients in both treatment arms at the March 2020 DCO were still alive. 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]), however due to the immaturity of the trial data, no robust conclusions can yet be drawn from the OS data[66]
- As of the September 2021 DCO, the objective response rate (ORR) was significantly higher in the lorlatinib arm compared with the crizotinib arm ([redacted]% [95% CI: [redacted]] versus [redacted]% [95% CI: [redacted]], 1-sided p[redacted]). Among those with measurable brain metastases, [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]), respectively, had an intracranial objective response (IC-OR), and [redacted]% of the patients who received lorlatinib had an intracranial complete response (CR)[66]
- Intracranial time to progression (IC-TTP) from the September 2021 DCO was significantly longer in the lorlatinib arm compared with the crizotinib arm, with a HR of [redacted] (95% CI: [redacted]; p[redacted]) corresponding to a [redacted]% reduction in the risk of IC-progression.[66]
- At the March 2020 DCO, mean (± standard error [SE]) baseline scores in measures of global quality of life (QoL) were 64.6±1.82 in the lorlatinib arm and 59.8±1.90 in the crizotinib arm. At the September 2021 DCO, patients in the lorlatinib arm had a significantly greater overall improvement from baseline in global QoL than those who received crizotinib (estimated mean difference = [redacted] [95% CI: [redacted]], although the difference did not reach the clinically meaningful difference)[66]
- Overall, the results of the CROWN trial clearly demonstrate the superior clinical efficacy of lorlatinib compared with crizotinib in patients with previously untreated advanced ALK-positive NSCLC, with meaningful improvements in PFS and response rates, including for those patients with measurable brain metastases

B.2.6.1 Progression-free survival

The CROWN study met its primary objective of demonstrating a statistically significant and clinically meaningful improvement in blinded independent central review (BICR)-assessed progression-free survival (PFS) in the lorlatinib arm compared with the crizotinib arm, with a [redacted]% reduction in the risk of progression or death in favour of lorlatinib at the September 2021 DCO (HR=[redacted] [95% CI: [redacted]]).[66]

Progression-free survival based on BICR assessment (RECIST v1.1)

At the September 2021 DCO, median duration of follow-up for PFS was [redacted] in the lorlatinib arm and [redacted] in the crizotinib arm. A [redacted] and clinically meaningful improvement in BICR-assessed PFS was demonstrated in the lorlatinib arm compared with the crizotinib arm with a HR of [redacted] (95% CI: [redacted]; stratified 1-sided p-value [redacted])

indicating a [redacted]% reduction in risk of progression or death in favour of the lorlatinib arm compared with the crizotinib arm. Results for PFS based on BICR assessment from the September 2021 DCO are consistent with those from the March 2020 DCO, which are presented in Appendix M.[66]

A summary of the BICR-assessed PFS results from the September 2021 DCO is presented in Table 11 and Figure 3.

Table 11: Summary of BICR-assessed PFS (RECIST v1.1), FAS (data cut-off: 20 September 2021)

Variable	Lorlatinib (N=149)	Crizotinib (N=147)
Patients with event		
n (%)	[redacted]	[redacted]
Type of event		
PD, n (%)	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]
Patients censored		
n (%)	[redacted]	[redacted]
Reason for censoring		
No adequate baseline assessment, n (%)	[redacted]	[redacted]
Start of new anticancer therapy, n (%)	[redacted]	[redacted]
Event after ≥2 missing or inadequate postbaseline assessments, n (%)	[redacted]	[redacted]
Withdrawal of consent, n (%)	[redacted]	[redacted]
Lost to follow-up, n (%)	[redacted]	[redacted]
No adequate postbaseline tumour assessment, n (%)	[redacted]	[redacted]
Ongoing without an event, n (%)	[redacted]	[redacted]
Probability of being event free		
At 12 months, (95% CI)[a]	[redacted]	[redacted]
At 24 months, (95% CI)[a]	[redacted]	[redacted]
At 36 months, (95% CI)[a]	[redacted]	[redacted]
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[b]	[redacted]	[redacted]
Median, (95% CI)[b]	[redacted]	[redacted]
Q3, (95% CI)[b]	[redacted]	[redacted]
Comparison versus crizotinib, stratified analysis[c]		
HR (95% CI)[d]	[redacted]	
1-sided p value[e]	[redacted]	
2-sided p value[e]	[redacted]	

[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. [e] Repeated CI method used to take into account the group-sequential nature of the design as per EAST v6.5. [f] P-value based on stratified log-rank test.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IRT: interactive response technology; NE: not evaluable; PD: progressive disease; PFS: progression-free survival; Q: quartile; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Figure 3: Kaplan–Meier plot of PFS based on BICR assessment (RECIST v1.1), FAS (data cut-off: 20 September 2021)

Tick marks on the survival curves indicate censoring of data.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; NR: not reached; PFS: progression-free survival; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Progression-free survival based on derived investigator assessment (RECIST v1.1)

Results for PFS based on derived investigator assessment (RECIST v1.1) at the September 2021 DCO continued to be consistent with those for PFS based on BICR assessment (RECIST v1.1).

At the September 2021 DCO, median investigator-assessed PFS was [redacted] (95% CI: [redacted]) in the lorlatinib arm and was [redacted] months (95% CI: [redacted]) in the crizotinib arm (HR [redacted] [95% CI: [redacted]: stratified 1-sided [redacted]]).[66] The probability of being event free at 24 months was [redacted]% (95% CI: [redacted]) in the lorlatinib arm and [redacted]% (95% CI: [redacted]) in the crizotinib arm.[66] Results at the March 2020 DCO are presented in Appendix M.

B.2.6.2 Overall survival

Overall survival data are still immature from the CROWN study, and were not measured at the September 2021 DCO, however at the March 2020 DCO, a general trend in favour of lorlatinib had been observed with a 28% reduction in the risk of death (HR=0.72 [95% CI: 0.41, 1.25]).

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. In addition, only 80% of the 177 events required for the final PFS analysis had occurred. As such, OS data were not analysed as of the September 2021 DCO, and therefore, only OS data from the March 2020 DCO are presented here.

At the March 2020 DCO, the majority of patients in both treatment arms were still alive. A total of 51 (26%) of the total 198 deaths required for the final OS analysis had occurred. The efficacy boundary for OS was not crossed.[35]

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 estimable (NE) 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 4, a separation between the curves can be seen from 10 months, indicating an improvement in OS in the lorlatinib arm, and is sustained until substantial censoring occurs at later time points due to the immaturity of data.[35]

Due to the immaturity of the trial data, no robust conclusions can yet be drawn from the OS data. Further data-cuts for OS of the CROWN trial are scheduled for [redacted] and [redacted], which will seek to reduce the uncertainty around these results. For context, at the equivalent stage of the ALEX study, which examined alectinib versus crizotinib in ALK-positive advanced NSCLC, the HR for OS was 0.76 (95% CI: 0.48, 1.20).[62] Comparisons to brigatinib are more challenging due to the cross-over trial design.[54] A full, indirect comparison of lorlatinib versus alectinib and brigatinib is presented in Section B.2.9.

A summary of the OS results from the March 2020 DCO is presented in Table 12 and Figure 4.

Table 12: Summary of OS, FAS (data cut-off: 20 March 2020)

Variable	Lorlatinib (N=149)	Crizotinib (N=147)
Patients with event		
n (%)	23 (15.4)	28 (19.0)
Patients censored		
n (%)	[redacted]	[redacted]
Reason for censoring		
Withdrawal of consent, n (%)	[redacted]	[redacted]
Lost to follow-up[a], n (%)	[redacted]	[redacted]
Alive, n (%)	[redacted]	[redacted]
Probability of being event free		
At 12 months, (95% CI)[b]	[redacted]	[redacted]

Variable	Lorlatinib (N=149)	Crizotinib (N=147)
At 24 months, (95% CI)[b]	[redacted]	[redacted]
At 36 months, (95% CI)[b]	[redacted]	[redacted]
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[c]	[redacted]	[redacted]
Median, (95% CI)[c]	NE (NE, NE)	NE (NE, NE)
Q3, (95% CI)[c]	[redacted]	[redacted]
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]	[redacted]	[redacted]
At 24 months (95% CI)[b]	[redacted]	[redacted]
At 35 months (95% CI)[b]	[redacted]	[redacted]
Kaplan–Meier estimates of duration of follow-up (months)		
Quartiles		
Q1, (95% CI)[c]	[redacted]	[redacted]
Median, (95% CI)[c]	[redacted]	[redacted]
Q3, (95% CI)[c]	[redacted]	[redacted]

[a] Included patients deemed to be lost to follow-up by the investigator and patients with last follow-up >365 days prior to 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.

Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IRT: interactive response technology; NE: not evaluable; OS: overall survival; Q: quartile.

Source: Pfizer Ltd Data on File (Interim Clinical Study Report) 2020 (Table 15 [Table 14.2.2.1], Table 14.2.2.3);[67] Shaw et al. 2020.[35]

Figure 4: Kaplan–Meier plot of OS; FAS (data cut-off: 20 March 2020)

Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IRT: interactive response technology; OS: overall survival.
Source: Adapted from Shaw et al. 2020 (Figure 2D).[35]

B.2.6.3 Response rates

Patients receiving lorlatinib demonstrated an improved and durable response to treatment with a significantly higher confirmed objective response rate (ORR) measured for lorlatinib than with crizotinib (September 2021 DCO: [redacted]% [95% CI: [redacted]] versus [redacted]% [95% CI: [redacted]]) and a total of [redacted]% of patients who received lorlatinib at the September 2021 DCO having a response that lasted at least 12 months, compared with [redacted]% for crizotinib.[66]

Objective response rate based on BICR assessment (RECIST v1.1)

At the September 2021 DCO, [redacted] patients in the lorlatinib arm achieved an objective response compared with [redacted] patients in the crizotinib arm, according to BICR assessment. ORR is significantly higher in the lorlatinib arm compared with the crizotinib arm ([redacted]% [95% CI: [redacted]] versus [redacted]% [95% CI: [redacted]]) (OR: [redacted] [95% CI: [redacted]]).[66]

A summary of the best overall response and OR (confirmed) from the September 2021 DCO are presented in Table 13. Results at the March 2020 DCO are presented in Appendix M.

Table 13: Summary of best overall response and OR (confirmed) based on BICR Assessment (RECIST v1.1), FAS (data cut-off: 20 September 2021)

Variable	Lorlatinib (N=149)	Crizotinib (N=147)
Confirmed best overall response		

Variable	Lorlatinib (N=149)	Crizotinib (N=147)
CR, n (%)	[redacted]	[redacted]
PR, n (%)	[redacted]	[redacted]
SD, n (%)	[redacted]	[redacted]
Non-CR/Non-PD, n (%)	[redacted]	[redacted]
PD, n (%)	[redacted]	[redacted]
NE, n (%)	[redacted]	[redacted]
OR (CR+PR)		
n (%)	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]
Comparison versus crizotinib, stratified analysis[b]		
Odds ratio (95% CI)[c]	[redacted]	
1-sided p-value[d]	[redacted]	
2-sided p-value[d]	[redacted]	

[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. [d] P-value based on Cochran-Mantel-Haenszel test.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; CR: complete response; FAS: full analysis set; 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; SD: stable disease.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Objective response rate based on derived investigator assessment (RECIST v1.1)

As of September 2021 DCO, the investigator-assessed ORR remained consistent with BICR-assessed ORR. Investigator-assessed ORR was [redacted]% (95% CI: [redacted]; n=120) in the lorlatinib arm versus [redacted]% (95% CI: [redacted]; n=92) in the crizotinib arm (OR: [redacted]; 95% CI, [redacted]).[66] Overall, the results of ORR based on derived investigator assessment were consistent with those based on BICR assessment.

Duration of response based on BICR assessment (RECIST v1.1)

At the September 2021 DCO, the BICR-assessed median (95% CI) DOR was [redacted] in the lorlatinib arm, with approximately [redacted]% of patients continuing to respond as of the data cut-off date. The median DOR in the crizotinib arm was [redacted] months (95% CI: [redacted]). The proportion of patients with a DOR ≥12 months was [redacted]% in the lorlatinib arm and [redacted]% in the crizotinib arm.[66]

A summary of the DOR based on BICR assessment (RECIST v1.1) results from the September 2021 DCO is presented in Table 15. Results at the March 2020 DCO are presented in Appendix M.

Table 14: Summary of DOR based on BICR assessment (RECIST v1.1) – Patients with confirmed CR or PR in the FAS (data cut-off: 20 September 2021)

Variable	Lorlatinib (N=115)	Crizotinib (N=86)
Patients with event		

Variable	Lorlatinib (N=115)	Crizotinib (N=86)
n (%)	[redacted]	[redacted]
Type of event		
PD, n (%)	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]
Patients censored		
n (%)	[redacted]	[redacted]
Reason for censoring		
No adequate baseline assessment, n (%)	[redacted]	[redacted]
Start of new anticancer therapy	[redacted]	[redacted]
Event after ≥2 missing or inadequate post-baseline assessments, n (%)	[redacted]	[redacted]
Withdrawal of consent, n (%)	[redacted]	[redacted]
Lost to follow-up, n (%)	[redacted]	[redacted]
No adequate post-baseline tumour assessment, n (%)	[redacted]	[redacted]
Ongoing without an event, n (%)	[redacted]	[redacted]
Probability of being event free		
At 12 months, (95% CI)[a]	[redacted]	[redacted]
At 24 months, (95% CI)[a]	[redacted]	[redacted]
At 36 months, (95% CI)[a]	[redacted]	[redacted]
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[b]	[redacted]	[redacted]
Median, (95% CI)[b]	[redacted]	[redacted]
Q3, (95% CI)[b]	[redacted]	[redacted]
DOR (months)		
Range (min, max)	[redacted]	[redacted]
Response duration		
≥6 months, n (%)	[redacted]	[redacted]
≥12 months, n (%)	[redacted]	[redacted]
≥24 months, n (%)	[redacted]	[redacted]
≥36 months, n (%)	[redacted]	[redacted]

[a] CIs were derived using the log-log transformation with back transformation to original scale. [b] CIs were calculated using Brookmeyer and Crowley method.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; CR: complete response; DOR: duration of response; FAS: full analysis set; Max: maximum; Min: minimum; NE: not evaluable; PD: progressive disease; PR: partial response; Q: quartile; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Time to tumour response based on BICR assessment (RECIST v1.1)

At the March 2020 DCO, in patients with a confirmed OR by BICR assessment, the median time to tumour response (TTR) was the same in both treatment arms (1.8 months [Q1, Q3: 1.7, 1.9]), and occurred at the approximate time of the first scan taken on treatment.[35]

A summary of the results for TTR based on BICR Assessment (RECIST v1.1) from the March 2020 DCO is presented in Table 15.

Table 15: Summary of TTR based on BICR Assessment (RECIST v1.1), patients with confirmed CR or PR in the FAS (data cut-off: 20 March 2020)

Variable	Lorlatinib (N=113)	Crizotinib (N=85)
TTR (months)		
Mean (SD)	[redacted]	[redacted]
Median (Q1, Q3)	1.8 (1.7, 1.9)	1.8 (1.7, 1.9)
Range (min, max)	[redacted]	[redacted]

Abbreviations: BICR: blinded independent central review; CR: complete response; FAS: full analysis set; Max: maximum; Min: minimum; PR: partial response; Q: quartile; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1; SD: standard deviation; TTR: time to tumour response.
Source: Pfizer Ltd Data on File (Interim Clinical Study Report) 2020 (Table 14.2.7.1);[67] Shaw et al. 2020.[35]

B.2.6.4 Intracranial outcomes

Lorlatinib was designed to be a CNS penetrant. In the CROWN trial, at the September 2021 DCO, the intracranial response among patients with measurable brain metastases at baseline was [redacted]%, with a complete intracranial response of [redacted]%, compared with [redacted]% and [redacted]% for crizotinib, respectively[35]

Intracranial time to progression based on BICR assessment (modified RECIST v1.1)

As of the September 2021 DCO, in the intention-to-treat (ITT) population, the IC-TTP was significantly longer in the lorlatinib arm compared with the crizotinib arm,[35] with a HR of [redacted] (95% CI: [redacted]; p[redacted]) corresponding to a [redacted]% reduction in the risk of IC-progression.[66]

A summary of the results for IC-TTP based on BICR assessment from the September 2021 DCO is presented in Table 16 and Figure 5.

Table 16: Summary of IC-TTP based on BICR assessment (modified RECIST v1.1), FAS (data cut-off: 20 September 2021)

Variable	Lorlatinib (N=149)	Crizotinib (N=147)
Patients with event		
n (%)	[redacted]	[redacted]
Patients censored		
n (%)	[redacted]	[redacted]
Reason for censoring		
No baseline assessment, n (%)	[redacted]	[redacted]
Start of new anticancer therapy, n (%)	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments, n (%)	[redacted]	[redacted]

Variable	Lorlatinib (N=149)	Crizotinib (N=147)
Death without progression, n (%)	[redacted]	[redacted]
Withdrawal of consent, n (%)	[redacted]	[redacted]
Lost to follow-up, n (%)	[redacted]	[redacted]
Ongoing without an event, n (%)	[redacted]	[redacted]
Probability of being event free		
At 12 months, (95% CI)[a]	[redacted]	[redacted]
At 24 months, (95% CI)[a]	[redacted]	[redacted]
At 36 months, (95% CI)[a]	[redacted]	[redacted]
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[b]	[redacted]	[redacted]
Median, (95% CI)[b]	[redacted]	[redacted]
Q3, (95% CI)[b]	[redacted]	[redacted]
Comparison versus crizotinib, stratified analysis[c]		
HR (95% CI)[d]	[redacted]	
Reliable change index[e]	[redacted]	
1-sided p value[f]	[redacted]	
2-sided p value[f]	[redacted]	

[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. [e] P-value based on stratified log-rank test.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IC-TTP: intracranial time to progression; IRT: interactive response technology; NE: not evaluable; Q: quartile; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1.

Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Figure 5: Kaplan–Meier plot of IC-TTP based on BICR assessment (modified RECIST v1.1), FAS (data cut-off: 20 September 2021)

Abbreviations: BICR: blinded independent central review; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IC-TTP: intracranial time to progression; NE: not evaluable; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Results for IC-TTP in patients with and without baseline brain metastases are presented in Appendix M.

Intracranial objective response based on BICR assessment (modified RECIST v1.1)

At the September 2021 DCO, among the [redacted] patients with any measurable or non-measurable brain metastases at baseline (including [redacted] and [redacted] patients in the lorlatinib and crizotinib arms, respectively), the confirmed intracranial objective response (IC-OR) rate by BICR was significantly higher in the lorlatinib arm compared with the crizotinib arm ([redacted]% [95% CI: [redacted]] versus [redacted]% [95% CI: [redacted]], p[redacted]), with IC CR rates of [redacted]% and [redacted]%, respectively.[66]

Among the [redacted] patients with at least one measurable brain metastasis at baseline (including [redacted] and [redacted] patients in the lorlatinib and crizotinib arms, respectively), the IC-OR rate was [redacted]% (95% CI: [redacted]) in the lorlatinib arm and [redacted]% (95% CI: [redacted]) in the crizotinib arm, with IC CR rates of [redacted]% and [redacted]%, respectively.[66]

A summary of the results for best IC overall response and OR (confirmed) based on BICR assessment (modified RECIST v1.1) in patients with brain metastases at baseline from the September 2021 DCO is presented in Table 17. Results at the March 2020 DCO are presented in Appendix M.

Table 17: Summary of best IC overall response and OR (confirmed) based on BICR assessment (modified RECIST v1.1), patients with brain metastases at baseline in the FAS (data cut-off: 20 September 2021)

Variable	Patients with any measurable or non-measurable brain metastases at baseline		Patients with at least one measurable brain metastasis at baseline	
	Lorlatinib (N=37)	Crizotinib (N=39)	Lorlatinib (N=18)	Crizotinib (N=13)
Confirmed best overall response				
CR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-CR/Non-PD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
NE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (CR+PR)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison versus crizotinib, stratified analysis[b]				
Odds ratio (95% CI)[c]	[redacted]		[redacted]	
1-sided p-value[d]	[redacted]		[redacted]	
2-sided p-value[d]	[redacted]		[redacted]	

[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. [d] P-value based on Cochran-Mantel-Haenszel test.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; CR: complete response; FAS: full analysis set; IC: intracranial; 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; SD: stable disease.

Sources: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

B.2.6.5 Health-related quality of life

At the September 2021 DCO, patients in the lorlatinib arm had a significantly greater overall improvement from baseline in global quality of life than those who received crizotinib (estimated mean difference [redacted]; 95% CI: [redacted]), although the difference [redacted].[66] Improvements in QoL were seen as early as Cycle 2 and were maintained over time in the lorlatinib arm.[66]

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).[35] Completion rates for the EORTC QLQ-C30 and QLQ-LC13 were [redacted]% through Cycle 18 in both treatment arms, with similar completion rates for the EQ-5D-5L.[67]

EORTC QLQ-C30

The EORTC QLQ-C30 was used to evaluate the global QoL, functional scales (physical, role, cognitive, emotional and social), and symptoms scales/items (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). A clinically meaningful change was defined as a 10-point change from baseline.[67, 68]

Mean baseline scores in global QoL were 64.6 (standard error [SE] ±1.82) in the lorlatinib arm and 59.8 (SE ±1.90) in the crizotinib arm. At the September 2021 DCO, patients in the lorlatinib arm showed a [redacted] greater improvement from baseline in the EORTC QLQ-C30 global QoL score compared with crizotinib. The mean change from baseline was [redacted] in the lorlatinib arm and [redacted] in the crizotinib arm, with a greater overall improvement with lorlatinib but non-clinically meaningful estimated mean difference of [redacted].[66] Improvements in mean change from baseline in global QoL were seen as early as Cycle 2 and were maintained over time in the lorlatinib arm (Figure 6).[66]

Figure 6: Mean change from baseline (± SE) from baseline to Cycle 18 for EORTC QLQ-C30 (Global QoL) by visit, PRO analysis set (data cut-off: 20 September 2021)

Based on EORTC QLQ-C30 PRO analysis set within each treatment group. Mean change from baseline were shown through cycle 34, not including end of treatment. Baseline was defined as the last assessment performed on or prior to date of the first dose of study treatment.

Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; PRO: patient-reported outcome; QoL: quality of life; SE: standard error.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

EORTC QLQ-LC13

The EORTC QLQ-LC13 was used to evaluate time to deterioration (TTD) in pain in chest, dyspnoea, and cough individually and as a composite endpoint, as these are three of the most commonly reported disease related symptoms experienced by patients with lung cancer.[67]

Baseline mean scores for symptoms of pain in chest, dyspnoea and cough reported in the September 2021 DCO were [redacted] between treatment arms. Similarly, the TTD in the composite endpoint was [redacted] between treatment arms, as presented in Table 18 and Figure 7.[66]

[redacted] were observed in any QLQ-LC13 symptoms; however, [redacted] (Figure 7).[66]

Table 18: TTD in composite of pain in chest, dyspnoea and cough from EORTC QLQ-LC13, PRO analysis set (data cut-off: 20 September 2021)

Variable	Lorlatinib (N=146)	Crizotinib (N=139)
Patients with event		
n (%)	[redacted]	[redacted]
Type of event		
Deterioration of chest, dyspnoea and cough, n (%)	[redacted]	[redacted]
Patients censored		
n (%)	[redacted]	[redacted]
Reason for censoring		
No deterioration, n (%)	[redacted]	[redacted]
Probability of being event free at 12 months		
Probability, (95% CI)[a]	[redacted]	[redacted]
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI)[b]	[redacted]	[redacted]
Median, (95% CI)[b]	[redacted]	[redacted]
Q3, (95% CI)[b]	[redacted]	[redacted]
Comparison versus crizotinib, stratified analysis[c]		
HR (95% CI)[d]	[redacted]	
1-sided p value[e]	[redacted]	
2-sided p value[e]	[redacted]	

[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; [e] P-value based on stratified log-rank test.
Abbreviations: CI: confidence interval; EORTC QLQ-LC13: European Organisation for Research and Treatment of Lung Cancer Quality of Life Questionnaire; HR: hazard ratio; IRT: interactive response technology; NE: not evaluable; PRO: patient-reported outcome; Q: quartile; TTD: time to deterioration.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Figure 7: Kaplan–Meier Plot of TTD in composite of pain in chest, dyspnoea and cough from EORTC QLQ-LC13, PRO analysis set (data cut-off: 20 September 2021)

Abbreviations: CI: confidence interval; EORTC QLQ-LC13: European Organisation for Research and Treatment of Lung Cancer Quality of Life Questionnaire; HR: hazard ratio; PRO: patient reported outcome; TTD: time to deterioration.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

EQ-5D VAS and EQ-5D-5L index values

At the March 2020 DCO, baseline mean scores for EQ-5D Visual Analogue Scale (EQ-VAS) scores and EQ-5D-5L index values were similar between treatment arms. The percentage of patients with a moderate, severe, or extreme problem in the different functional assessed dimensions per the EQ-5D-5L was low in both treatment arms at baseline and did not change notably from baseline.[67]

B.2.7 *Subgroup analysis*

At the September 2021 DCO, PFS benefit in the lorlatinib arm compared with the crizotinib arm was consistently observed across pre-specified subgroups based on baseline patient demographics and disease characteristics, supporting the robustness of PFS findings within the study population.

Forest plot of PFS based on BICR assessment (RECIST v1.1) by subgroups for the September 2021 DCO is presented in Figure 8.

Figure 8: Forest plot of PFS based on BICR assessment (RECIST v1.1) by subgroups; FAS (data cut-off: 21 September 2021)

Presence of the brain metastases subgroup was based on mRECIST BICR baseline data. Hazard ratios were not calculated due to insufficient numbers of events (<10 events on either treatment arm within the defined subset), as dictated by the statistical analysis plan, for patients who had ECOG performance status of 2 (2 versus 8 events), extent of disease of locally advanced (5 versus 3 events), or histology of non-adenocarcinoma (6 versus 5 events). Stratified by presence of brain metastases (yes/no) and ethnic origin (Asian/non-Asian) at randomization from item response theory stratification values. Percentages were calculated based on the number of patients in the full analysis set in each treatment group. Plot presented on log scale (base = 2).
Abbreviations: BICR: blinded independent central review; CI: confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; PFS: progression-free survival; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

B.2.8 *Meta-analysis*

A meta-analysis was not necessary for this evaluation. The only evidence for lorlatinib in untreated patients with ALK-positive advanced NSCLC is the pivotal phase 3, CROWN study which directly compared lorlatinib to crizotinib.[35] The individual patient-level data are available from the clinical trial and form the basis of this submission.

B.2.9 *Indirect and mixed treatment comparisons*

In a network meta-analysis (NMA), lorlatinib showed a statistically significant reduction in the risk of progression or death, reducing the risk of progression by [redacted]% and [redacted]% compared with alectinib and brigatinib, respectively

- Ten RCTs were identified in an SLR and considered for inclusion in an NMA including the CROWN trial. Of the ten RCTs, only four considered interventions of relevance to the decision problem in this appraisal
- Overall, the inclusion criteria, baseline characteristics and treatment doses were generally comparable across the studies. Criteria relating to disease stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), central nervous system (CNS) metastases, tumour requirements and age were consistent. There were no clear outliers in baseline characteristics other than race, which was accounted for with the exclusion of ALESIA that contained a 100% Asian population
- In the NMA, lorlatinib showed a [redacted] improvement in PFS using data from the September 2021 DCO, with a HR of [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) compared with alectinib and brigatinib, respectively
- Using OS data from the March 2020 DCO for lorlatinib, there were [redacted] in OS, with a HR of [redacted] and [redacted] compared with alectinib and brigatinib, respectively. Given the OS data from the CROWN trial is still very immature, no conclusions could be drawn from these analyses. Further data cuts for OS from the CROWN trial are planned.

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. Full details of the methodology and results of the SLR are presented in Appendix D.

As the pivotal RCT for lorlatinib (CROWN) provides direct head-to-head evidence versus crizotinib, a network meta-analysis (NMA) has been conducted for the purposes of this appraisal to demonstrate the comparative efficacy between lorlatinib, alectinib and brigatinib. The methodology and results of the NMA are presented below.

Overall, a total of ten RCTs (including CROWN) were included in the SLR and considered for inclusion within the NMA. An overview of the ten RCTs included in the SLR and considered for the NMA is provided in Table 19.

Finally, 79 non-RCTs were also identified in the SLR, however, these were not considered for the NMA (see Section B.2.9.2); a full list of these trials is presented in Appendix D.

Table 19: 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
Shaw 2020[35]	CROWN[a]	Lorlatinib (100 mg QD)	Crizotinib (250 mg BID)	First-line	No	Yes	Yes	Yes
Camidge 2019[63]	ALEX	Alectinib (600 mg BID)	Crizotinib (250 mg BID)	First-line	No	Yes	Yes	Yes
Zhou 2019[69]	ALESIA	Alectinib (600 mg BID)	Crizotinib (250 mg BID)	First-line	Yes	Yes	Yes	Yes
Hida 2017[70]	J-ALEX	Alectinib (300 mg BID)	Crizotinib (250 mg BID)	Mixed	Yes	No	Yes	No – not the licensed dose
Camidge 2018[54]	ALTA-1L	Brigatinib (180 mg QD)	Crizotinib (250 mg BID)	Mixed	No	Yes	Yes	Yes
Soria 2017[60]	ASCEND-4	Ceritinib (750 mg QD)	Chemotherapy	First-line	No	Yes	Yes	No – not a relevant comparator
Cho 2019[71]	ASCEND-8	Ceritinib (450 mg, 600 mg, 450 mg QD)		Mixed	No	No	Yes	No – not a relevant comparator
Solomon 2018[72]	Profile 1014	Chemotherapy	Crizotinib (250 mg BID)	First-line	No	Yes	Yes	No – not a relevant comparator
Wu 2018[73]	Profile 1029	Chemotherapy	Crizotinib (250 mg BID)	First-line	Yes	Yes	Yes	No – not a relevant comparator
Horn 2020[74]	eXalt3	Ensartinib (225 mg QD)	Crizotinib (250 mg BID)	Mixed	No	Yes	Yes	No – not a relevant comparator

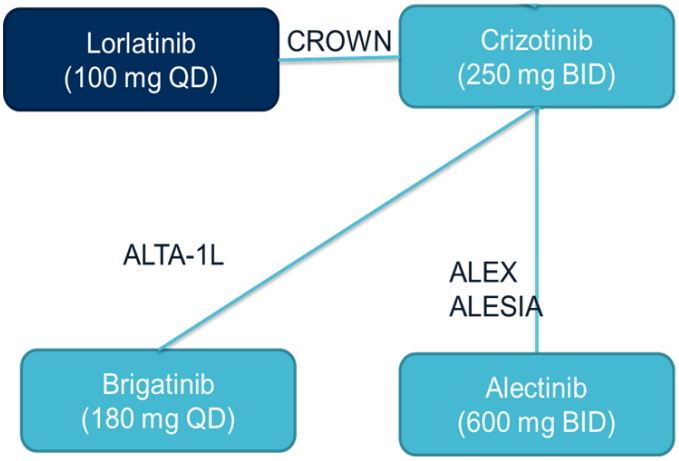
Abbreviations: BID: twice a day; OS: overall survival; PFS: progression-free survival; QD: once a day; RCT: randomised controlled trial; SLR: systematic literature review.

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.

Of the ten RCTs, only four considered interventions of relevance to the decision problem in this appraisal. A relevant network could be formed from these four studies and as such the other studies were excluded; reasons for their exclusion from the NMA are provided in Table 19. The network based on identified studies considered in the feasibility assessment is presented in Figure 9.

Figure 9: Initial network of evidence from the RCTs identified in the SLR



Abbreviations: BID: twice daily; QD: once daily; RCT: randomised controlled trial; SLR: systematic literature review.

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. Therefore, ALESIA was excluded from the NMA as this study was not considered representative of the UK population due to differences in subsequent treatment options and healthcare systems between Asia and the NHS in England. The importance of excluding this study to reduce the impact of heterogeneity is demonstrated in the CROWN trial where, at the September 2021 DCO, PFS was found to differ in patients who were Asian ([redacted]) compared with those who were non-Asian ([redacted]) (Figure 8 in Section B.2.7). In the September 2021 DCO, the p-value for race was significant ([redacted]). Exclusion of this study is in line with the approach favoured by the NICE Committee during the appraisal of brigatinib in the same population (TA670).[1]

Inclusion and exclusion criteria

Overall, the inclusion criteria were generally comparable across the studies. Criteria relating to disease stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), CNS metastases, tumour requirements and age were consistent across studies.

ALTA-1L included ALK-inhibitor naïve patients but also patients with prior chemotherapy (24–36% of the 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%.

A summary of the study inclusion and exclusion criteria is provided in Table 20. Details of the prior treatment received by patients in ALTA-1L are presented in Appendix D.

Baseline characteristics

In general, while there was some variation in baseline characteristics across the trials, there were no clear outliers other than race. Patients in the CROWN study were generally slightly older (median age of 61 and 56 for the lorlatinib and crizotinib arms, respectively) 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%).

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%). However, these differences were considered unlikely to affect the relative treatment effects. A summary of the most commonly presented baseline characteristics are presented in Table 21.

Table 20: 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
Shaw 2020[35]	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)
Camidge 2019; Mok 2020[63]	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 2019[69]	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 2018[54]	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 seven days prior to randomisation	≥1 measurable target lesion (RECIST v1.1)	≥18 years

Abbreviations: ALK: anaplastic lymphoma kinase positive; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NR: not reported; NSCLC: non-small-cell lung cancer; RECIST v1.1: Response Evaluation Criteria in Solid Tumour version 1.1.

Table 21: 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[35]	Lorlatinib	149	61 [redacted]	44	26	44	54/46	98	[redacted]
	Crizotinib	147	56 [redacted]	38	27	44	64/35	94	[redacted]
ALEX[63]	Alectinib	152	58 (25, 88)	45	42	45	61/40	93	0 (NR)
	Crizotinib	151	54 (18, 91)	42	38	46	65/35	93	0 (NR)
ALESIA[b69]	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[54]	Brigatinib	137	58 (27, 86)	50	29	43	61/39	96	26
	Crizotinib	138	60 (29, 86)	59	30	36	54/46	96	27

[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.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITT: intention-to-treat; NMA: network meta-analysis; NR: not reported.

Treatments

All doses were comparable for studies that investigated the same treatments. Only ALTA-1L allowed treatment crossover:

- In ALTA-1L, crossover was permitted after progression from crizotinib to brigatinib only. 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; however, the NICE appraisal for brigatinib (TA670) investigated multiple methods for adjusting OS and deemed the rank-preserving structural failure time (RPSFT) method the most appropriate. This analysis was conducted on a later data-cut than was presented in the primary publication, therefore the HR from the NICE appraisal with the crossover adjustment was used in the OS NMA[1]

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.

Please refer to Appendix D for full details on the treatment arms including the doses, route of administration and whether crossover was permitted in the trial.

B.2.9.3 Network meta-analysis: network and methodology

The NMA has been conducted for both PFS and OS.

Table 22 and Table 33 present the availability of PFS and OS in the trials considered in the network, and Figure 10 presents the resulting network diagram, following the exclusion of ALESIA. Networks for IC-progression response and time on treatment (ToT) were also explored for use in the cost-effectiveness model (see Section B.3.3.3). However, of the relevant four RCTs, IC-progression and ToT was only reported in CROWN and as such no network could be formed between lorlatinib, alectinib and brigatinib ruling out any comparisons on these endpoints.

Table 22: PFS data reported by included studies

Study name	Trial name	Treatment 1	Treatment 2	PFS available ITT (IRR)	PFS available (investigator assessed)	PFS in strictly treatment naïve population
Shaw 2020[35]	CROWN	Lorlatinib	Crizotinib	Yes	Yes	Same as ITT
Camidge 2019; Mok 2020 [63, 75]	ALEX	Alectinib	Crizotinib	Yes	Yes	Same as ITT
Camidge 2018[54]	ALTA-1L	Brigatinib	Crizotinib	Yes	Yes	Yes

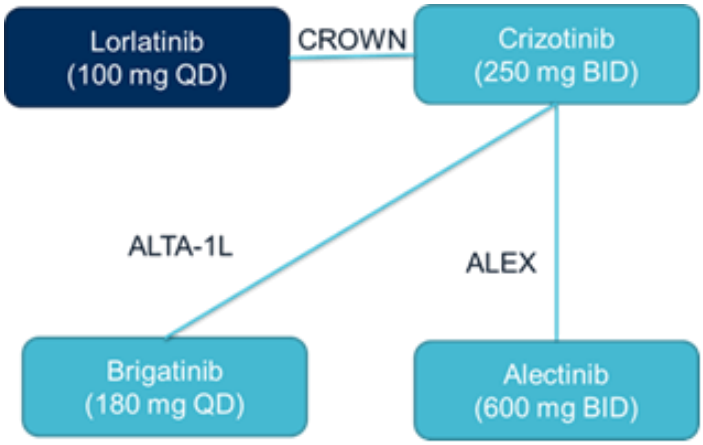
Abbreviations: IRR: independent radiological review; ITT: intention-to-treat; NA: not applicable; PFS: progression-free survival.

Table 23: OS data reported by included studies

Study name	Trial name	Treatment 1	Treatment 2	OS available ITT (IRR)	OS in strictly treatment naïve population
Shaw 2020[35]	CROWN	Lorlatinib	Crizotinib	Yes	Same as ITT
Mok 2020[75]	ALEX	Alectinib	Crizotinib	Yes	Same as ITT
Camidge 2018[54]	ALTA-1L	Brigatinib	Crizotinib	Yes	No

Abbreviations: IRR: independent radiological review; ITT: intention-to-treat; NA: not applicable; OS: overall survival.

Figure 10: PFS and OS network diagram



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

Where available, the reported PFS and OS HRs, and an associated variance estimate such as the SE 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.[76]

The log-cumulative hazard plot of PFS (BICR) in CROWN is presented in Figure 11. The curves cross several times early in the plot, suggesting that the proportional hazards assumption is violated for PFS (BICR). The Schoenfeld residual plot presented in Figure 12 shows that the HR between lorlatinib and crizotinib initially decreases between 0 and 8 months and then begins to increase. The Schoenfeld individual p-value is less than 0.05, suggesting there is evidence that the proportional hazards assumption between lorlatinib and crizotinib is violated. The survival time points in the quantile-quantile plot in Figure 13 do not appear to be evenly scattered around the straight line, suggesting that there is evidence that the AFT assumption is violated. The smoothed hazard plot in Figure 14 shows that the risk of progression or death decreases over time for lorlatinib. For crizotinib the risk of progression or death increases between 0 and 9 months and then decreases after this time. These plots suggest that hazard functions in the lorlatinib and crizotinib treatment arms are different, and all of the descriptive plots suggest that fitting separate parametric survival models is justified.

Figure 11. Log-cumulative hazard plot for progression-free survival (BICR) in CROWN

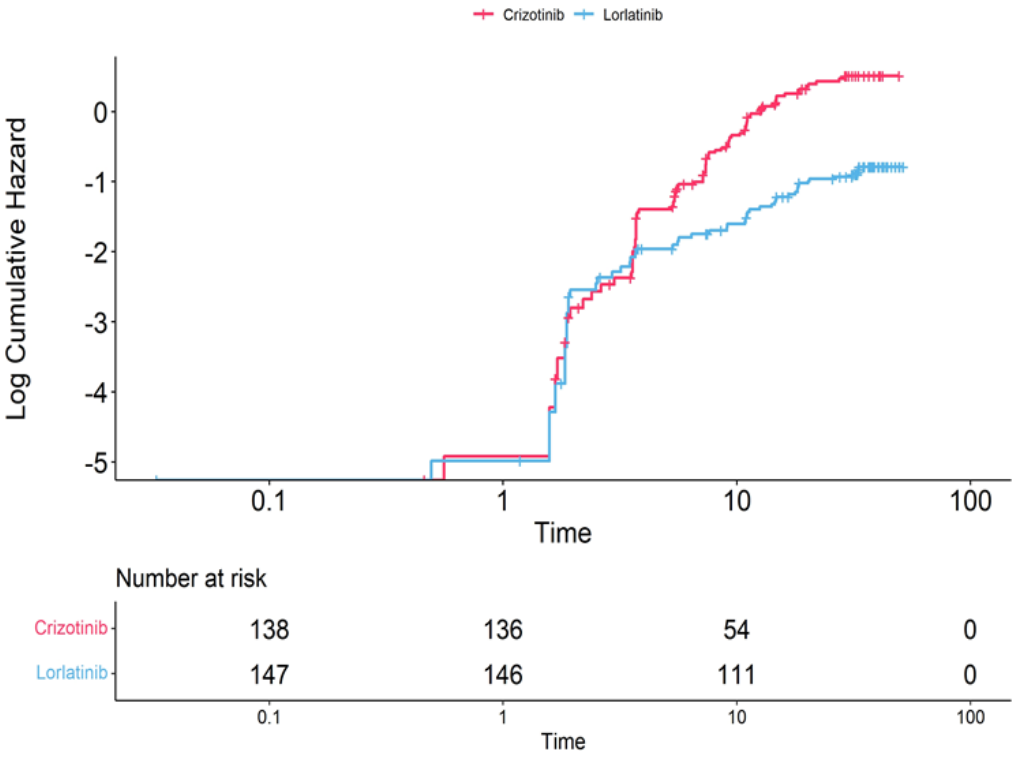


Figure 12. Schoenfeld residual plot for progression-free survival (BICR) in CROWN

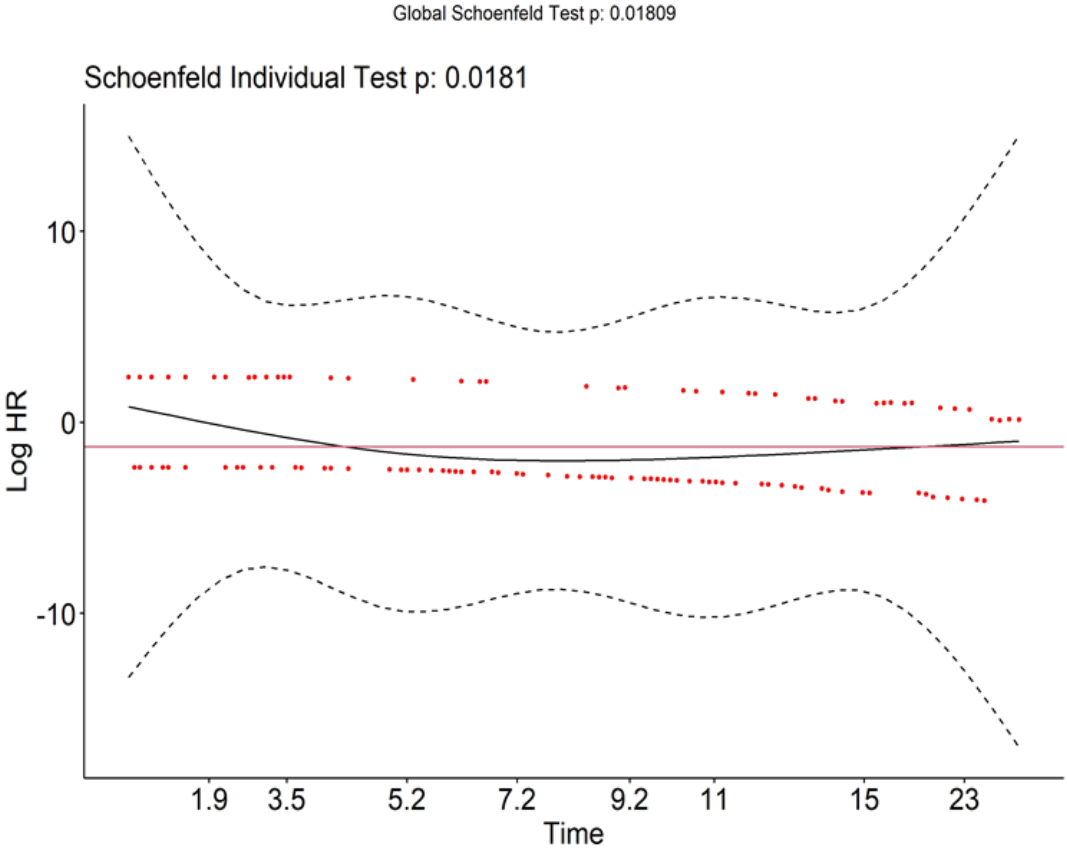


Figure 13. Quantile-quantile plot for progression-free survival (BICR) in CROWN

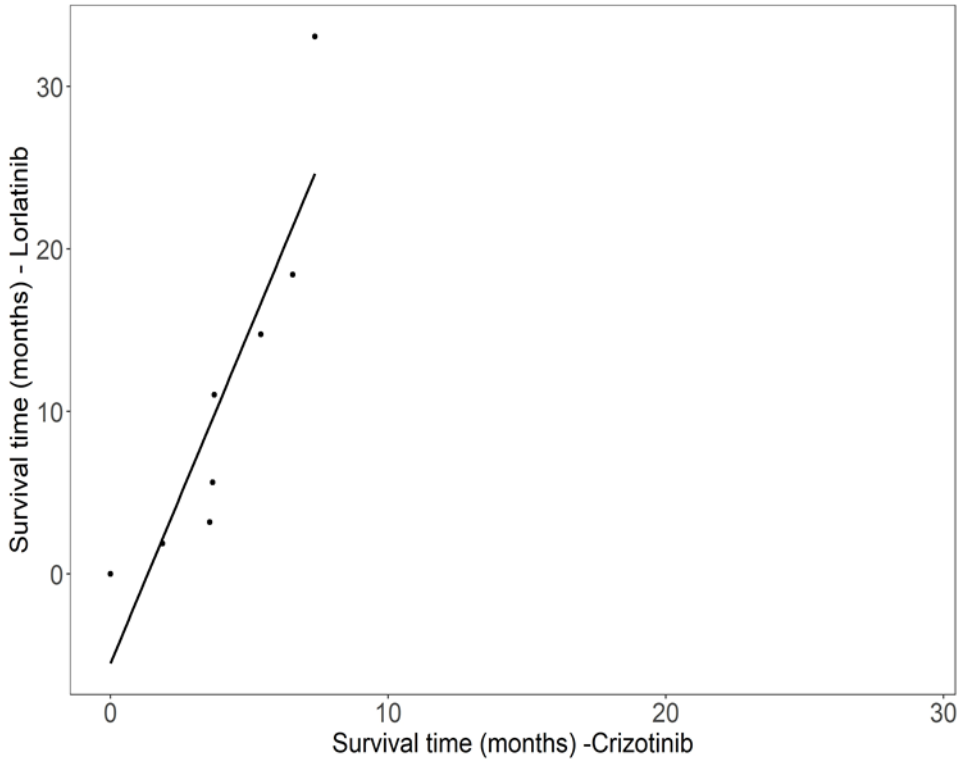
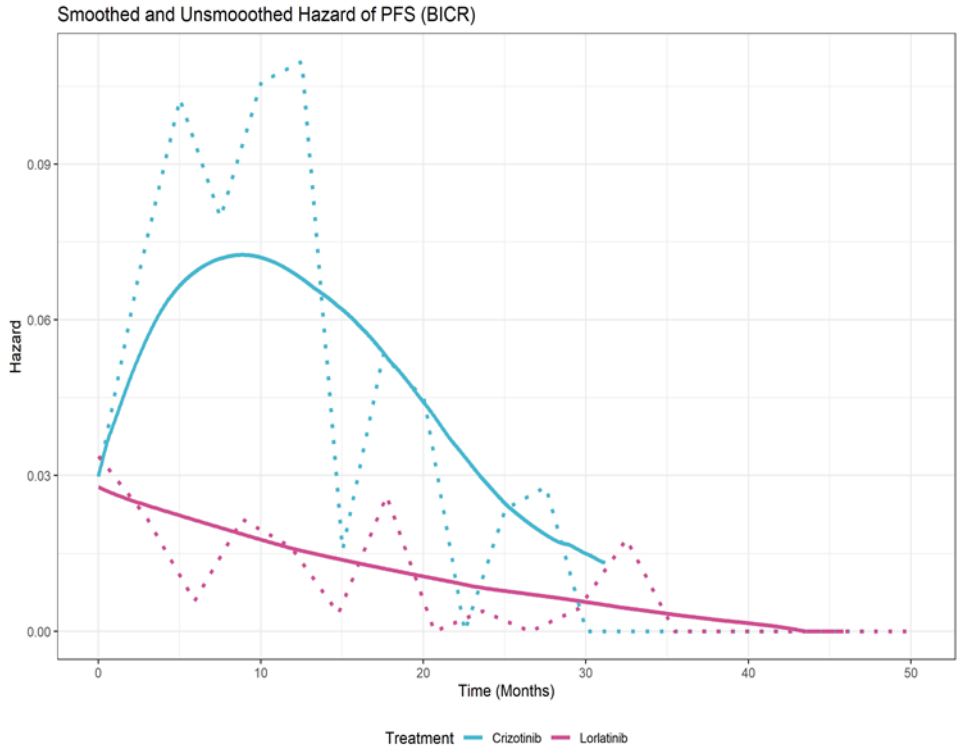


Figure 14. Smoothed and unsmoothed hazard of progression-free survival (BICR) in CROWN



To assess whether the proportional hazards assumption holds between treatments within each of the studies ALTA-1L and ALEX, individual patient-level data were generated using the method of Guyot et al. (2012) and two approaches were adopted:

1. The production of log-cumulative hazard plots

2. Tests of non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time (Grambsch and Therneau [1994]).

In the log-cumulative hazard plot for alectinib and crizotinib shown in Figure 15, the curves cross at the beginning of the plot, correlating with the separation of the Kaplan-Meier curves at approximately 6 months. After this initial period, the log-cumulative hazards curves appear parallel. Since the crossing occurs within the first 6 months of the trial and is likely due to trial protocol rather than treatment effect, there is little evidence of non-proportional hazards.

In the Schoenfeld residual plot shown in Figure 16, the line plotting varying log HR versus time appears relatively straight and close to the constant log HR line. The p-value from the Schoenfeld test is less than 0.05, which can indicate evidence to suggest that the proportional hazards assumption doesn't hold. However, as the low p-value is likely due to the crossing of curves at the start of follow-up which is likely to be protocol driven only.

Figure 15. Log-cumulative hazard plot for progression-free survival (IRC) in ALEX

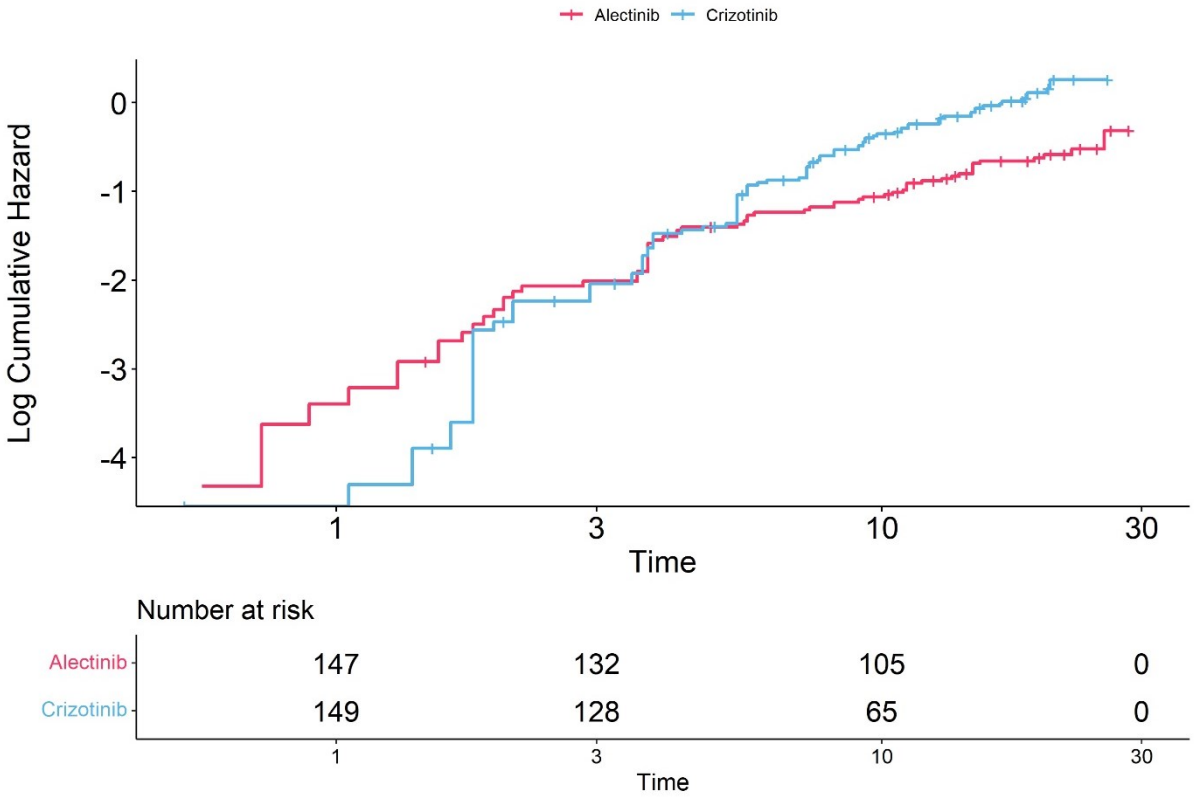
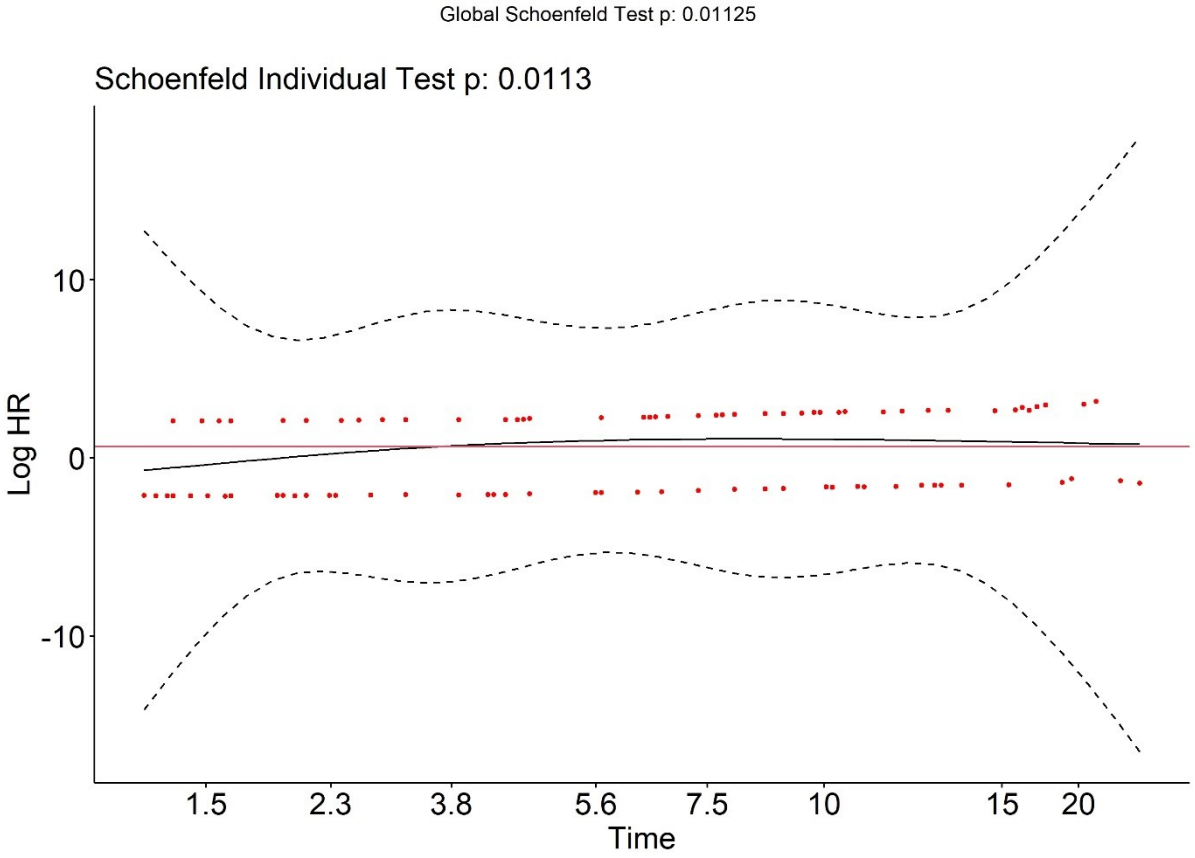


Figure 16: Schoenfeld plot for progression-free survival (IRC) in ALEX



In the log-cumulative hazards plot shown in Figure 17, the curves cross at the beginning of the figure. This correlates with the crossing of KM curves during the first 4 months (2 assessment visits) due to the assessment schedule for PFS and is likely due to trial protocol rather than treatment effect. Therefore, given that after this initial period, the log-cumulative hazards curves appear parallel, there is little evidence of non-proportional hazards.

In the Schoenfeld residual plot presented in Figure 18, the line plotting varying log HR versus time appears relatively straight and close to the constant log HR line (and very similar to that in the Schoenfeld residual plot for ALEX). The p-value from the Schoenfeld test is greater than 0.05, which indicates that the proportional hazards assumption is valid.

Figure 17: Log-cumulative hazard plot for progression-free survival (BICR) in ALTA-1L

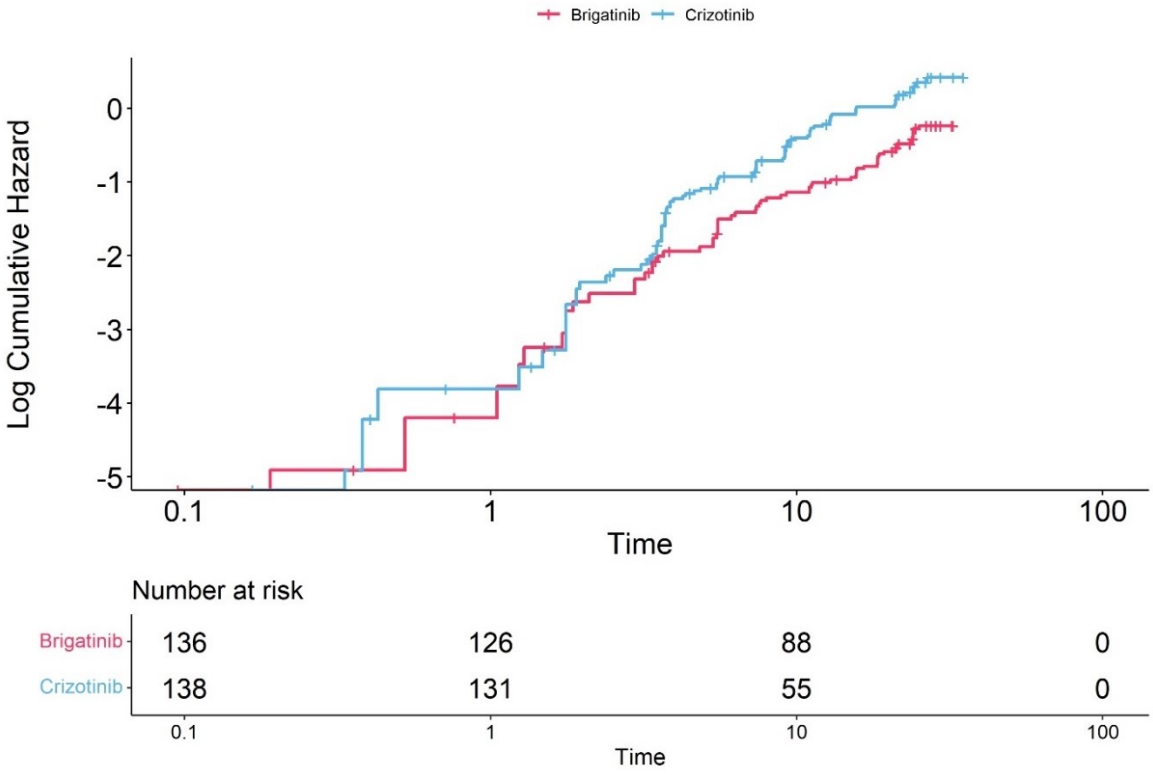
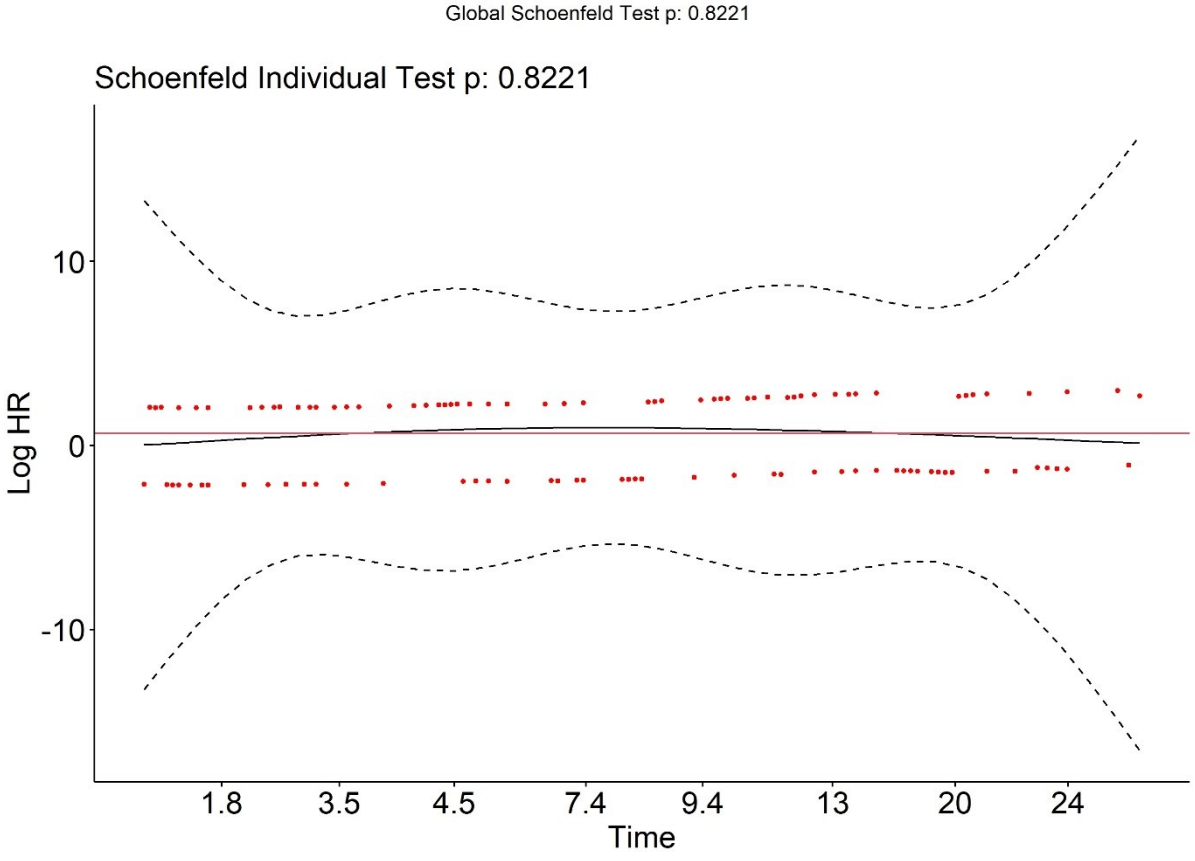


Figure 18: Schoenfeld plot for progression-free survival (BICR) in ALTA-1L



The above assessments suggest that the proportional hazards assumption does hold between crizotinib, alectinib and brigatinib. Therefore, a standard Bayesian NMA was conducted to demonstrate the relative efficacy of all treatments. For details of the relative efficacy applied the cost-effectiveness model, please see Section B.3.3.2. Furthermore, if some non-proportionality of the hazards is present, the HR obtained is expected to be some type of average over the event times (Royston and Parmar)[77] and the model estimates generated from the application of the HRs from the NMA were validated (Section B.3.3.2).

Further details on the methodology of the NMA are presented in Appendix D.

B.2.9.4 Network meta-analysis results

B.2.9.4.1 Progression-free survival

Data for lorlatinib from the September 2021 DCO have been used in the NMA for PFS. The relative effects of lorlatinib compared with alectinib and brigatinib in terms of PFS are presented in Table 26. For both comparisons, lorlatinib showed a [redacted] improvement in PFS. The resulting HRs were [redacted] versus alectinib and [redacted] versus brigatinib, demonstrating lorlatinib to be associated with a [redacted] and [redacted] reduction in the risk of progression or death versus alectinib and brigatinib, respectively.

Table 24: PFS relative effect of lorlatinib compared with all treatments (fixed effects)

Treatment	HR (95% CrI)
Alectinib (600 mg BID)	[redacted]
Brigatinib	[redacted]

Abbreviations: BID: twice daily; CrI: credible interval; HR: hazard ratio; NR: not reported; PFS: progression-free survival.

B.2.9.4.2 Overall survival

Data for lorlatinib from the March 2020 DCO have been used in the NMA for OS, as OS was not reported as of September 2021 DCO. The relative effects of lorlatinib compared with alectinib and brigatinib in terms of OS are presented in Table 25. The resulting HRs were [redacted] versus alectinib and [redacted] versus brigatinib, demonstrating [redacted] between lorlatinib and alectinib and brigatinib. 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 are 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 (0.48-1.20) compared to 0.67 (0.46 – 0.98) with a median follow-up of 48.2 months.

Table 25: OS relative effect of lorlatinib compared with all treatments (fixed effects)

Treatment	HR (95% CrI)
Alectinib (600 mg BID)	[redacted]
Brigatinib	[redacted]

Abbreviations: BID: twice daily; CrI: credible interval; HR: hazard ratio; NR: not reported; OS: overall survival.

B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

A fixed effects model was used in both analyses of PFS and OS. 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 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 DCO, a total of only 51 (26%) of the total 198 deaths required for the final OS analysis of CROWN had occurred. The NICE Committee for the evaluation of brigatinib (TA670) also highlighted the immaturity of OS data from ALTA-1L, and as these data are the same data utilised in this NMA, the same limitations are maintained in this evaluation also.[37] Therefore, no robust conclusions can yet be drawn from the OS data.

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. Whilst the HR from the crossover adjustment using RPFST modelling is utilised in the NMA, the Committee of TA670 noted that a robust analysis of the effect of crossover was not possible due to the immaturity of the data and high levels of crossover observed.[37] Therefore, the uncertainty of the HR for brigatinib carries through to the NMA.

B.2.10 *Adverse reactions*

The results demonstrated lorlatinib to be tolerable, with an acceptable adverse event (AE) profile

- At the September 2021 DCO, almost all patients experienced at least one AE, with [redacted]% and [redacted]% of patients experiencing a serious adverse event (SAE) in the lorlatinib and crizotinib arms, respectively
- The most common AEs with lorlatinib in the CROWN study were [redacted]
- Grade 3 or 4 AEs occurred in [redacted]% of patients who received lorlatinib and [redacted]% of those who received crizotinib; all-cause Grade 3 AEs reported more frequently (≥5% absolute difference) in the lorlatinib arm than the crizotinib were [redacted]
- Permanent discontinuation due to AEs was low in both treatment arms, occurring in [redacted]% and [redacted]% of patients receiving lorlatinib and crizotinib, respectively
- At the March 2020 DCO, 23 (15%) of patients in the lorlatinib arm and 28 (19%) of patients in the crizotinib arm had died; survival data were not reported for the September 2021 DCO[35]
- Overall, lorlatinib is generally tolerable and the AEs experienced are manageable with dose reduction, temporary discontinuation, and/or standard supportive medical therapy, when needed.[78]

B.2.10.1 Adverse events

Adverse effects of treatment with either lorlatinib or crizotinib were captured as secondary outcomes in the CROWN trial. An overview of all-causality and treatment-related AEs observed in September 2021 DCO of the CROWN trial are presented in Table 26.

Table 26: AEs (all cycles), SAS (data cut-off: 20 September 2021)

Variable	Lorlatinib (N=149)[a]	Crizotinib (N=142)[a]
All causalities		
Number of AEs	[redacted]	[redacted]
Patients with AEs, n (%)	[redacted]	[redacted]
Patients with SAEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 3 or 4 AEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 5 AEs, n (%)	[redacted]	[redacted]
Patients discontinued from study due to AEs, n (%)[b]	[redacted]	[redacted]
Patients discontinued study treatment due to AEs, n (%)[c]	[redacted]	[redacted]
Patients with dose reduced or temporary discontinuation due to AEs, n (%)	[redacted]	[redacted]
Treatment related		
Number of AEs	[redacted]	[redacted]
Patients with AEs, n (%)	[redacted]	[redacted]
Patients with SAEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 3 or 4 AEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 5 AEs, n (%)	[redacted]	[redacted]
Patients discontinued from study due to AEs, n (%)[b]	[redacted]	[redacted]
Patients discontinued study treatment due to AEs, n (%)[c]	[redacted]	[redacted]
Patients with dose reduced or temporary discontinuation due to AEs, n (%)	[redacted]	[redacted]

[a] Patients evaluable for AEs. [b] Patients who had an AE record that caused study discontinuation. [c] Patients who had an AE record that caused treatment discontinuation.
Abbreviations: AE: adverse event; SAE: serious adverse event; SAS: safety analysis set.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

All-causality adverse events

AEs that differed by >10% in frequency between the treatment arms in the September 2021 DCO are presented by Grade in Table 27. Please refer to Appendix M for AEs reported in ≥10% of patients in either treatment arm.

Any grade all-causality adverse events

All-causality AEs reported more frequently (≥10% absolute difference) in the lorlatinib arm than the crizotinib arm were [redacted] All-causality AEs reported more frequently (≥10% absolute difference) by decreasing frequency in the crizotinib arm than the lorlatinib arm were [redacted].[66]

Grade 3 and 4 all-causality adverse events

Grade 3 or 4 AEs occurred in [redacted]% of the patients who received lorlatinib and [redacted]% of those who received crizotinib. The most common Grade 3–4 AEs in the lorlatinib group were [redacted] The most common Grade 3–4 AEs in the crizotinib group were [redacted][66]

[redacted](≥5% absolute difference) in the lorlatinib arm than the crizotinib arm by decreasing frequency were [redacted].[66]

Table 27: Summary of AEs, SAS (data cut-off: 20 September 2021)

Event, n (%)[a]	Lorlatinib (N=149)			Crizotinib (N=142)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypercholesterolaemia[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertriglyceridemia[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral neuropathy[b, c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive effects[b, c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased ALT level	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mood effects[b, d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased AST level	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperlipidaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Shown are AEs that differed by >10% in frequency between the groups. Patients were counted only once per event. The listed events occurred after the first dose of trial treatment through the end of trial follow-up or the start of new anticancer therapy, whichever took place first. Data for all grades in the lorlatinib arm are listed in decreasing order of frequency. [b] This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes. [c] Cognitive effects with a frequency of ≥1% included memory impairment, disturbance in attention, confusion, amnesia, cognitive disorder, and delirium. [d] Mood effects with a frequency of ≥1% included anxiety, depression, affect lability, affective disorder, agitation, irritability, and altered mood.
Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAS: safety analysis set.
Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Treatment-related adverse events

Any grade treatment-related adverse events

At the March 2020 DCO, treatment-related AEs reported more frequently (≥10% absolute difference) by decreasing frequency in the lorlatinib arm than the crizotinib arm were [redacted]. Treatment-related AEs reported more frequently (≥10% points difference) by decreasing frequency in the crizotinib arm than the lorlatinib arm were [redacted].[67]

Grade 3 and 4 treatment-related adverse events

At the March 2020 DCO, treatment-related Grade 3 AEs reported more frequently (≥5% absolute difference) in the lorlatinib arm than the crizotinib arm by decreasing frequency were [redacted]. The only treatment-related Grade 3 AE reported more frequently (≥5% absolute difference) in the crizotinib arm than the lorlatinib arm by decreasing frequency difference was [redacted].[67]

The most frequent (≥5% of patients) treatment-related Grade 3 AEs in the lorlatinib arm by decreasing frequency were [redacted]. The most frequent (≥2% of patients) treatment-related Grade 4 AE in the lorlatinib arm was [redacted].[67]

The most frequent (≥5% of patients) treatment-related Grade 3 AE in the crizotinib arm was [redacted]. The most frequent (≥2% of patients) treatment-related Grade 4 AE in the crizotinib arm was [redacted].[67]

B.2.10.2 Treatment discontinuation due to adverse events

At the September 2021 DCO, there were fewer all-causality AEs leading to permanent treatment discontinuation in the lorlatinib arm ([redacted]%) than the crizotinib arm ([redacted]%), with the frequencies of treatment-related AEs leading to permanent treatment discontinuation remaining [redacted] between treatment arms ([redacted] in the lorlatinib arm and [redacted] in the crizotinib arm).[66]

The frequency of all-causality AEs leading to dose reduction or temporary treatment discontinuation was [redacted] between the treatment arms ([redacted] for the lorlatinib arm and [redacted] for the crizotinib arm). The frequency of treatment-related AEs leading to dose reduction or temporary treatment discontinuation was also [redacted] between the treatment arms ([redacted] for the lorlatinib arm and [redacted] for the crizotinib arm).

B.2.10.3 Patient deaths

At the March 2020 DCO, all deaths were captured on the “Notice Of Death” electronic case report form (eCRF) page, regardless of when the death occurred. Overall, as of the March 2020 DCO, 23 (15%) patients in the lorlatinib arm and 28 (20%) patients in the crizotinib arm died.[35] In both treatment arms, the most frequent reason for death on study was disease progression (lorlatinib arm: [redacted]; crizotinib arm: [redacted]).

A summary of patient death data and AEs leading to death at the March 2020 DCO in the CROWN trial are provided in Table 28 and Table 29.

Table 28: Summary of patient deaths, SAS (data cut-off: 20 March 2020)

Variable	Lorlatinib (N=149)	Crizotinib (N=142)
Death		
n (%)	[redacted]	[redacted]
Cause of death		
AE not related to study treatment	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Other	[redacted]	[redacted]
Study treatment toxicity	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Deaths within 28 days after last does of study treatment		
n (%)	[redacted]	[redacted]
Cause of death		
AE not related to study treatment	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Study treatment toxicity	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Deaths within 30 days after first does of study treatment		
n (%)	[redacted]	[redacted]

Abbreviations: AE: adverse event; SAS: safety analysis set.
Source: Pfizer Ltd Data on File (Interim Clinical Study Report) 2020 (Table 43 [Table 14.3.2.]).[67]

Table 29: AEs leading to patient death, SAS (data cut-off: 20 March 2020)

Event	Lorlatinib (N=149)	Crizotinib (N=142)
Any Grade 5 AE, n (%)	7 (5)	7 (5)
Pneumonia, n (%)	1 (1)	0
Respiratory failure, n (%)[a]	1 (1)	0
Pericardial effusion, n (%)	0	1 (1)
Pulmonary embolism, n (%)	1 (1)	0
Cardiac failure acute, n (%)[a]	1 (1)	0
Death from unknown cause, n (%)[b]	1 (1)	1 (1)
Disease progression, n (%)	1 (1)	1 (1)
Lung neoplasm malignant, n (%)	1 (1)	0
Neoplasm progression, n (%)	0	1 (1)
Clostridium difficile colitis, n (%)	0	1 (1)
Malignant neoplasm progression, n (%)	0	2 (1)

[a] Two deaths in the lorlatinib group were reported by investigators as possibly related to study treatment: one due to acute cardiac failure that occurred approximately two months after discontinuation of lorlatinib; and one due to respiratory failure in the setting of infectious pneumonia. [b] No information was available to the investigators
Abbreviations:. AE: adverse event; SAS: safety analysis set.

Source: Shaw et al. (supplementary appendix) 2020 (Table S4).[35]

At the September 2021 DCO, the frequencies of all-causality serious adverse events (SAEs) of any grade remained [redacted] (≤10% absolute difference) between treatment arms, occurring in [redacted] patients in the lorlatinib group and [redacted] of those in the crizotinib group.[35] Treatment-related SAEs occurred in [redacted] and [redacted] of the patients in the lorlatinib and crizotinib arms, respectively.

B.2.10.4 Adverse events of special interest.

As of the March 2020 DCO, key AEs of special interest, which are safety topics most relevant to lorlatinib, were hyperlipidaemia associated (hypercholesterolaemia and hypertriglyceridemia), oedema, weight gain, CNS-related effects (cognitive effects, mood effects, [redacted]), and [redacted]. Other AEs of special interest, which are safety topics not specific to lorlatinib, were peripheral neuropathy, vision disorder, pneumonitis, liver function test increased, QT prolongation, and pancreatitis.[67]

A summary of the AEs of special interest from the March 2020 DCO is provided in Table 30.

Table 30: AEs of special interest, SAS (data cut-off: 20 March 2020)

Any Grade event	Lorlatinib (N=149)	Crizotinib (N=142)
Hypercholesterolaemia	[redacted]	[redacted]
Hypertriglyceridemia	[redacted]	[redacted]
Oedema	[redacted]	[redacted]
Peripheral neuropathy	[redacted]	[redacted]
Vision disorder	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Liver function test increased	[redacted]	[redacted]
QT prolongation	[redacted]	[redacted]
Atrioventricular block	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
CNS effects		
Cognitive effects	[redacted]	[redacted]
Mood effects	[redacted]	[redacted]
Speech effects	[redacted]	[redacted]
Psychotic effects	[redacted]	[redacted]

Abbreviations: AE: adverse event; CNS: central nervous system; SAS: safety analysis set.
Source: Pfizer Ltd Data on File (Interim Clinical Study Report) 2020 (Section 12.3.4.); [67] Shaw et al. 2020 (Table 3).[35]

B.2.11 *Ongoing studies*

The CROWN trial is still ongoing; the final study completion date is estimated to be in December 2028.[79] Interim and final data cuts for OS are planned for [redacted] and [redacted] when 70% and 100% of OS events required for analysis are expected to 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 Principal findings from the clinical evidence base

Lorlatinib is a novel, third-generation inhibitor that has demonstrated significantly longer PFS and a higher frequency of IC-OR than the first-generation inhibitor crizotinib in patients with untreated ALK-positive advanced NSCLC. At the September 2021 DCO of the pivotal CROWN trial, lorlatinib was associated with a HR of [redacted] (95% CI: [redacted]; p[redacted]) for reducing the risk of progression or death when compared with crizotinib. Moreover, at the September 2021 DCO, among patients with measurable brain metastases at baseline, [redacted]% (95% CI:[redacted]) of those that received lorlatinib had an IC-OR compared to [redacted]% (95% CI: [redacted]) of patients that received crizotinib, and [redacted]% of patients who received lorlatinib had an intracranial CR. Of particular note, the IC-TTP was significantly longer in the lorlatinib arm compared with the crizotinib arm,[35] with a HR of [redacted] (95% CI: [redacted]; p[redacted]) corresponding to a [redacted]% reduction in the risk of IC-progression. Patients who received lorlatinib also reported a significantly greater improvement in global QoL than those who received crizotinib (although this did not reach levels of clinical meaningfulness), with improvements seen as early as Cycle 2 and that were subsequently maintained over time.[66] Data for OS are immature from the CROWN study, and were not measured at the September 2021 DCO, however, the March 2020 DCO showed a general trend in favour of lorlatinib with a 28% reduction in the risk of death (HR=0.72 [95% CI: 0.41, 1.25]).[35]

While no head-to-head trial data exists for lorlatinib compared to the key second-generation inhibitors alectinib and brigatinib, the results of the NMA described in Section B.2.9.4 indicate that lorlatinib was associated with a [redacted] improvement in PFS using data from the September 2021 DCO, with a HR of [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) respectively. These results suggest lorlatinib to be associated with a [redacted] and [redacted] reduction in the risk of progression or death versus alectinib and brigatinib, respectively.

This result is further supported by a recent publication of a similar, independent analysis comparing lorlatinib, alectinib and brigatinib in an NMA, which concluded that lorlatinib prolonged PFS compared with both brigatinib (HR = 0.57; p = 0.03) and alectinib (HR = 0.65; p = 0.05).[80]

Using OS data from the March 2020 DCO for lorlatinib, there were [redacted] in OS, with a HR of [redacted] and [redacted] compared with alectinib and brigatinib, respectively. However, OS data are still immature and no robust conclusions can be made at this stage; a further data cut for OS is planned for [redacted]. Nonetheless, given the substantial PFS improvement it is reasonable to assume that this will translate into improve survival despite the change in treatment sequence.

Lorlatinib is generally tolerable and the AEs experienced are manageable with dose reduction, temporary discontinuation, and/or standard supportive medical therapy, when needed; permanent treatment discontinuations due to AEs were low in the CROWN study.[67]

ALK-resistance mutations, most of which are difficult to treat, are common with second-generation ALK inhibitors.[31, 32] Compared with other ALK inhibitors, lorlatinib has the broadest coverage of ALK resistance mutations that have been identified.[3, 32, 35, 74] Lorlatinib's design allows high blood-brain barrier penetration, leading to high exposures in the CNS and marked IC activity.[35, 81] As a result, lorlatinib has been recognised as innovative at the regulatory level in the

UK, where the MHRA granted lorlatinib an Innovation Passport on 1st March, 2020 [ILPA/IP/41969/001].

In conclusion, the available evidence demonstrates that in untreated ALK-positive advanced NSCLC patients, lorlatinib is an highly effective treatment, prevents brain metastases and significantly improves patients time to progression and later lines of therapy.

B.2.12.2 Strengths and limitations of the evidence base

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:[35, 67]

- 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 to 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
- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis and preserving randomisation

External validity of CROWN

The results of the CROWN trial can be generalised to the UK population, considering the patient demographics were generally similar to that expected of patients with ALK-positive NSCLC in the UK. The trial was well designed with a low risk of bias. The results are also well aligned with the decision problem specified in the NICE scope. The external validity of the CROWN study is supported by the following:

- **Population –** The study population of CROWN was patients with advanced ALK-positive NSCLC who had received no previous systemic treatment for metastatic disease. Patients with NSCLC often have no or light smoking history and are typically diagnosed at a relatively young age compared with the overall lung cancer population.[13] In line with these characteristics, the patients in the CROWN trial had a mean age of 57.4 and the majority had never smoked (59%). Although there were some slight imbalances in gender and ethnicity, demographics were generally similar to that expected of patients with ALK-positive NSCLC in the UK.
- **Comparators –** The efficacy and safety of lorlatinib was directly compared with that of crizotinib. The evidence presented in this submission (Section B.2.9) used an NMA to compare lorlatinib with the comparators, brigatinib and alectinib.

- **Outcomes –** A wide range of outcomes were evaluated, including all outcomes outlined in the scope that are relevant to patients and to clinicians (OS, PFS, response rates, adverse effects of treatment, HRQoL) and key intercranial endpoints relevant to those with the highest unmet need.

Feedback from UK clinicians is that CROWN is a well-designed trial in general; with some limitations in terms of the clinical relevance of the comparator arm and lack of comparability with ALTA-1L and ALEX in terms of measuring IC outcomes.

Limitations

- There has been no direct comparison of efficacy and safety between lorlatinib and the relevant comparators in a clinical trial setting, necessitating an indirect comparison to be performed. However, NMAs are a robust statistical method for comparing data from different trials and provide useful evidence of the relative difference in treatment effects among competing treatments in the absence of head to head trial data.[82]
- Overall survival data are still immature from the CROWN study with only 18 months of follow-up data available for lorlatinib; however, immaturity of OS data is a common limitation of clinical trials in the first-line setting and comparisons of OS at similar stages of trial evolution for brigatinib and alectinib are included in this submission. Further OS data cuts are planned for [redacted] and [redacted].

B.2.12.3 Conclusion

The quality of the evidence provided by the CROWN study is supported by robust and well-reported methodology, and the trial results are directly relevant to the treatment of patients with untreated advanced ALK-positive NSCLC in NHS clinical practice.

While a number of ALK inhibitors are currently available, limitations still exist with these treatments including suboptimal safety and tolerability profiles,[65, 83] varying efficacy in the presence of ALK-resistance mutations, [31, 32] and varying ability to penetrate the blood-brain barrier and thereby, target CNS metastases.[64, 65] ALK-resistance mutations, most of which are difficult to treat, are common with second-generation ALK inhibitors. Compared with other ALK inhibitors, lorlatinib has the broadest coverage of ALK resistance mutations that have been identified.[3, 32, 35, 74] Lorlatinib's design allows high blood-brain barrier penetration, leading to high exposures in the CNS and marked IC activity.[35, 81]

Lorlatinib's high blood-brain barrier penetration and coverage of ALK-resistance mutations translated into the high efficacy demonstrated in the CROWN study. Data from the September 2021 DCO and resulting NMA suggest that lorlatinib is associated with a [redacted] and [redacted] reduction in the risk of progression or death versus alectinib and brigatinib, respectively. The results of the NMA also indicated that lorlatinib had similar benefits on OS as alectinib and brigatinib using CROWN OS data from the March 2020 DCO for lorlatinib, however the OS data remain immature and no robust conclusions have yet be drawn from the OS NMA.

Therefore, lorlatinib offers patients with untreated ALK-positive advanced NSCLC a new, effective treatment option, with a tolerable and manageable safety profile, that can overcome some of the limitations associated with currently available therapies in this indication and provide improved outcomes for patients in the first-line setting.

B.3 Cost effectiveness

A four-state partitioned survival model was developed to evaluate the cost-effectiveness of lorlatinib versus brigatinib and alectinib in untreated ALK-positive NSCLC from the NHS and Personal Social Services (PSS) perspective

- A four-state partitioned survival model was developed to assess the cost-effectiveness of lorlatinib versus relevant comparators (brigatinib and alectinib) in untreated ALK-positive NSCLC. The model health states comprised 'progression-free', 'CNS-progressed', 'non-CNS progressed' and 'death' to sufficiently capture the burdensome impact of CNS metastases on patient prognosis, quality of life and resource use
- The primary source of efficacy data for lorlatinib and comparators in the patient population (patients with untreated ALK-positive NSCLC) was the CROWN trial and the NMA described in Section B.2.9
- Utility values were informed by EQ-5D-5L questionnaire (mapped to EQ-5D-3L) data from the CROWN trial for lorlatinib, brigatinib and alectinib. Utility adjustments were applied to account for the deterioration in wellbeing as a patient gets older and the impact of CNS progression
- The cost-effectiveness analysis was conducted from an NHS and PSS perspective over a lifetime horizon (30 years). Costs and resource use associated with each health state and treatment status were derived from NHS Reference Costs (2019/2020) and PSSRU (2021).[84,85] Grade 3 or higher all-cause AE and subsequent treatments following progression and cessation of initial treatment were also included in the model

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify any published literature on relevant economic analyses of treatments for patients with untreated ALK-positive advanced NSCLC. As no prior cost-effectiveness models were identified in this SLR, a *de novo* cost-utility analysis has been conducted for the purpose of this appraisal and is described below. The cost-utility model employed for this economic analysis was built in Microsoft Excel®.

Full details of the methods and results of published economic evaluations included in the systematic literature review are presented in Appendix G.

B.3.2 *Economic analysis*

B.3.2.1 Patient population

The patient population considered in the economic analysis was adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor , in line with the marketing authorisation as noted in Section B.1.1.

B.3.2.2 Model structure

A four-state partitioned survival model was developed to assess the cost-effectiveness of lorlatinib versus relevant comparators in untreated ALK-positive NSCLC, as presented in Figure 19. The model health states comprise 'progression-free', 'CNS-progressed', 'non-CNS progressed' and 'death' to sufficiently capture the burdensome impact of CNS metastases on patient prognosis, quality of life and resource use. This four-state structure has also recently been used in the NICE technology appraisals in first-line ALK-positive NSCLC for brigatinib (TA670) and alectinib (TA536), which aligns with the availability of second-generation ALK-

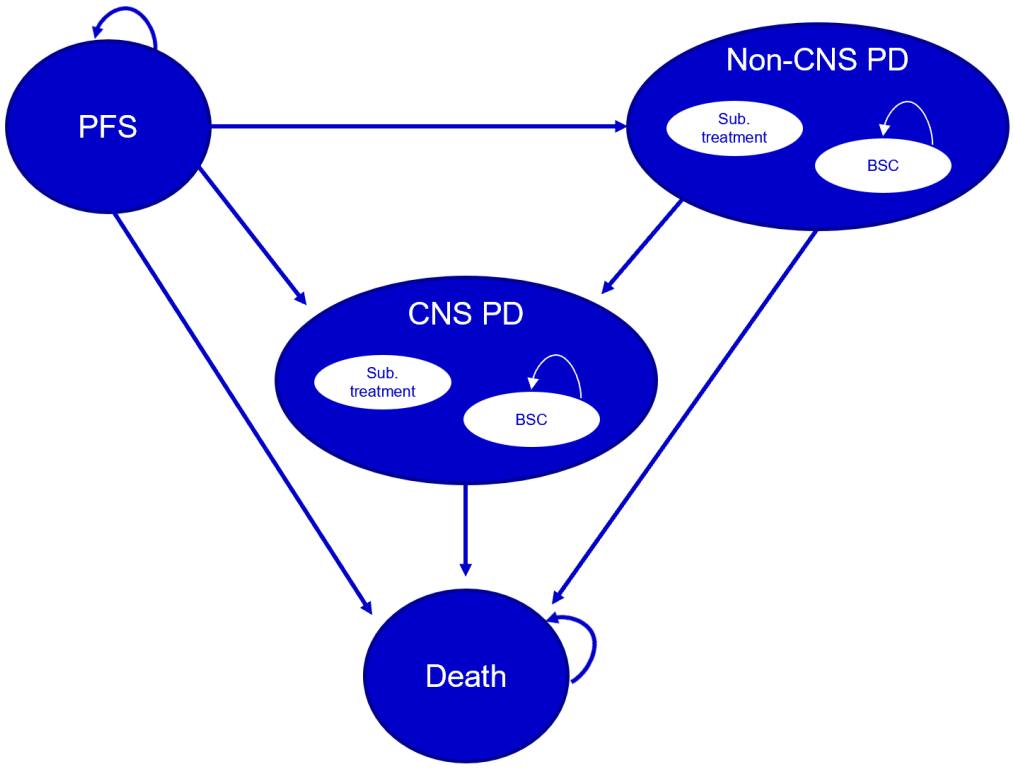
inhibitors which are considered to have intracranial activity and an impact on intracranial progression.[86, 87] As lorlatinib was designed to cross the blood-brain barrier to achieve high exposures in the CNS, and has been demonstrated to have a significant benefit on intracranial outcomes, this four-state structure better captures the value of lorlatinib compared with a more traditional three-state model.

All patients enter the model in the 'progression-free state', receiving lorlatinib or comparator treatment. Patients may remain progression-free, their disease may progress to non-CNS or CNS-progression, or they may die. Patients whose disease has progressed can remain alive with progressed disease or die. Non-CNS progressed patients may experience a CNS progression or die. Death is an absorbing state.

Patients receiving first-line therapy may also progress to subsequent therapies prior to progression off-treatment or death. Patients progressing beyond first-line treatment had the cost and utility of subsequent treatment applied once at the point of progression. The extrapolation of OS data (see Section B.3.3.2) was then considered to account for survival impact of patients receiving subsequent therapies.

Health state membership (or the rate at which patients transition through the model) was determined using a partitioned survival analysis approach to exploit the unidirectional nature of transitions in a progressive model structure, as patients cannot restart treatment or regress to a pre-progressed state.

Figure 19: Base case model structure



Abbreviations: BSC: best supportive care: CNS: central nervous system.

The area-under-the-curve approach used to determine health state occupancy at any given time point, T, is presented in Table 34.

Table 31: Health state occupancy

Health state	Occupancy at time *T*
Progression-free	PFS^T
Non-CNS progressed	MAX (0, $CNS\text{-}PFS^T$ minus PFS^T)
CNS-progressed	MAX (0, $CNS\text{-}PFS^T$)
Death	1 minus OS^T

Footnotes: The CNS-PFS, PFS, and ToT curves in the model are capped to be less than OS at any given time.
Abbreviations: CNS: central nervous system; MAX: maximum; MIN: minimum; OS: overall survival; PFS: progression-free survival; T: time; ToT: time on treatment.

Perspective

The analysis was performed from an NHS and PSS perspective.

Time horizon and cycle length

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) to improve the accuracy of the results by averaging outcomes between the beginning and end of each cycle

A lifetime horizon of 30 years was considered in the model. Based on the mean baseline age of 57.4 years observed in the CROWN study and used in the model, the maximum modelled cohort age is 87 years and after these 30 years, less than 5% of patients remained alive across all treatment arms. All recent NICE appraisals in first-line ALK-positive NSCLC have used lifetime horizons (ranging from 10 to 30 years).[8]

Discounting

Discount rates of 3.5% were applied to both costs and benefits, in line with the NICE Methods Guide.[88]

The features of the economic model are described in Table 32, 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.

Table 32: Features of the economic analysis

	Previous evaluations				Current evaluation	
	Crizotinib (TA406)	**Ceritinib (TA500)**	**Alectinib (TA536)**	**Brigatinib (TA670)**	**Chosen values**	**Justification**
Time horizon	15 years	20 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.	Scenario analyses capped OS and PFS treatment effect duration at 10- and 20- years	Given median PFS has not been met with median [redacted] of follow up in CROWN, it was considered inappropriate to assume treatment waning at 3- , 5- and 7- years in line with the final committee decisions in previous appraisals.
Source of utilities	The company estimated health state utilities from PROFILE 1014 for progression free disease with crizotinib or with chemotherapy. The	Utility values for the progression-free health state was estimated using data from ASCEND-464 for ceritinib and for crizotinib, PROFILE	The company estimated health state utilities from ALEX for progression free disease and non-CNS progression. The company	Health state utilities for the pre-progression health state and progressed disease on-treatment with an ALK-inhibitor are derived from the	Utilities were informed from EQ-5D-5L data collected during the CROWN trial, with the UK value set applied (mapped 5L to 3L). Age	Utilities for pre-progression and progressed disease from CROWN, as per the NICE reference case. The use of the multiplier from Roughley et

	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.[89]	1014 (Solomon et al. 2014).[55] Values for the progressed disease health states were derived from Chouaid et al. (2013).[90]	estimated utility values for CNS progression from Peters et al. (2016) and Roughley et al. (2014)[91]	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 HRQoL for CNS progression, progressed disease receiving chemotherapy and progressed disease receiving BSC. The literature includes: Peters et al. (2016) and Roughley et al. (2014) (for CNS progression), PROFILE 1007 (for chemotherapy in progressed disease) and Nafees et al. (2008) (for BSC in progressed disease).	adjusted utility values have been incorporated into the model. Due to data limitations within the CROWN trial for CNS-progressed patients, a multiplier (Roughley et al. 2014)[91] has been applied to account for the impact of CNS- progression.	al. (2014)[91] is aligned with previous appraisals.
Source of costs	Drugs costs from MIMs and eMIT. Resource use and adverse events were based on TA296,[92] TA162,[93] TA188,[94] TA181[95] and TA258[96] and costed using NHS	Drugs costs from MIMs and eMIT. Resource use and adverse events were based on TA406,[28] TA296,[92] TA162,[97] TA181[95] and TA258[96] and costed using NHS	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	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	Drug costs from MIMS and eMIT. Resource use derived from TA536[30] and TA670[1] and updated and/or validated by clinical experts. Resource	To ensure the analysis captures all relevant costs for these treatments and this indication, as per the NICE reference case.

	Reference costs and PSSRU. Cost year: 2014/2015.[84]	Reference costs, PSSRU. Cost year: 2015/2016.[84]	and PSSRU. Cost year: 2014/2015/2016.[84]	and PSSRU. Cost year: 2018/2019.[84]	use and AEs costed using the NHS Reference costs and PSSRU. Cost year: 2019/2020.[84,85]	

Abbreviations: AE: adverse event; ALK: anaplastic lymphoma kinase; BNF: British National Formulary; BSC: best supportive care; CNS: central nervous system; eMIT; drugs and pharmaceutical 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 Five Dimensions 5 Levels; MIMS: Monthly Index of Medical Specialities; HRQoL: health-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

B.3.2.3 Intervention technology and comparators

Intervention

As described in Section B.1.2, the recommended dose of lorlatinib is 100 mg administered orally once daily. Treatment is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity. Doses may be interrupted or reduced as needed until toxicity resolution. Depending on when an AE is resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even delay the initiation of the subsequent cycle. Table 33 details the available dose level reductions reported in the SmPC.[98]

Table 33: Lorlatinib dose level reductions

Recommended dose	First dose reduction	Second dose reduction
100 mg daily	75 mg daily	50 mg daily

Comparators

As discussed in Section B.1.3.2, ceritinib and crizotinib are rarely used in untreated ALK-positive patients, with the vast majority of patients in this setting anticipated to receive either alectinib or brigatinib only. Therefore, alectinib (600 mg BID) and brigatinib (180 mg QD) represent the primary comparators of interest in this evaluation and as such were both considered in the cost-effectiveness analysis. 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 Approach to extrapolation and NMA

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 described in Section B.2.9.

To allow for the potential violation of the proportional hazard assumption within the CROWN trial independent parametric survival curves were fitted to time-to-event endpoints to inform efficacy in the lorlatinib arm of the model; the endpoints used in the model are described in Table 34. The 'standard' selection of parametric models were fit to patient-level data, in line with NICE Decision Support Unit guidance, to extrapolate outcomes beyond the observed data for a lifetime horizon.[99] These comprised exponential, Weibull, log-normal, log-logistic, Gompertz, gamma, and generalised gamma models.

For comparator treatments, given that there was no clear evidence that the proportional hazards assumption was violated in the ALEX and ALTA-1 trials, parametric survival curves were fit to time-to-event endpoints of the crizotinib treatment arm from the CROWN trial in the same way as described for the lorlatinib arm. HRs for comparators versus baseline (crizotinib) produced by the NMA (Section B.2.9) were then applied to baseline crizotinib to predict outcomes for each comparator.

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. It is also generally

considered unnecessary to rely on the proportional hazards assumption when patient-level data are available, as reported in NICE Technical Support Document 14.[99]

In Section B.2.9.4.2, no conclusions could be draw from the OS NMA and as described in B.3.3.2, it is expected that OS for lorlatinib will exceed that of alectinib and brigatinib. It has therefore been assumed that the modelled PFS gain of [redacted] months translates into an equivalent OS gain, to better reflect the impact of the treatment sequencing on survival (see Section 3.2.2). An alternative scenario in which lorlatinib offers a survival gain of [redacted] months over alectinib is explored, which assumes an equivalent time spent in the progressed disease state, minus time on treatment (ToT) for patients receiving second-line lorlatinib.

Given that cross-over was permitted after progression from crizotinib to brigatinib in ALTA-1L, the crossover-adjusted NMA HRs were used in the cost-effectiveness model base case. These results were considered to provide a fairer comparison across all trials. In all cases, the hazard of survival was capped based on the expected survival of the general population.

Table 34: Clinical endpoint definitions

Endpoint	Definition
OS	Defined as the time from date of randomisation to the date of death due to any cause.
CNS-PFS	• Intracranial PFS was derived using intracranial time to progression and OS data • Intracranial PFS was defined as the time from randomisation to the date of first documentation of objective progression of intracranial disease, based on either new brain metastases or progression of existing brain metastases, or death due to any cause
PFS	• PFS (based on BICR) was defined as the time from randomisation to the date of the first documentation of progressive disease per RECIST v1.1, as assessed by the independent radiologist, or death due to any cause, whichever occurred first • PFS based on investigator assessment was also explored in the model where available
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.

Abbreviations: BICR: blinded independent central review; CNS: central nervous system; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours; ToT: time on treatment.

Curve selection for each endpoint is described in the following sections and was largely driven by the clinical plausibility of long-term extrapolations, consistency with clinical validation from previous NICE appraisals in first-line ALK-positive NSCLC where appropriate, consistency of extrapolations across correlated modelled endpoints where plausible, and statistical goodness-of-fit to the observed data where appropriate.

In line with TA536[30] and TA670[1], the impact of treatment waning was explored. However, given that median PFS has not been reached after a median follow-up of 36.7 months, earlier waning scenario of 3 and 5 years were not considered plausible for lorlatinib. Therefore, 10- and 20-years waning scenarios were explored in scenario analyses for completeness, by assuming equivalent survival hazards to the crizotinib survival curve beyond the specified timepoint.

B.3.3.2 Overall survival

OS curves were independently fit to each arm of the CROWN population as described in Section B.3.3.1. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) for the

OS lorlatinib and crizotinib parametric curves are presented in Table 35 and Table 37, respectively. Given the immaturity of the CROWN survival data, the AIC/BIC may not be considered as informative as is typical in curve selection. Consequently, the AIC/BIC parametric models were within five points of one another, which suggests there was not a meaningful difference in the goodness-of-fit to the observed data.

An overview of the modelled OS at key time points for lorlatinib and crizotinib by survival extrapolation are presented in Table 36 and Table 37, respectively. These results indicate that the generalised gamma, Gompertz, 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). Furthermore, the log-normal and log-logistic curves predict >5% survival at 50 years for crizotinib patients, and the Gompertz and generalised gamma curves predict >35% at 50 years for crizotinib patients, at which point the modelled cohort would be over 107 years old.

Feedback from a UK clinician was sought to validate the survival extrapolations. Clinical opinion was that the Weibull, gamma and exponential curves would be appropriate to use, however all other extrapolations are unrealistic.

Therefore, exponential curves were selected to model OS in the lorlatinib and crizotinib arms, based on the plausibility of the long-term extrapolation. As shown in Figure 20 and Figure 21, the exponential curves provide conservative survival estimate in both treatment arms, compared with alternative 'heavier tailed' curves. Furthermore, this approach is in line with NICE Technical Support Document 14, which recommends selecting the same distribution for each treatment arm.[99]

Table 35: Fit statistics of OS extrapolation – lorlatinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	**1**	[redacted]	**1**
Generalised gamma	[redacted]	3	[redacted]	7
Gompertz	[redacted]	6	[redacted]	5
Log-logistic	[redacted]	4	[redacted]	3
Log-normal	[redacted]	2	[redacted]	2
Weibull	[redacted]	7	[redacted]	6
Gamma	[redacted]	5	[redacted]	4

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

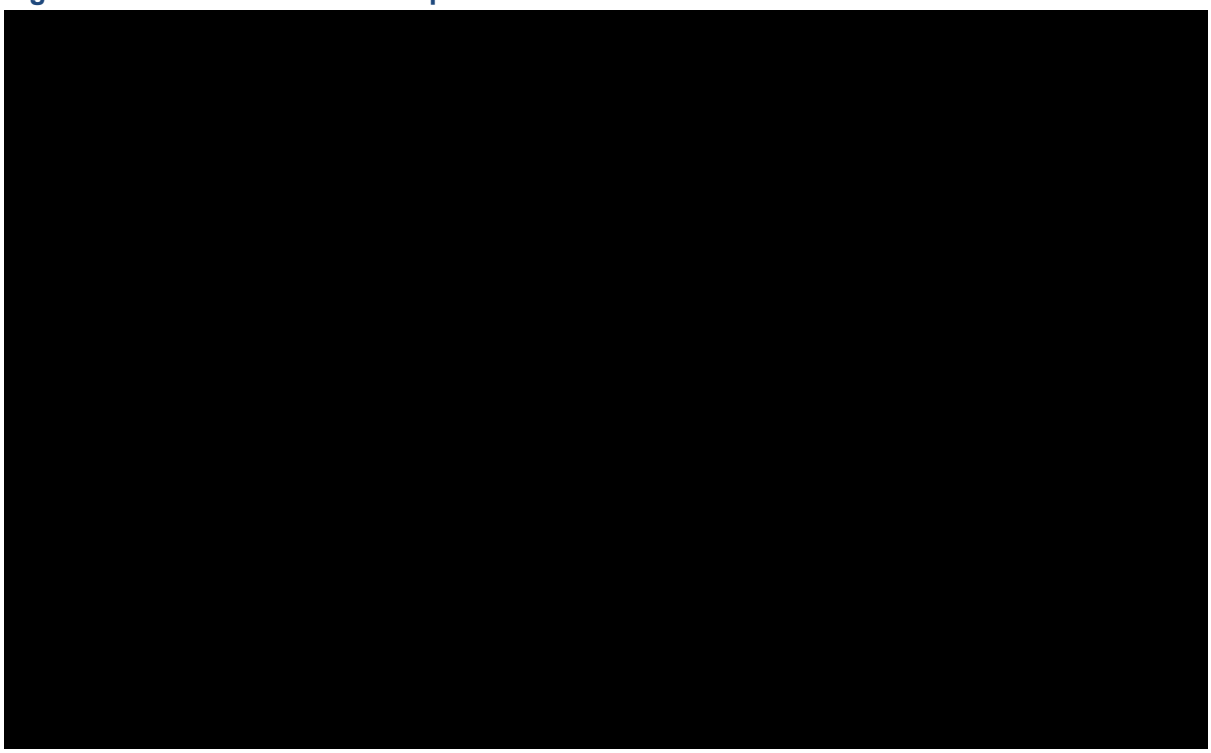
Table 36: Proportion of patients alive at key time points – lorlatinib

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 20: Overall survival extrapolations for lorlatinib



Abbreviations: KM: Kaplan–Meier; OS: overall survival.

Table 37: Fit statistics of OS extrapolation – crizotinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	**3**	[redacted]	**1**
Generalised gamma	[redacted]	1	[redacted]	4
Gompertz	[redacted]	7	[redacted]	7
Log-logistic	[redacted]	4	[redacted]	3
Log-normal	[redacted]	2	[redacted]	2
Weibull	[redacted]	6	[redacted]	6
Gamma	[redacted]	5	[redacted]	5

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

Table 38: Proportion of patients alive 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 21: Overall survival extrapolations for crizotinib

[redacted]

Abbreviations: KM: Kaplan–Meier; OS: overall survival.

Table 39: Overall survival for alectinib and brigatinib

Weibull distribution	Modelled landmarks						
	1 year	4 years	5 years	10 years	15 years	20 years	30 years
	12 months	48 months	60 months	120 months	180 months	240 months	360 months
OS: alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS: brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival.
Footnotes: The per-cycle probability of death was capped at the age- and sex-matched general population.

The OS extrapolations using the exponential distribution for crizotinib with hazard ratios applied for alectinib and brigatinib are supported by long-term trial data:

- In PROFILE-1014, the median follow-up duration of crizotinib was 45.7 months. Survival probability at 48 months was 56.6% (95% CI: 48.3%, 64.1%), which is consistent with the modelled survival using the exponential distribution of [redacted]% at four years.[72]
- In ALTA-1L, the median follow up duration was 40.4 months and 15.2 months for brigatinib and crizotinib, respectively. At four years, the survival probability in the brigatinib arm was 66% (95% CI: 56%, 74%), compared to [redacted]% modelled using the exponential distribution. In the crizotinib arm, four year survival probability was 60% (95% CI: 51%, 68%), compared to [redacted]% modelled using the exponential distribution.[100]
- In ALEX, the median follow up duration was 48.2 months and 23.3 months for alectinib and crizotinib, respectively. Survival probability for alectinib at five years was 62.5% (95% CI: 54.3%, 70.8%) compared to [redacted]% in the model using the exponential distribution. Survival probability for crizotinib at five years was 45.5% (95% CI: 33.6%, 57.4%), compared to [redacted]% in the model using the exponential distribution.[75]

Despite the above providing validation that the alectinib and brigatinib estimates of OS are well aligned with long-term observed data when assumed equivalent to lorlatinib, when sufficient follow-up has been observed from the CROWN trial, it is expected that lorlatinib will result in improved OS compared to alectinib and brigatinib. This is not only due to the alectinib and brigatinib HRs improving over time when within their clinical studies, but given the substantial statistically significant improvement in PFS (see Section 2.9.4) over alectinib and brigatinib, it is expected that this improved PFS will translate into improved OS despite a change in the treatment sequence.

As of the September 2021 DCO with median follow-up of lorlatinib at 36.7 months, median PFS was not reached. However, the most conservative extrapolated PFS for lorlatinib results in a median PFS of [redacted], which alone exceeds the median PFS of alectinib/brigatinib, followed by second line lorlatinib treatment, as shown in **Error! Reference source not found.**.

Figure 22. Median PFS of first line lorlatinib versus first line alectinib and second line lorlatinib

Abbreviations: PFS – progression-free survival
Source:
Footnotes: [a] Lowest median extrapolation of lorlatinib PFS (exponential), see Section B.3.3.4; [b] Taking maximum of alectinib and brigatinib investigator assessed PFS

This estimated median [redacted] PFS gain of lorlatinib (PFS1) alone versus alectinib (PFS1) plus lorlatinib (PFS2) was applied by assuming a direct translation into OS benefit i.e. the same prognosis post primary progression on lorlatinib first line and post-secondary progression following

progression on alectinib/brigatinib first line and lorlatinib second line. An exponential with rate [redacted] was calculated using the goal seek function to generate an additional [redacted] LYs for lorlatinib compared to alectinib. The resulting survival extrapolation is presented in Figure 23. Please see Section B.3.10.3 for results.

However, this [redacted] survival gain is still expected to substantially underestimate the overall survival benefit offered by lorlatinib. Therefore, an alternative scenario is presented which assumes patients spend an equal amount of time in the progressed disease state, minus the time on treatment for patients receiving lorlatinib in second-line, to give an estimated survival gain for lorlatinib of [redacted]. An exponential with rate [redacted] was calculated using the goal seek function to generate an additional [redacted] LYs for lorlatinib compared to alectinib. The resulting survival extrapolation is presented in

Figure 24.

Figure 23: Overall survival of all treatments with [redacted] median gain applied

[redacted]

Figure 24. Overall survival of all treatments with [redacted] median gain applied

[redacted]

B.3.3.3 Central nervous system progression-free survival

CNS-PFS curves were independently fit to IC-TTP from each arm of the CROWN population, as described in Section B.3.3.1. CNS-PFS data observed in the CROWN study for patients in the lorlatinib arm were immature; however, crizotinib CNS-PFS was approximately 60% mature. This is consistent with real-world expectation, as crizotinib does not show the same intracranial activity as lorlatinib. However, due to this immaturity, the lorlatinib survival extrapolations for CNS-PFS were associated with uncertainty, with all models producing higher CNS-PFS estimates than OS, which is implausible. Therefore, a cap was introduced into the model to ensure the CNS-PFS curve does not lie above the OS curve at any time point.

In the same way as the OS extrapolation, the immaturity of data meant that the AIC/BIC parametric models were within five points of one another, which suggests there was not a large difference in the goodness-of-fit to the observed data. Therefore, the exponential curve was selected for the lorlatinib base case as the most conservative long-term extrapolation. Moreover, all other distributions for lorlatinib were likely clinically implausible (estimating >25% of patients to be alive and free of intracranial progression at 30 years), as shown in Table 41. In line with NICE recommendations to select the same distribution for each treatment arm,[99] the exponential curve was also selected for the crizotinib base case, despite not being the most conservative estimate of CNS-PFS. Whilst the generalised gamma has the lowest AIC/BIC criterion, the extrapolation was likely to be clinically implausible (5% of patients alive and free of intracranial progression at 30 years in the crizotinib arm), as shown in Table 43.

Table 40: Fit statistics of CNS-PFS extrapolation – lorlatinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CNS-PFS: intracranial progression-free survival.

Table 41: Proportion of patients alive and free of intracranial progression at key time points – lorlatinib

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]					
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 42: Fit statistics of CNS-PFS extrapolation – crizotinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CNS-PFS: intracranial progression-free survival.

Table 43: Proportion of patients alive and free of intracranial progression of patients alive and free of intracranial progression 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 25: CNS-PFS for lorlatinib

Footnotes: The curves in the figure do not account for the OS cap applied to CNS-PFS in the model.
Abbreviations: CNS: central nervous system; KM: Kaplan–Meier; PFS: progression-free survival.

Figure 26: CNS-PFS for crizotinib

Abbreviations: CNS, central nervous system; KM, Kaplan–Meier; PFS, progression-free survival.

In the NMA (Section B.2.9), it was not possible to form a network for the CNS-PFS endpoint, as these data were not commonly reported across trials. Therefore, the PFS HR for comparator

treatments versus crizotinib were assumed to be applicable to CNS-PFS, in line with the approach undertaken in the appraisal for brigatinib (TA536).[87] The resulting CNS-PFS curves are presented in Figure 27.

Figure 27: CNS-PFS of all treatments

Abbreviations: CNS, central nervous system; PFS, progression-free survival.

B.3.3.4 Progression-free survival

PFS based on BICR assessment curves were independently fit to each arm of the CROWN population as described in Section B.3.3.1. The statistics fit for lorlatinib and crizotinib PFS are presented in Table 44 and Table 46, and the resulting survival extrapolations are presented in Figure 28 and Figure 29, respectively. As previously described for CNS-PFS (Section B.3.3.3), the exponential curve was selected for both the lorlatinib and crizotinib base case as this curve represents the most conservative long-term extrapolation for lorlatinib compared to other curves (such as the Gompertz, generalised gamma, log-normal and log-logistic), which are likely to be clinically implausible (>13% alive and progression-free after 30 years).

In line with NICE recommendations to select the same distribution for each treatment arm and the NICE appraisals for first line brigatinib (TA670) and alectinib (TA536),[87, 99] the exponential curve was also selected for crizotinib. Although the AIC/BIC suggested the log-normal 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).

Table 44: Fit statistics of BICR assessed PFS extrapolation – lorlatinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	AIC	AIC rank	BIC	BIC rank
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 45: Proportion of patients alive and progression free at key time points – lorlatinib

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 46: Fit statistics of BICR assessed PFS extrapolation – crizotinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 47: Proportion of patients alive and progression free 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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

Figure 28: BICR assessed PFS for lorlatinib

Abbreviations: BICR: blinded independent central review; KM: Kaplan–Meier; PFS: progression-free survival.

Figure 29: BICR assessed PFS for crizotinib

Abbreviations: BICR: blinded independent central review; KM: Kaplan–Meier; PFS: progression-free survival.

The BICR assessed PFS extrapolations for each comparator, using the exponential curves for lorlatinib and crizotinib, and HRs versus crizotinib from the NMA (Section B.2.9) are presented in Figure 30.

Figure 30: Progression-free survival of all treatments

Abbreviations: PFS: progression-free survival

B.3.3.5 Time on treatment

Sufficient ToT data were not reported for alectinib and brigatinib to allow comparison and as demonstrated in Figure 30, ToT for lorlatinib was slightly less than PFS, throughout the observed period. Therefore, ToT was conservatively assumed to be equal to PFS for all treatments.

Figure 31: Observed time on treatment compared to PFS for lorlatinib

Figure 32: Time on treatment

B.3.3.6 Adverse reactions

It was assumed that Grade 1/2 AEs had negligible impact on HRQoL and costs, and these were excluded from the model in line with prior appraisals.

Grade 3 or higher all-cause 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 were considered in the model.

This list of AEs and proportions applied to each treatment arm are presented in Table 48. Average treatment exposures were used to calculate yearly AE rates, to avoid biasing in favour of treatments with a shorter trial follow up.

Table 48: Adverse events proportions

Adverse event	Lorlatinib (CROWN)[66]	Alectinib (ALEX)[61]	Brigatinib (NICE TA670)[1]
Hypertriglyceridemia	[redacted]	0.00%	0.00%
Weight increased	[redacted]	0.00%	0.00%
Increased lipase level	[redacted]	0.00%	12.50%
Hypercholesterolemia	[redacted]	0.00%	0.00%
Aspartate aminotransferase increased	[redacted]	5.26%	2.21%
Gamma-glutamyltransferase increased	[redacted]	0.00%	0.74%
Hypertension	[redacted]	0.00%	7.35%
Anaemia	[redacted]	5.92%	1.47%
Amylase increased	[redacted]	0.00%	5.88%
Neutropenia	[redacted]	0.00%	0.00%
Blood creatine phosphokinase increased	[redacted]	3.29%	23.53%

B.3.4 *Measurement and valuation of health effects*

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

Estimation of health state utilities from CROWN quality of life data

As discussed in Section B.2.6.5, the CROWN trial collected HRQoL data using the EQ-5D-5L questionnaire, the EORTC QLQ-C30 and the EORTC QLQ-LC13. All questionnaires were scheduled for completion once every 28-day cycle.

Utilities subsequently used in the model were stratified by health state, treatment status and treatment arm and were informed by EQ-5D-5L questionnaire results (ITT; September 2021 data cut) mapped to the equivalent EQ-5D-3L questionnaire results, using the mapping function developed by the DSU using the 'EEPRU' dataset (see Section B.3.4.2 for further details).[101]Utilities for alectinib and brigatinib were assumed equal to lorlatinib. A summary of the parameters informing the utility values is shown in Table 49, and the resulting utility values are shown in Table 50.

Table 49: Utility parameters

Parameter	Utility data from CROWN	Health state parameters			
		Progression-free (on treatment)	Progression-free (off treatment)	Progressed (on treatment)	Progressed (off treatment)
(Intercept)	[redacted]	[redacted]			
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline brain metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib: baseline brain metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age: post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib: post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Pfizer Ltd Data on File (IA2 data from the CROWN trial).[66]

Table 50: Final utility values

Utility value	Progression-free (on treatment)	Progression-free (off treatment)	Progressed (on treatment)	Progressed (off treatment)
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]

Source: Pfizer Ltd Data on File (IA2 data from the CROWN trial).[66]

B.3.4.2 Mapping

In lieu of data collected using the EQ-5D-3L questionnaire in the CROWN trial, EQ-5D-5L questionnaire results collected in CROWN were mapped to the equivalent EQ-5D-3L questionnaire results.

Patient responses from the EQ-5D-5L questionnaire were mapped to the EQ-5D-3L using the mapping function developed by the DSU using the 'EEPRU' dataset.[101] After the application of the mapping algorithm, the UK EQ-5D-3L value set was applied to the data to produce utility values (see Section B.3.4.5). 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 with the exception of 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 prior to the date of objective progression of disease
- Post-progression includes observations on and after the date of objective progression of disease
- Observations recorded after a censored progression date were included in the exploratory analysis or mixed effects regression models, as it is unknown which health state they are in at that time
- Health state was defined based on PFS assessed by BICR
- The health states further split by CNS progression were also investigated

B.3.4.3 Health-related quality-of-life studies

Utility systematic literature review

An SLR was conducted to identify relevant utility 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. In total, the 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. Utility values from one study, the NICE appraisal of alectinib (TA536) were included in scenario analysis. Full details of the SLR search strategy, study selection process and results can be found in Appendix H.

Age-related disutility

An age-related utility adjustment was applied to account for the deterioration in wellbeing 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 51):[102]

$$\text{General population utility} = \beta 0 + \beta 1 \text{male} + \beta 2 \text{age} + \beta 3 \text{age}^2$$

Table 51: 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.[102]

Impact of central nervous system progression

In line with the brigatinib appraisal (TA670),[87] multipliers were applied to utility values to account for the impact of CNS progression. 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.[91] Roughley et al. 2014 reported that the utility value associated with brain metastases was 0.52 compared with 0.69 for contralateral lung metastases. 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.

One-off utility for subsequent treatments

A one-off utility benefit was also applied to patients upon progression to account for QoL benefits of subsequent treatment. This was derived from the distribution of subsequent treatments (Section B.3.5.4), average duration (Section B.3.5.4) and the difference between on- and -off treatment in CNS and non-CNS progressed derived from the CROWN trial (Section 3.4.5).

B.3.4.4 Adverse reactions

AE disutility values were excluded from the analysis, with the assumption that health state utilities already captured the effect of any AEs.

B.3.4.5 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 52.

Table 52: Summary of utility values for cost-effectiveness analysis

	State	Utility value: mean	Reference in submission (section)	Source and justification
Utility values	**Progression-free (on treatment)**			
	Lorlatinib	0.84	B.3.4.1; B.3.4.2	Derived from EQ-5D-5L (mapped to the EQ-5D-3L) questionnaire completed by patients enrolled in the CROWN trial (September 2021 data cut).
	Brigatinib	0.84		
	Alectinib	0.84		
	Progression-free (off treatment)			
	Lorlatinib	0.76	B.3.4.1; B.3.4.2	Derived from EQ-5D-5L (mapped to the EQ-5D-3L) questionnaire completed by patients enrolled in the CROWN trial (September 2021 data cut).
	Brigatinib	0.76		
	Alectinib	0.76		
	Progressed (on treatment)			
	CNS-progressed			
	Lorlatinib	0.62	B.3.4.1; B.3.4.2	Derived from EQ-5D-5L (mapped to the EQ-5D-3L) questionnaire completed by patients enrolled in the CROWN trial (September 2021 data cut).
	Brigatinib	0.62		
	Alectinib	0.62		
	Non-CNS-progressed			
	Lorlatinib	0.83	B.3.4.1; B.3.4.2	Derived from EQ-5D-5L (mapped to the EQ-5D-3L) questionnaire completed by patients enrolled in the CROWN trial (September 2021 data cut).
	Brigatinib	0.83		
	Alectinib	0.83		
	Progressed (off treatment)			
	CNS-progressed			
	Lorlatinib	0.57	B.3.4.1; B.3.4.2	Derived from EQ-5D-5L (mapped to the EQ-5D-3L) questionnaire completed by patients enrolled in the CROWN trial (September 2021 data cut).
	Brigatinib	0.57		
	Alectinib	0.57		
	Non-CNS-progressed			
	Lorlatinib	0.75	B.3.4.1; B.3.4.2	
	Brigatinib	0.75		

	Alectinib	0.75		Derived from EQ-5D-5L (mapped to the EQ-5D-3L) questionnaire completed by patients enrolled in the CROWN trial (September 2021 data cut).	
One-off utility for subsequent treatment (non-CNS/CNS)	Lorlatinib		0.009/0.007	B.3.4.3, B.3.5.4	Difference between on- and -off treatment from CROWN trial multiplied by subsequent treatment proportions and durations
	Brigatinib		0.097/0.073		
	Alectinib		0.097/0.073		
Utility multiplier	CNS multiplier	75.36%	B.3.4.3	CNS multiplier applied in line with brigatinib NICE submission (TA670)	
Utility decrement	Age	0.84	B.3.4.3	Age utility decrement applied in line with brigatinib NICE submission (TA670)	

Abbreviations: CI: confidence interval; CNS: central nervous system; 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

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

An SLR was conducted to identify relevant cost and healthcare resource use 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.

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 53 alongside the costs for lorlatinib.[103] For lorlatinib, a confidential discount of [redacted] from the list price has been applied. The base case results use this proposed patient access scheme (PAS) discount for lorlatinib and list prices for brigatinib and alectinib, both of which have confidential discounts applied in UK practice. However, as these discounts are confidential and unknown, they cannot be incorporated within this evaluation.

Table 53: Drug unit costs

Treatment	Form	Unit	Pack size	Pack price (list price)
Lorlatinib	Tablets	25 mg	120	£7,044.00 With PAS: [redacted]
	Tablets	25 mg	90	£5,283.00 With PAS: [redacted]
	Tablets	100 mg	30	£5,283.00 With PAS: [redacted]
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.[103]

Dosing schedules were informed by the SmPCs for each product, as shown in Table 54. Treatment cycles and subsequent treatment cycle cost were automatically 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 54: Dosing schedules

Treatment	Dose	Frequency	Administration
Lorlatinib	100 mg	Once daily	Oral

Treatment	Dose	Frequency	Administration
Alectinib	600 mg	Twice daily	Oral
Brigatinib (cycle 1)	Starter pack	Once daily	Oral
Brigatinib (cycle 2+)	180 mg	Once daily	Oral

Source: Lorlatinib SmPC;[104] Alectinib SmPC;[33] Brigatinib SmPC.[34]

Administration costs for oral therapies in the model were captured as pharmacist dispensing time. An administration cost of £10.80 was applied per pack, sourced from the Personal Social Services Research Unit (PSSRU) 2020 as the cost for 12 minutes of work for a Band 6 community-based scientific and professional staff member (£54 per hour).[84]

For lorlatinib, detailed dosing data from the CROWN study were used to accurately reflect dose reductions of lorlatinib on treatment costs (Table 55). The CROWN dose level distribution was used to calculate a weighted average per-treatment-cycle drug and administration cost (which was then adjusted to account for the 30-day model cycle length) as shown in Table 56.

Table 55: CROWN – lorlatinib dose distributions (data cut-off: 20 September 2021)

Lorlatinib dose	n (doses)	Distribution (%)	Corresponding pack	Tablets (per day)
100 mg	[redacted]	[redacted]	100 mg	1
75 mg	[redacted]	[redacted]	25 mg (90 pack)	3
50 mg	[redacted]	[redacted]	25 mg (90 pack)	2
25 mg	[redacted]	[redacted]	25 mg (90 pack)	1
0 mg	[redacted]	[redacted]	25 mg (90 pack)	0

Source: Pfizer Ltd Data on File (September 2021 DCO data from the CROWN trial).[66]

Table 56: Lorlatinib – detailed dosing costs (PAS price)

Lorlatinib dose	Treatment cycle (days)	Per treatment cycle drug costs	Per model cycle (30 day) drug costs	Per model cycle (30 day) administration costs
100 mg	30	[redacted]	[redacted]	£10.80
75 mg	30	[redacted]	[redacted]	£10.80
50 mg	45	[redacted]	[redacted]	£7.20
25 mg	90	[redacted]	[redacted]	£3.60
0 mg	0	[redacted]	[redacted]	£0.00
Weighted average cost			[redacted]	**£10.24**

Abbreviations: PAS: Patient Access Scheme.

For 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 57). In line with the brigatinib appraisal (TA670), it was assumed that the NHS would save half of costs associated with reduced dose intensity.[1]

Table 57: Relative dose intensity

Treatment	Mean RDI	SD	Source
Alectinib	95.6%	0.10	NICE TA536[30]
Brigatinib	85.5%	0.19	NICE TA670[1]

Abbreviations: NICE: National Institute for Health and Care Excellence; NR: not reported; RDI: relative dose intensity, SD: standard deviation.

The overall drug and administration costs applied in the base case are presented in Table 58.

Table 58: Treatment cycle and model cycle costs (PAS price)

Treatment	Selected pack	Selected pack size	Treatment cycle (days)	Treatment cycle cost	Model cycle cost	Admin cost per model cycle
Lorlatinib	See detailed dosing information (Table 55)			[redacted]	[redacted]	£10.80
Alectinib	150 mg	224	28	£5,032.00	£5,272.82	£11.57
Brigatinib (cycle 1)	Starter pack	28	28	£4,900.00	£4,869.64	£11.57
Brigatinib (cycle 2+)	180 mg (28 pack)	28	28	£4,900.00	£4,869.64	£11.57

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 (TA546) appraisals, whereby the frequencies of individual resources were broken down depending on the health state and treatment status.[1,30] Medical resources for monitoring NSCLC patients based on the progression-free and post-progression health states are presented in

Table 59 and Table 60, respectively.

Additional resource use was applied for patients in the CNS-progressed health state to reflect the resource-intensive nature of this site of progression. The proportion of patients experiencing CNS progression resources was informed by an advisory board (January 2020) conducted by the manufacturer of brigatinib during its appraisal (TA670).[1] Medical resources for monitoring NSCLC patients based on CNS progression applied in the base case are presented in Table 61.

All monitoring costs for NSCLC patients with and without CNS progression were derived from the latest NHS reference costs (2019–2020) and from the PSSRU, as shown in

Table 62 and Table 63.[84, 85]

Table 59: Medical resources for monitoring patients based on progression-free/on treatment

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%	£253.20	£249.57
Tests and procedures	Full blood test	1	100%	£2.53	£2.50
	Biochemistry	1	100%	£1.20	£1.18
Total cost per cycle					£253.24
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%	£102.27	£100.80
	GP visit	1	10%	£3.90	£3.84
	Cancer nurse	1	50%	£49.65	£48.94
Tests and procedures	Full blood test	1	100%	£2.53	£2.50
	Biochemistry	1	100%	£1.20	£1.18
	CT scan	0.5	100%	£39.58	£39.01
	MRI	0.2	50%	£21.13	£20.83
	X-ray	0.3	50%	£4.91	£4.84
	ECG	1	100%	£70.69	£69.67
Total cost per cycle					£291.61

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

Table 60: Medical resources for monitoring patients based on progression/off treatment

Resource use - progressed/off treatment					Cost per month	Cost per cycle
Category		**Item**	**Frequency per month**	**Proportion of patients requiring resource**		
Physician visits	Oncology outpatient (s)	1.25	100%	£170.44	£167.99	
	GP visit	1	50%	£19.50	£19.22	
	Cancer nurse	1.5	80%	£119.17	£117.45	

Resource use - progressed/off treatment					Cost per month	Cost per cycle
Category		Item	Frequency per month	Proportion of patients requiring resource		
Tests and procedures	Full blood test	1.5	100%	£3.80	£3.75	
	Biochemistry	1.5	100%	£1.80	£1.77	
	CT scan	0.75	100%	£59.36	£58.51	
	MRI	0.5	80%	£84.53	£83.32	
	X-ray	0.5	60%	£9.82	£9.68	
Total cost per cycle						£461.69

Abbreviations: CT: computerised tomography; GP: general practitioner; MRI: magnetic resonance imaging.

Table 61: Medical resources for monitoring patients based on CNS progression

Resource	Proportion of patients	Lifetime exposure limit (dose)	Total cost
SRS (stereotactic radiotherapy)	50%	6	£7,197.15
WBRT (whole brain radiotherapy)	5%	6	£302.20
Surgical resection	5%	NA	£722.02
CNS management lump sum (one-off cost for all patients in CNS progression state)			£8,221.37
Steroids (dexamethasone)	10%	NA	£1.65

Abbreviations: CNS: central nervous system; SRS: stereotactic radiotherapy; WBRT: whole brain radiotherapy.

Table 62: Resource use unit costs

Resource	Cost	Source	Description
Oncology outpatient (first)	£253.20	NHS Reference Costs (2019/20)	CL. WF01B, 370, Medical Oncology Non-Admitted F2F Attendance, First.
Oncology (subsequent)	£136.36	NHS Reference Costs (2019/20)	CL, WF01C, 370, Medical Oncology Non-Admitted F2F Attendance, Follow up
GP visit	£39.00	PSSRU (2021)	Per surgery consultation lasting 9.22 minutes, including direct care staff costs with qualification costs
Cancer nurse	£99.30	NHS Reference Costs (2019/20)	CHS, N10AF, specialist nursing, cancer related, adult face to face
Biochemistry	£1.20	NHS Reference Costs (2019/20)	DAPS, DAPS04, Clinical Biochemistry
Full blood test	£2.53	NHS Reference Costs (2019/20)	DAPS, DAPS05, Haematology
CT scan	£79.15	NHS Reference Costs (2019/20)	Total HRGs, Weighted average: RD20A, RD20b, RD20C, RD21A, RD21B, RD21C and RD22Z
X-ray	£32.73	NHS Reference Costs (2019/20)	DADS, DAPF, Direct Access Plain Film
MRI	£211.33	NHS Reference Costs (2019/20)	IMAGOP Outpatient RD03Z
ECG	£70.69	NHS Reference Costs (2019/20)	IMAGOP Outpatient RD51A

Abbreviations: CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; MRI: magnetic resonance imaging; NHS: National Health Service.

Table 63: CNS progression management unit costs

Resource	Cost	Source
SRS (stereotactic radiotherapy)	£2,399	NHS Reference Costs 2019/20 Total HRGs; Stereotactic Intracranial Radiosurgery, for Neoplasms or Other Neurological Conditions, with CC Score 4+; https://www.england.nhs.uk/wpcontent/uploads/2018/07/Stereotactic-ablativebody-radiotherapy-for-non-small-cell-lungcancer-adults.pdf
WBRT (whole brain radiotherapy)	£1,007	NHS Reference Costs 2019/20 RAD; OP SC46Z Preparation for Complex Conformal Radiotherapy, with Technical Support and OP SC23Z Deliver a Fraction of Complex Treatment on a Megavoltage Machine
Surgical resection	£14,440	NHS Reference Costs 2019/20 EL; AA82Z Intracranial Telemetry, with Cortical Mapping or Resection of Brain
Steroids (dexamethasone)	£16.46	NICE TA670

Abbreviations: CNS: central nervous system; SRS: stereotactic radiotherapy; TA: technology appraisal; WBRT: whole brain radiotherapy

B.3.5.3 Adverse reaction unit costs and resource use

As discussed in Section B.3.3.6, 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.

Grade 3 or higher all-cause AE costs were informed by NHS reference costs and the brigatinib appraisal (TA670), as shown in Table 64.[87, 105] 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.

Table 64: Adverse event costs per event

Adverse event	Cost	Source	Resource assumption
Hypertriglyceridemia	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Weight increased	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Increased lipase level	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Hypercholesterolemia	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Aspartate aminotransferase increased	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Gamma-glutamyltransferase increased	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Hypertension	£638.81	NHS Reference Costs (2019/20)	Total HRGs, Hypertension, EB04Z
Anaemia	£672.11	NHS Reference Costs (2019/20)	Total HRGs, Iron deficiency anaemia with CC score 0–1, 2–5, 6–9, 10–13 and 14+
Amylase increased	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Neutropenia	£363.00	TA670	As per alectinib, brigatinib submissions
Blood creatine phosphokinase increased	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits
Neutrophil count decreased	£277.78	NHS Reference Costs (2019/20)	2 additional blood tests, 2 outpatient visits

Abbreviations: TA: technology appraisal.

B.3.5.4 Miscellaneous unit costs and resource use

Subsequent treatment

Subsequent treatments following progression and cessation of initial treatment were included in the model and were assumed to affect cost as well as utilities. Subsequent treatments were also factored into any adjustments to efficacy in the base-case as their impact was assumed to impact the modelled OS estimates.

In line with utility, the cost of subsequent treatments were applied once at the point of progression. The proportion of patients receiving the cost of subsequent treatments in each cycle was estimated as the proportion of patients who transitioned out of the pre-progression health state in each model cycle without dying. This was estimated using the proportion of BICR assessed PFS events that were deaths (PFS is a composite endpoint whereby an event can be either progression or death) from the March 2020 data cut-off of the CROWN trial ([redacted]) for the full population (not treatment arm specific). The inverse of this proportion was applied to the proportion of patients leaving the progression-free health state in each cycle to estimate the proportion of patients whose PFS events were progression (i.e. the proportion of patients leaving the PFS health state who transition into the progressed health state).

The probability of progression was assumed to be constant over time, and it was assumed that this can be applied to all treatment arms. This approach was consistent with that used in the second-line lorlatinib model (TA628), and was a simplifying assumption to enable an estimation of the proportion of patients in each cycle who are entering the progressed health state and hence are eligible for subsequent treatment. This was necessary within the partitioned survival modelling framework, where transitions between health states were not explicitly modelled, but health state membership at each cycle was derived using survival curves.

Subsequent treatment distributions for lorlatinib were applied based of clinical feedback from the UK advisory board. Advisors reported that currently available ALK TKIs are unlikely to be used second-line following lorlatinib treatment, therefore most patients receiving lorlatinib 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.[106]

Table 65: Re-weighted trial based subsequent treatment distributions

Subsequent treatments	First-line treatment		
	Lorlatinib	Alectinib	Brigatinib
Brigatinib	0%	0%	0%
Lorlatinib	0%	100%	100%
Chemotherapy	100%	54%	54%

Subsequent treatment durations were sourced from the literature and are presented in Table 66.

Table 66: Subsequent treatment durations (weeks)

Subsequent treatment	TA670	Source	ToT durations (weeks)	Source
Lorlatinib	45.66		64.36	Lorlatinib second-line trial: subgroup of patients previously treated with one or more ALK TKIs
Chemotherapy	NR	NR	6.3	Shaw et al. 2017 (ASCEND-5)[107]

Abbreviations: ALK: anaplastic lymphoma kinase; NR: not reported; TKI: tyrosine kinase inhibitor; ToT: time on treatment.

Costs (excluding administration costs) of subsequent treatments not used in the first-line are presented in Table 67.

Table 67: Subsequent treatment costs (other than first-line treatments)

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	£8.97
	Vial	50 mg	1	£6.03

Source: MIMS.[103]

Table 68 presents the final calculated one-off treatment cost applied upon progression for each treatment, considering the subsequent treatment distributions, drug costs, administration costs and subsequent treatment durations.

Table 68: One-off subsequent treatment cost applied upon progression in the model

First-line treatment	Cost
Lorlatinib	£3,398
Alectinib	£44,043
Brigatinib	£44,043

End-of-life care costs

A one-off end-of-life cost was applied in the model on entering the death health state sourced from Round et al. 2015.[108] Round et al. 2015 evaluates end-of-life costs for patients with various cancers. 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).[108] In the cost-effectiveness model it was assumed that costs reported for lung cancer in Round et al. 2015 were generalisable to ALK-positive NSCLC.[108] The costs were inflated to 2019/20 for application within the model, as shown in Table 69.

Table 69: End-of-life costs

End-of-life costs	Cost	Source
Mean health cost per condition	£3,157	Round et al. 2015[108]
Mean social care cost per condition	£1,358	Round et al. 2015[108]
Total end of life cost	£5,123.24	Uplifted using PSSRU (2021)[84]

Abbreviations: PSSRU: Personal Social Services Research Unit.

Testing costs

As mentioned in Section B.1.3.1, NICE guidelines in lung cancer recommend that ALK status testing should be undertaken for all patients with non-squamous NSCLC at diagnosis, as the mutation is more common in this subgroup.[51] Therefore, ALK status testing was assumed to take place along with other diagnostic testing prior to first-line treatment. Given it was assumed that

for the population of interest the ALK status was known, testing costs were not included in the model.

B.3.6 *Uncertainty*

Despite 36.7 months of follow-up, given lorlatinib represents a transformational change in treatment for patients with ALK-positive NSCLC, significant uncertain remains as only a small number of progression events and deaths have occurred in the lorlatinib treatment arm. As described, 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 DCO.

The NMA results do not estimate an OS benefit for lorlatinib versus alectinib and brigatinib, which is inconsistent with increased PFS observed in CROWN. With 18 months follow up in ALEX, the HR for survival was 0.76 (95% CI: 0.48 – 1.20) which improved with 36 months of follow up to 0.67 (95% CI: 0.46 – 0.98). Improvement in lorlatinib OS is also expected, however no conclusions can currently be drawn from the OS estimates.

There is an inherent complexity in the current treatment paradigm given the current treatment sequence is altered by using lorlatinib in the first-line setting. This results in uncertainty in the survival estimates which was unavoidable given evidence of the current treatment sequence and substantial follow-up from CROWN. It is expected that the increased median PFS observed in CROWN will translate into improved OS, and additional OS will reduce the uncertainty in the long-term survival estimates.

The NMA results do not estimate an OS benefit for lorlatinib versus alectinib and brigatinib, which is inconsistent with increased PFS observed in CROWN. With 18 months follow up in ALEX, the HR for survival was 0.76 (95% CI: 0.48 – 1.20) which improved with 36 months of follow up to 0.67 (95% CI: 0.46 – 0.98). Improvement in lorlatinib OS is also expected, however no conclusions can currently be drawn from the OS estimates.

B.3.7 *Managed access proposal*

Due to the immaturity of OS data which has been addressed in this submission, lorlatinib is considered to be a candidate for the CDF. Further OS data cuts in [redacted] and [redacted] will reduce the uncertainty around the survival estimates for lorlatinib.

B.3.8 *Summary of base-case analysis inputs and assumptions*

B.3.8.1 Summary of base-case analysis inputs

A summary of the model parameters of the base-case is presented in Table 70.

Table 70: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
Time horizon	Lifetime (30 years)	N/A	B.3.1.2
Cycle length	30 days	N/A	B.3.1.2
Discount rate (costs and outcomes)	3.5%	N/A	B.3.1.2
Perspective	NHS/PSS	N/A	B.3.1.2
Intervention	Lorlatinib	N/A	B.3.1.3
Active comparators	• Alectinib • Brigatinib	N/A	B.3.1.3
Treatment waning	Treatment waning applied to cap OS, CNS-PFS and PFS treatment effect duration at 10- and 20-years	10- and 20-years	B.3.3.1
Population			
Population	Patients with untreated ALK-positive advanced NSCLC	Scenario analyses	B.3.1.1
Age	57.38	55.854 to 58.910 (Normal)	B.2.3.2
Weight	65.36	63.742 to 66.977 (Normal)	B.2.3.2
Height	164.13	163.025 to 165.230 (Normal)	B.2.3.2
% with brain metastases	26.35%	21.5% to 31.5% (Beta)	B.2.3.2
% male	40.88%	35.3% to 46.5% (Beta)	B.2.3.2
Clinical inputs			
Source of efficacy – PFS	Lorlatinib: Independent model, exponential Comparators: HR from NMA applied to independent model of crizotinib, exponential	Multivariate normal	B.3.2.4
Source of efficacy – OS	Lorlatinib: Independent model, exponential with adjustment Comparators: HR from NMA applied to	Multivariate normal	B.3.2.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	independent model of crizotinib, exponential		
Source of efficacy – CNS PFS	Lorlatinib: Independent model, exponential Comparators: Assumed HRs equal to PFS	Multivariate normal	B.3.2.3
Source of efficacy – ToT	Lorlatinib: Independent model, exponential Comparators: Assumed equal to PFS	Multivariate normal	B.3.2.5
Adverse reactions incidence	CROWN (lorlatinib);[67] ALEX (alectinib);[61] NICE TA670 (brigatinib)[1] (Table 48)	Beta	B.3.2.6
Utility inputs			
Baseline utility	0.76	0.738 to 0.788 (Normal)	B.3.4.1

Health state utility values (assumed equal for intervention and comparators)	• Progression-free (on treatment): 0.84
	• Progression-free (off treatment): 0.77
	• Progressed (on treatment):
	  ○ CNS-progressed: 0.64
	  ○ Non-CNS-progressed: 0.84
	• Progressed (off treatment):
	  ○ CNS-progressed: 0.58
	  ○ Non-CNS-progressed: 0.77
	Derived from EQ-5D-5L (mapped to the EQ-5D-3L) questionnaire completed by patients enrolled in the CROWN trial (September 2021 data cut)[67] (Table 52)
		Multivariate normal	B.3.4.1; B.3.4.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
CNS utility multiplier	75.36% sourced from Roughley et al. 2014 (Table 52)	Beta	B.3.4.3
Age utility decrement	0.84 sourced from Ara and Brazier 2010[102] (Table 52)	Multivariate normal	B.3.4.3
Drug acquisition and administration			
Unit cost lorlatinib	£5,283.00 With PAS: [redacted] (100 mg; 30 pack); (Table 53)[103]	None	B.3.4.1
Unit cost alectinib	£5,032.00 (150 mg; 224 pack); (Table 53)[103]	None	B.3.4.1
Unit cost brigatinib	£4,900.00 (starter pack; 28 pack); £4,900.00 (180 mg; 28 pack); (Table 53)[103]	None	B.3.4.1
Administration cost (oral therapies)	£10.80 per pack (PSSRU 2020)[84]	Normal (£8.68 - £12.92)	B.3.4.1
Health-state unit costs and resource use			
Resource use and costs (micro-costing approach for each health state)	NHS reference costs (2019–2020) and PSSRU;[84, 85] (**Error! Not a valid result for table.**; Table 60; **Error! Not a valid result for table.**; Table 61; Table 63	Normal and beta distributions used for resource use costs	B.3.4.2
Adverse events			
Grade 3 or higher all-cause AE costs	NHS Reference Costs (2019–2020) and TA670[87, 105] (Table 64)	Normal distribution used for AE costs	B.3.4.3
Miscellaneous units costs			
Subsequent treatments	MIMS[103] (Table 67)	Normal distribution used for subsequent treatment costs	B.3.4.4
End-of-life costs	Total: £5,123.24, sourced from Round et al. 2015[108] (Table 69)	Normal £4,119.10 - £6,127.37	B.3.4.4

Abbreviations: ALK: anaplastic lymphoma kinase; CNS: central nervous system; EQ-5D-3L: EuroQol Five Dimensions 3 Levels; EQ-5D-5L: EuroQol Five Dimensions 5 Levels; MIMS: Monthly Index of Medical Specialities; NHS: National Health Service; NMA: network meta-analysis; NSCLC: non-small-cell lung cancer; PAS: patient access scheme; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; TA: technology appraisal.

B.3.8.2 Assumptions

The model made several key assumptions, which are outlined in Table 71.

Table 71: Key assumptions for the base case analysis

Assumption	Justification	Reference section in submission
Partitioned survival analysis	In partitioned survival analysis models, time-to-event endpoints are modelled independently, hence the model did not include a structural link between discontinuation, progression, and death. However, CNS-PFS, PFS and OS are correlated outcomes. The model used 'caps' to ensure logically inconsistent scenarios (for example a CNS-PFS estimate greater than OS) were not produced.	B.3.1.2
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.3.1.2
Application of independent models and hazard ratios	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 – i.e., that the HR was constant over time.	B.3.2
Overall survival	Exponential survival curves were fitted to lorlatinib and crizotinib following clinical feedback on the plausibility of long-term extrapolations, and in line with previous appraisals. Hazard ratios for alectinib and brigatinib were applied versus crizotinib. A [redacted] survival gain for lorlatinib over alectinib was assumed in the base case, with a [redacted] survival gain explored as an alternative scenario.	B.3.3.2
Comparator ToT	KM data for ToT was not reported for any comparators outside of the CROWN study, therefore an alternative method of estimating comparator ToT was required. ToT was therefore assumed to be equal to PFS.	B.3.3.5
AE criteria	Grade ≥ 3 AEs were captured within the model, with an inclusion criterion of being observed in at least 5% of patients in either arm of CROWN, the alectinib arm of ALEX, or the brigatinib arm of ALTA-1L.	B.3.2.6

Assumption	Justification	Reference section in submission
Subsequent treatments	Subsequent treatments are applied as one-off cost and utility benefit upon entry to the progressed disease states.	B.3.5.4
Subsequent treatment options	Subsequent treatment distributions in clinical practice were estimated based on clinical feedback from the UK advisory board and UK market share data.	B.3.4.4
Subsequent treatment duration	Subsequent treatment durations were obtained from available lorlatinib second line data, the previous brigatinib appraisal and the literature.	B.3.4.4
Resource use	In the micro-costing approach, resource use was assumed equal to that reported in the alectinib (TA536) and brigatinib (TA670) NICE submissions. Additional resource use was applied for patients in the CNS progressed health state, to reflect the resource intensive nature of the CNS progression health state.	B.3.4.2
ALK testing costs were not included in the model	ALK TKIs are now considered current clinical practice for ALK-positive NSCLC. Therefore, ALK testing was assumed to take place along with other diagnostic testing prior to first-line treatment to allow an ALK TKI to be used. Hence, it was assumed that for the population of interest the ALK status would be known.	B.3.4.4

Abbreviations: AE: adverse event; ALK: anaplastic lymphoma kinase; CNS: central nervous system; HR: hazard ratio; HRQoL: 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; TA: technology appraisal; TKI: tyrosine kinase inhibitor; ToT: time on treatment.

B.3.9 *Base-case results*

B.3.9.1 Base-case incremental cost-effectiveness analysis results

Probabilistic results are presented with the incorporation of a [redacted] lorlatinib PAS, with list prices applied to alectinib and brigatinib The PSA was performed with 2,000 iterations. Pairwise analyses versus alectinib and brigatinib are presented in Table 77 and respectively. Assuming a [redacted] survival gain over alectinib, lorlatinib was estimated to generate an additional [redacted] QALYs versus alectinib in the model, and an additional [redacted] QALYs versus brigatinib.

Table 72. Probabilistic base case results versus alectinib

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

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

Table 73. Probabilistic base case results versus brigatinib

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Brigatinib							
Lorlatinib							

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

Results of the alternative scenario, in which the survival gain of lorlatinib versus alectinib is [redacted] months, are presented in Table 74 and Table 75. In this scenario, lorlatinib was estimated to generate an additional [redacted] QALYs versus alectinib, and an additional [redacted] QALYs versus brigatinib.

Table 74. Probabilistic base case results versus alectinib

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Alectinib							
Lorlatinib							

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

Table 75. Probabilistic base case results versus brigatinib

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Brigatinib							
Lorlatinib							

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

B.3.9.2 Deterministic results

Pairwise deterministic results versus alectinib and brigatinib are presented in Table 76 and Table 77, assuming a [redacted] survival gain with lorlatinib over alectinib. In this scenario, the model predicts an additional [redacted] QALYs versus alectinib, and an additional [redacted] QALYs versus brigatinib. At a £30,000 willingness to pay threshold, lorlatinib is cost-effective versus alectinib and brigatinib if they are offered at a [redacted] and [redacted] discount, respectively.

Table 76. Base case results versus alectinib

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Alectinib							
Lorlatinib							

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

Table 77. Base case results versus brigatinib

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Brigatinib							
Lorlatinib							

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

An alternative scenario is presented in Table 78 and Table 79, which assumes a [redacted] survival gain with lorlatinib over alectinib. In this scenario the model predicts an additional [redacted] QALYs versus alectinib, and an additional [redacted] QALYs versus brigatinib. At a £30,000 willingness to pay threshold, lorlatinib is cost-effective versus alectinib and brigatinib if they are offered at a [redacted] and [redacted] discount, respectively.

Table 78. Base case results versus alectinib

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

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

Table 79. Base case results versus brigatinib

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

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

B.3.10 *Sensitivity analysis*

B.3.10.1 Probabilistic sensitivity analysis

The visual results of the PSA are presented in Figure 33 which plots the incremental cost and QALY results for each PSA iteration.

Figure 33. Cost-effectiveness plane from 2,000 PSA iterations ([redacted] survival gain)

[redacted]

From the PSA, a cost effectiveness acceptability curve (CEAC) was constructed. The CEAC is presented in Figure 34 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 [redacted].

Figure 34: Incremental cost-effectiveness acceptability curve ([redacted] survival gain)

B.3.10.2 Deterministic sensitivity analysis

Figure 35 presents a tornado diagram showing the parameters that have the greatest impact on the ICER in the base case analysis, with descending sensitivity.

Figure 35: Tornado diagram showing the 10 most influential parameters on the base case ICER ([redacted] survival gain) versus alectinib

As expected the largest driver of the cost-effectiveness was the overall survival estimation for the comparator, followed by the PFS estimate and progressed disease utilities. Similar results were observed for the comparison with brigatinib.

B.3.10.3 Scenario analysis

Several additional scenario analyses were considered to explore the uncertainty around various assumptions. A list of the scenarios and results are presented in Table 80.

Table 80. Results of scenario analyses ([redacted] survival gain) versus alectinib

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	Base-case	[redacted]	[redacted]	[redacted]
1	Discounting set to 6%	[redacted]	[redacted]	[redacted]
2	Discounting set to 0%	[redacted]	[redacted]	[redacted]
3	Time horizon set to 20 years	[redacted]	[redacted]	[redacted]
4	Time horizon set to 40 years	[redacted]	[redacted]	[redacted]
5	Do not use detailed lorlatinib dosing	[redacted]	[redacted]	[redacted]
6	Include all RDI savings	[redacted]	[redacted]	[redacted]
7	Exclude RDI	[redacted]	[redacted]	[redacted]
8	TA670 EOL cost source	[redacted]	[redacted]	[redacted]
9	Jointly fitted parametric models	[redacted]	[redacted]	[redacted]
10	Utility source: TA670 (ALTA-1L)	[redacted]	[redacted]	[redacted]
11	Include AE disutility values	[redacted]	[redacted]	[redacted]
12	Treatment waning at 10 years	[redacted]	[redacted]	[redacted]
13	Treatment waning at 20 years	[redacted]	[redacted]	[redacted]
14	Societal perspective	[redacted]	[redacted]	[redacted]
15	Lorlatinib OS - Equal PD	[redacted]	[redacted]	[redacted]

The scenarios that had the largest impacts were related to OS, PFS, time horizon and the discount rates.

B.3.11 *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-VAS and EORTC QLQ-C30 global health status and greater work and activity impairment with worsening ECOG performance status,[50] therefore the benefit of lorlatinib in delaying CNS disease progression is likely to have a substantial impact on QoL for patients. The impact of CNS progression on utilities, as calculated by applying a CNS multiplier from Roughley et al. (2014)[91], may not fully capture the QoL impact of CNS metastases, and this input has a high impact on the ICER as shown in the DSA.

Furthermore, CNS progression incurs a one-off cost of progression in the model, which is expected to be an underestimate as it does not capture the additional costs of increase ongoing management, the ongoing cost of social care is not captured, the increased impact on and requirement for caregivers and lost productivity.

On average, patients with advanced NSCLC and have reported missing 15.2% of work, increasing with worsening ECOG PS, which has not been fully captured with the cost per QALY.

The impact of CNS progression on utilities, as calculated by applying a CNS multiplier from Roughley et al. (2014)[91], may not fully capture the QoL impact of CNS metastases, and this input has a high impact on the ICER as shown in the DSA.

Utility values in the progressed disease state are expected to be an overestimate as these data are collected close to the point of progression, which will underestimate the value of patient remaining progression-free. Furthermore, CNS progression incurs a one-off cost of progression in the model, which is not expected to fully capture the additional costs of care and lost productivity.

The QoL impact of advanced lung cancer to caregivers is also substantial which has not been included within the cost per QALY. Caregivers also report greater activity impairment and higher burden of caring for patients (as measured by ZBI) with worsening ECOG performance status. Caregivers report missing 6.9% of work time.[109] The increased impact on carers of CNS progression is also significant in terms of reduced QoL and ability to work further amplifying the missed value within the model framework.

B.3.12 *Validation*

B.3.12.1 Validation of cost-effectiveness analysis

External validation – versus data sources

Validation of the modelled outcomes versus the respective trials are presented in Table 81. The comparison indicates that the model predicts median PFS for alectinib and brigatinib with relative accuracy. For comparison with long-term follow-up landmark survival please see B.3.3.2.

Table 81: Summary of model results compared with clinical data

Treatment	Average OS (months)			Average PFS (months)			Source
	Model result		Median (external data source)	Model result		Median (external data source)	
	Median	Mean		Median	Mean		
Lorlatinib	[redacted]	[redacted]	NR	[redacted]	[redacted]	NR	CROWN (Shaw 2020)[35]
Alectinib	[redacted]	[redacted]	NR	[redacted]	[redacted]	25.7	ALEX (Peters 2017)[62]
Brigatinib	[redacted]	[redacted]	NR	[redacted]	[redacted]	24.0	ALTA-1L (Camidge 2020)[54]

Internal validation

Health economists working on the model routinely checked the internal validity and technical accuracy of the model through all stages of model development. The internal validity and technical accuracy of the model were also checked by an independent health economist using an extensive quality check list. The errors identified by the quality check were addressed in the final economic model.

B.3.13 *Interpretation and conclusions of economic evidence*

B.3.13.1 Strengths of the economic evaluation

The economic analysis has number of key strengths:

- The model structure was aligned with previous appraisals in ALK+ NSCLC. The incorporation of a fourth state for CNS progression allows some of the benefit of lorlatinib impact on IC-TTP to be captured. The additional incorporation of a one-off utility for subsequent treatment also allows the treatment sequence to be better reflected.

- The incorporation of independent models and HRs allowed the violation of proportional hazard in the CROWN trial to be incorporated with the ALEX and ALTA trials where there was not evidence of a violation of proportion hazards

- 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 UK general population tariff). In addition, the regression applied allowed for utilities across the health to be generated.

- All resource usage and costs (administration, PF and PD disease management and terminal care costs) have been validated and accepted in multiple previous NSCLC appraisals, providing an element of certainty in these values.

B.3.13.2 Limitations of the economic evaluation

The key limitation discussed throughout is the immaturity of the overall survival from the CROWN trial. This uncertainty has reflected in the results of the sensitivity and scenario analysis. Despite this immaturity, two alternatives have been presented in the base-case where survival gains are anticipated based upon the gains in PFS and the potential impact of subsequent treatments.

An additional limitation of the analysis was the lack of head-to-head data. A robust SLR and NMA was undertaken to address this gap in the evidence. There will always be underlying uncertainty within these types of analyses.

B.3.13.3 Conclusions from the economic evidence

Lorlatinib demonstrates a clinical benefit over comparators in terms of improved PFS and IC-TTP, which translated into substantial QALYs/LYs gains in the progression-free state of [redacted] and [redacted] versus alectinib and brigatinib, respectively. When assuming this benefit translates into a survival benefit with allowance for the use of subsequent treatments, with a survival gain of [redacted] over alectinib, lorlatinib generates an total of [redacted] QALYs versus alectinib, and a total of [redacted] QALYs versus brigatinib. When assuming a survival benefit of [redacted] over alectinib, lorlatinib was estimated to generate an additional [redacted] QALYs versus alectinib, and an additional [redacted] QALYs versus brigatinib.

The results of the cost-effectiveness demonstrate that the uncertainty in the overall survival estimates has a substantial impact on the number of additional QALYs generated, and subsequently on the ICER.

Given the confidentiality of the comparator PASs, a threshold analyses across the two OS scenarios indicated that the PAS for alectinib and brigatinib would have to exceed [redacted] and [redacted] respectively for the ICER to be above the £30,000 per QALY threshold.

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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 [ID3896]

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
Lorlatinib EAG clarification letter to PM	**FINAL**	**Yes**	**24 June 2022**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

CROWN trial

A1. Please provide further details relating to the CROWN trial CONSORT diagram (Figure 10 Appendix). Specifically, please state the reasons why the five randomised crizotinib patients did not take crizotinib. Please also provide the following pre-randomisation data:

- **Number of patients screened for eligibility**
- **Number ineligible/excluded**
- **Number who declined participation (split by reason for declining, if a significant number declined participation)**

In study B7461006 (CROWN) a stratified randomisation was adopted and patients were centrally allocated across all investigational sites via an interactive response technology system. A central randomisation process was implemented due to the high number of participating investigational sites with an anticipated small number of participants expected to be randomised at each site. Therefore, a central randomisation process would avoid potential selection bias. While the reasons for participants screening failure (SF) were not collected in the clinical database, they

were captured in the Screening and Enrollment Form at each investigational site, as required by the International Conference on Harmonization Good Clinical Practice Guideline. Most recently, the company worked with the investigational sites to collect these log forms and has summarised the reasons for SF as shown in Table 1. Of note, among patients who did not meet eligibility (80 patients), inclusion criterion #1 was the main reason. Specifically, 55 participants did not meet inclusion criteria #1 and the reason for the majority of them (48 participants) was that they did not have histologically or cytologically confirmed diagnosis of locally advanced or metastatic ALK-positive NSCLC. Other reasons for screening failure were consent withdrawn (17 patients), clinical worsening (7 patients), exceeded screening/rescreening (7 patients). In 6 patients, investigators decided to initiate alternative treatment options due to clinical urgency. Overall, reasons for screen failures were within expectations for the general ALK-positive NSCLC population and study protocol.

Table 1. Reasons for Screening Failure from Screening and Enrollment Forms.

Screening Failure Reason	**participants N**	**participants %**

Eligibility not met:
• Inclusion Criterion #1 (N=55)
  ○ no confirmed diagnosis of locally advanced or metastatic ALK-positive NSCLC (N=48)
  ○ Other IC#1 (N=7)
• Other inclusion/exclusion criteria (N=25)
	80	62

Consent withdrawn	17	13
Clinical worsening / Disease progression	7	5
Exceeded screening/re-screening period	7	5
Urgent/other treatment	6	5
Death	5	4
Unknown	5	4
Investigator decision	1	1
Occurrence of SAE (unrelated to study drug)	1	1
TOTAL	**129**	**100**

Five patients randomised to crizotinib did not take crizotinib. Four patients withdrew and one patient was not eligible, was randomised by mistake, and received crizotinib outside of the study.

A2. Please provide further detailed results for the CROWN subgroup analyses (p27 and Figure 9, Document B), specifically all subgroup results for ORR.

Detailed results for ORR subgroup analyses can be found in Table 14.2.3.2 of the clinical study report.

A3. Please present results for a test of interaction for the ethnic origin subgroup analysis.

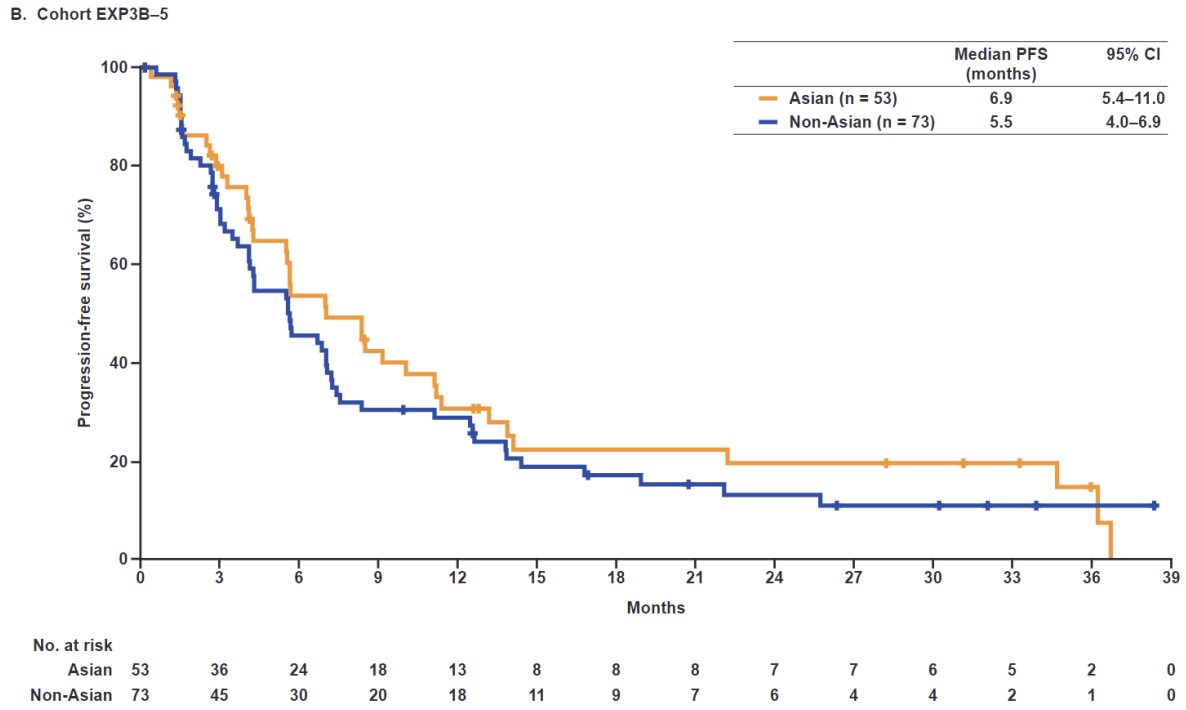
Results for a test of interaction for the ethnic origin subgroup analysis for PFS are provided in Table 14.2.1.13. The interaction p-value is [redacted]

A4. There is an indication from the CROWN trial subgroup results that ethnicity could be an effect modifier for lorlatinib. Please provide ethnicity subgroup data for any other lorlatinib studies in ALK-positive advanced non-small-cell lung cancer patients.

Lorlatinib has shown to be effective in both Asian and non-Asian populations. A previous analysis of lorlatinib pharmacokinetics found no inherent differences in lorlatinib PK between healthy subjects and cancer patients, or between Asian and non-Asian patients (Chen 2021; https://doi.org/10.1007/s40262-021-01015-z).

The efficacy and safety of lorlatinib in Asian and non-Asian patients from cohorts EXP2-3A and EXP3B-5 of Study 1001, a global Phase II trial (NCT01970865), were reported by Soo et al. (2022; https://doi.org/10.1016/j.lungcan.2022.05.012).
In EXP3B-5, median PFS was 6.9 months (95% CI: 5.4–11.0) in Asian patients and 5.5 months (95% CI: 4.0–6.9) in non-Asian patients (Figure 1).

Figure 1. PFS Asian and non-Asian patients in Cohort EXP3B–5 (safety analysis set)



Furthermore, treatment with lorlatinib showed substantial overall and intracranial activity in previously treated ALK-positive patients, evident in both Asian and non-Asian populations. AEs were consistent with the known safety profile of lorlatinib and similar between Asian and non-Asian patients. These efficacy results in Asian patients are consistent with those from a real-world analysis that included 76 ALK-positive TKI-refractory patients (79% Asian) who received lorlatinib in early or expanded access programs (Zhu 2020; https://doi.org/10.1016/j.jtho.2020.04.019). A poster was presented at the 2021 Virtual ESMO Congress (Zhou et al. 2021; https://doi.org/10.1016/j.annonc.2021.08.1802) reporting on Asian subgroup analysis of CROWN (March 2020 DCO). Results are presented in Table 2 below. This data shows that in the Asian subgroup of CROWN, a consistent and clinically meaningful improvement in PFS was observed for lorlatinib versus crizotinib. Baseline characteristics were similar to the overall population. The efficacy and safety of lorlatinib versus crizotinib in the Asian subgroup of CROWN was consistent with the overall population.

Table 2. Asian subgroup analysis of CROWN

	Asian subgroup		Overall population[a]	
	Lorlatinib (n=59)	Crizotinib (n=61)	Lorlatinib (n=149)	Crizotinib (n=147)
PFS (BICR)				
HR (95% CI)	0.44 (0.24 – 0.78)		0.28 (0.19 – 0.41)	
P-Value	0.002[b]		<0.001	

Event-free at 12m, % (95% CI)	72 (59-82)	48 (32-62)	78 (70-84)	39 (30-48)
ORR (BICR) n (%) 95% CI	 45 (76.3) 63.4 – 86.4	 35 (57.4) 44.1-70.0	 113 (75.8) 68.2 – 82.5	 85 (57.8) 49.4 – 65.9
IC ORR (BICR)[c] n (%) 95% CI	(n=11) 8 (72.7) 39.0 – 94.0	(n=16) 4 (25.0) 7.3 – 52.4	(n=38) 25 (65.8) 48.6 – 80.4	(n=40) 8 (20.0) 9.1 – 35.6
[a]Shaw et al. N Engl J Med. 2020; 383:2018-2029. [b]No adjustment for multiplicity. [c]Patients with brain metastases at baseline by neuroradiologist. BICR, blinded independent central review				

ORR and IC-ORR outcomes from cohorts EXP-3B:EXP-5 of the trial NCT01970865 for Asian and non-Asian patients are shown in Table 3 below.

Table 3. ORR and IC ORR by Baseline Characteristics in Patients with ALK-Positive NSCLC - ITT Population in Cohort EXP-3B:EXP-5 (Phase II trial NCT01970865) – February 2018 DCO

Baseline characteristic	N	ORR N (%) [CI]	N	IC ORR N (%) [CI]
Asians	53	26 (49.1) [35.1, 63.2]	22	12 (54.5) [32.2, 75.6]
Non-Asians	73	23 (31.5) [21.1, 43.4]	28	13 (46.4) [27.5, 66.1]
Unspecified	13	7 (53.8) [25.1, 80.8]	7	6 (85.7) [42.1, 99.6]

A5. Priority question: Please provide the CROWN trial protocol and statistical analysis plan documents (the CSR has links to these documents which do not work).

The CROWN study protocol and SAP have been provided with this response.

A6. The submission states that "*Longer-term results from the second interim analysis (IA2) based on the September 2021 data-cut are presented in Document B where available*". Please describe why results for some outcomes are available for the September 2021 cut-off dataset, whilst others are not. The answer should be detailed enough to allay EAG concerns about possible bias in the selection of reported results.

All analyses were performed in accordance with the SAP (provided in response to A5). Analyses generated based on the September 2021 data cut were performed to further characterise tumor-related endpoints with a longer follow-up and were presented descriptively only. A number of outcomes were not reported in the September 2021 data-cut and are discussed below.

OS data are immature and as outlined in the SAP, a maximum of three analyses are planned for OS:

1. A projected a first interim analysis at the projected time of the final analysis for PFS (provided PFS is significant
2. A second interim analysis when 139 deaths (70% of the total events planned for final OS analysis) are observed;
3. A final analysis when 198 deaths are observed

Therefore, no updated analysis of OS was performed in the September 2021 DCO, as the protocol-specified second interim analysis of overall survival will be performed after at least [redacted] have occurred ([redacted]). A further OS analysis is planned when 100% (final OS analysis) of the 198 OS events have occured. A Lan-DeMets (O'Brien-Fleming) α-spending function would be used.

Time to tumour response based on BICR assessment was only assessed at the March 2020 data-cut as it is based on initial response to therapy. Time to tumor Response (TTR) is defined, for participants with a confirmed OR, as the time from the date of randomisation to the first documentation of objective response (CR or PR) which is subsequently confirmed.

For completeness Appendix M of the original submission included details of March 2020 data-cut for all remaining endpoints.

A7. Priority question: Please present a summary table of rates of AEs of special interest for all other lorlatinib studies (i.e. regardless of indication).

Table 4 below presents adverse reactions of special interest occurring in 476 adult patients treated with lorlatinib 100 mg once daily with advanced NSCLC from Study A (N=327) and CROWN study (N=149). The adverse reactions listed in the table below are presented by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10).

Table 4. Adverse events

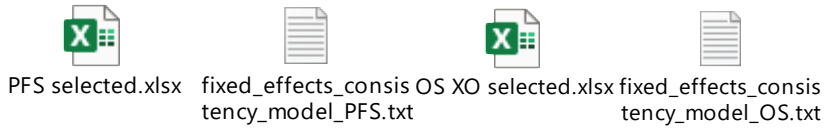
System organ class and adverse reaction	Frequency category	All Grades %	% Grades 3-4
Psychiatric disorders			
Mood effects	Very common	21.0	1.5
Psychotic effects	Common	6.9	0.6
Mental status changes	Common	1.3	1.1
Nervous system disorders			

Cognitive effects Peripheral neuropathy	Very common Very common	27.7 43.7	2.9 2.7

Indirect Treatment Comparisons/Network Meta-analysis

A8. Priority question: Please provide the R and/or JAGS code and all input data for all NMAs as executable R scripts and txt/csv files so that all analyses, including analyses requested in A9-A12, can be reproduced. Please also detail the exact versions of all R packages used.

Please see embedded the JAGS code and input data for PFS and OS NMAs.



We are unable to share the full NMA R code script, however, using the described methods and detail on choices used in the code alongside the NMA datasets will enable the NMA to be conducted. Settings used in the analysis are detailed in Table 5.

Table 5. NMA model settings

Analysis	Model type	Prior distribution	Iterations	Burn in iterations	Thinning factor
PFS BICR	Fixed effect	NA	50,000	50,000	1
OS	Fixed effect	NA	50,000	50,000	1

Key: BICR, blinded independent central review; NA, not applicable; OS, overall survival; PFS, progression-free survival.

Our vendors analysis codes are listed below. At time of analysis the package version was not recorded. Versions of R packages have been extracted by the analyst, however, may have been updated since last analysis:

gemtc v1.0.1

dplyr v1.0.8

BresNMA v3.1.1

Readxl v1.3.1

Hmisc v4.6.0

XLConnect v1.0.5

officer v0.4.1

flextable 0.6.10

magrittr v2.0.1

A9. Priority question: The PFS NMA results in Table 24 (section B.2.9.4.1) appear incorrect for brigatinib. The EAG ran the NMA model using the input data in Table 16, Appendix D and obtained different results. Please clarify what data were used to obtain the results in Table 24 and correct the table if necessary. Please provide the correct data and model files as requested in A8.

Table 6 presents the input data for the PFS NMA that gives the results in Table 7. The HR (95% CI) for ALTA-1L differs between Table 6 and Table 16, Appendix D. The HR (95% CI) in Table 6 is quoted from TA670 Table 12 (p47) for the ITT population. Table 16, Appendix D quotes the HR (95% CI) from Cambridge 2018 Figure 2B for the subgroup of patients who did not receive prior chemotherapy (i.e. strictly first line treatment). The value in Table 16, Appendix D is a typo, the correct values are shown on page 29 of Appendix D.

Table 6. PFS NMA input data

Study	Treatment	Number analysed	HR (95% CI)
CROWN[1]	Crizotinib	147	
	Lorlatinib	149	0.280 (0.195, 0.401)
ALEX[2]	Crizotinib	151	

	Alectinib (600 mg)	152	0.500 (0.360, 0.700)
ALTA-1L[3]	Crizotinib	138	
	Brigatinib	137	0.489 (0.350, 0.680)
References: [1], HR from CROWN without stratification; [2], Peters, S., Camidge, D.R., Shaw, A.T., Gadgeel, S., Ahn, J.S., Kim, D.W., Ou, S.H.I., Pérol, M., Dziadziuszko, R., Rosell, R. and Zeaiter, A., 2017. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. New England Journal of Medicine, 377(9), pp.829-838. (Figure S1); [3], https://www.nice.org.uk/guidance/ta670/documents/committee-papers (p47).			

Table 7. PFS NMA results

Treatment	HR (95% CrI)
Alectinib (600mg)	0.56 (0.34 to 0.91)
Brigatinib	0.57 (0.35 to 0.93)
Crizotinib	0.28 (0.20 to 0.40)

A10. PFS results from the ALEX study of alectinib show no ethnicity subgroup effect (Asian vs non-Asian). Please re-run and present results for the PFS NMA with the ALESIA trial included in the network and ensure data files and code are provided as requested in question A8.

ALESIA was not included in the NMA, on the basis that ALESIA only included Asian patients and was not considered to be generalisable to the UK population. This was also the agreed approach in TA536 and TA670.

Table 8 summarises the PFS data in ALESIA. ALESIA was included in the NMA from a global perspective which has been provided as a scenario in the updated model for completeness.

Table 8: PFS NMA input data including ALESIA

Study	Treatment	Number analysed	HR (95% CI)

CROWN[1]	Crizotinib	147	
	Lorlatinib	149	0.280 (0.195, 0.401)
ALEX[2]	Crizotinib	151	
	Alectinib (600 mg)	152	0.500 (0.360, 0.700)
ALTA-1L[3]	Crizotinib	138	
	Brigatinib	137	0.489 (0.350, 0.680)
ALESIA[4]	Crizotinib	62	
	Alectinib (600 mg)	125	0.37 (0.22, 0.61)

References: [1], HR from CROWN without stratification; [2], Peters, S., Camidge, D.R., Shaw, A.T., Gadgeel, S., Ahn, J.S., Kim, D.W., Ou, S.H.I., Pérol, M., Dziadziuszko, R., Rosell, R. and Zeaiter, A., 2017. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. New England Journal of Medicine, 377(9), pp.829-838. (Figure S1); [3], https://www.nice.org.uk/guidance/ta670/documents/committee-papers (p47); [4], Zhou, C., Kim, S.W., Reungwetwattana, T., Zhou, J., Zhang, Y., He, J., Yang, J.J., Cheng, Y., Lee, S.H., Bu, L. and Xu, T., 2019. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. *The Lancet Respiratory Medicine*, *7*(5), pp.437-446..

The relative effect of lorlatinib compared to alectinib and brigatinib is shown in **Error! Reference source not found.** for BICR PFS including ALESIA (PFS BICR ITT).

Table 9. BICR and Investigator-assessed PFS NMA results

Treatment	PFS BICR ITT: FE HR (95% CrI)	PFS INV: FE HR (95% CrI)	PFS BICR (Excluding ALESIA): FE HR (95% CrI)
Alectinib (600 mg)	0.61 (0.39 to 0.97)	0.57 (0.37 to 0.88)	0.56 (0.34 to 0.91)
Brigatinib	0.57 (0.35 to 0.93)	0.48 (0.3 to 0.79)	0.57 (0.35 to 0.93)

Key: CrI, creditable interval; FE, fixed effects; HR, hazard ratio; IC-TTP, time to intracranial progression; INV, investigator; ITT, intention-to-treat; NR, not reported; PFS, progression-free survival; RE, random effects

A11. Priority question: Please run and present results for a sensitivity analysis where the final data cuts from ALTA-1L and ALEX are used in the NMA to inform the HR of brigatinib and alectinib respectively. If the latest available data cut is based on investigator-assessed PFS, please use this for all treatments. Please also add an additional similar analysis including the ALESIA study for PFS. Please provide all data and model files as requested in A8.

The relative effect of lorlatinib compared to alectinib and brigatinib is shown in **Error! R eference source not found.** above for investigator-assessed PFS, including ALESIA (PFS INV). Investigator assessed PFS has been explored as a scenario analysis in the updated model. The investigator-assessed PFS has minimal difference versus alectinib, and the use of BICR PFS is conservative for lorlatinib versus brigatinib.

A12. Priority question: A recent NMA (Ando et al 2021, DOI: 10.3390/cancers13153704) found greater risk of Grade 3 or higher AEs for lorlatinib compared with alectinib.

a) **Please carry out an NMA and provide results on risk of Grade 3 or higher AEs. Please provide all data and model files as requested in A8.**

Adverse events for patients receiving lorlatinib can be managed with dose modifications and reductions. Lorlatinib has been approved at a regulatory level based on the safety and efficacy profile of CROWN.

However, due to the heterogeneity in the type of adverse events included across trials, there is limited value in conducting an NMA. Table 10 summarises the data available for Grade 3 or higher AEs (including ALESIA). The frequency of Grade 3 or higher AEs is similar between CROWN and ALTA-1L while the frequency of AEs is fewer for alectinib.

Table 10. Grade 3 and 4 AE NMA input data including ALESIA

Study	Treatment	Number analysed	Number with Grade 3 and 4 AE
CROWN[1]	Crizotinib	147	79/142 (55.6%)

	Lorlatinib	149	108/149 (72.5%)
ALEX[2]	Crizotinib	151	85/151 (56.3%)
	Alectinib (600 mg)	152	79/152 (52.0%)
ALTA-1L[3]	Crizotinib	138	84/137 (61%)
	Brigatinib	137	99/136 (73.0%)
ALESIA[4]	Crizotinib	62	30/62 (48.0%)
	Alectinib (600 mg)	125	36/125 (29%)

References: [1], Shaw, A.T., Bauer, T.M., de Marinis, F., Felip, E., Goto, Y., Liu, G., Mazieres, J., Kim, D.W., Mok, T., Polli, A. and Thurm, H., 2020. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. New England Journal of Medicine, 383(21), pp.2018-2029.; [2], Mok, T., Camidge, D.R., Gadgeel, S.M., Rosell, R., Dziadziuszko, R., Kim, D.W., Pérol, M., Ou, S.H., Ahn, J.S., Shaw, A.T. and Bordogna, W., 2020. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Annals of oncology*, *31*(8), pp.1056-1064.; [3], Camidge, D.R., Kim, H.R., Ahn, M.J., Yang, J.C., Han, J.Y., Hochmair, M.J., Lee, K.H., Delmonte, A., Campelo, M.R.G., Kim, D.W. and Griesinger, F., 2020. Brigatinib versus crizotinib in advanced ALK inhibitor–naive ALK-positive non–small cell lung cancer: Second interim analysis of the phase III ALTA-1L trial. *Journal of Clinical Oncology*, *38*(31), p.3592.; [4], Zhou, C., Kim, S.W., Reungwetwattana, T., Zhou, J., Zhang, Y., He, J., Yang, J.J., Cheng, Y., Lee, S.H., Bu, L. and Xu, T., 2019. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. *The Lancet Respiratory Medicine*, *7*(5), pp.437-446..

b) In addition, please carry out an NMA and provide results on risk of any grade AEs for peripheral neuropathy, cognitive effects, and mood effects (judged by our clinical advisor to be key AEs). Please provide all data and model files as requested in A8.

Peripheral neuropathy, cognitive effects and mood effects are AEs of interest for lorlatinib. Grade 3 and higher AE rates for lorlatinib are presented in Table 11.

Comparator incidence of adverse events from registrational studies is available at https://doi.org/10.1016/j.jtho.2021.07.035 Supplementary table S6 for brigatinib, and https://doi.org/10.1016/j.jtho.2019.03.007 Supplementary tables S4-S7 for alectinib. AE rates for peripheral neuropathy, cognitive effects and mood effects were not reported for alectinib and brigatinib, therefore in the absence of comparator data, an NMA was not conducted.

Table 11. AEs of special interest

	Lorlatinib (CROWN, n=149)	Alectinib (ALEX, n=152)	Brigatinib (ALTA-1L, n=136)
Peripheral neuropathy	2 (1.3%)	NR	NR
Cognitive effects	5 (3.4%)	NR	NR
Mood effects	1 (1.3%)	NR	NR

A13. Please document which subsequent anticancer systemic therapies patients received post-progression across all the trials included in the NMAs.

Table 12 below summarises the subsequent anticancer systemic therapies patients received post-progression across all trials.

Table 12. Anticancer systemic therapies after first-line treatment

	CROWN		ALTA-1L		ALEX	
First subsequent therapy, n	**Lorlatinib (n=149)**	**Crizotinib (n=147)**	**Brigatinib (n=137)**	**Crizotinib (n=138)**	**Alectinib (n=152)**	**Crizotinib (n=151)**
Systemic therapy, n/N (%)	33/149 (22.1)	103/147 (70.1)	34/137 (24.8)	96/138 (69.6)	40/152 (26.3)	44/151 (29.1)
ALK TKI, n/N (%)	21/33 (63.6)	96/103 (93.2)	30/137 (21.9)	93/138 (67.4)	18/152 (11.8)	36/151 (23.8)
Alectinib, n/N (%)	12/21 (57.1)	65/96 (67.7)	10/137 (7.3)	24/138 (17.4)	0	10/151 (6.6)
Alectinib hydrochloride, n/N (%)	NA	NA	0	1/138 (0.7)	NA	NA
Crizotinib, n/N (%)	4/21 (19.0)	5/96 (5.2)	11/137 (8.0)	6/138 (4.3)	9/152 (5.9)	2/151 (1.3)
Ceritinib, n/N (%)	3/21 (14.3)	3/96 (3.1)	4/137 (2.9)	4/138 (2.9)	4/152 (2.6)	14/151 (9.3)
Brigatinib, n/N (%)	1/21 (4.8)	20/96 (20.8)	1/137 (0.7)	73/138 (52.9)	NA	NA
Lorlatinib, n/N (%)	1/21 (4.8)	3/96 (3.1)	13/137 (9.5)	11/138 (8.0)	NA	NA
Other, n/N (%)	NA	NA	NA	NA	6/152 (3.9)	10/151 (6.6)
Chemotherapy ± anti-angiogenic drugs, n/N (%)	11/33 (33.3)	3/103 (2.9)	13/137 (9.5)	13/138 (9.4)	39/152 (25.7)	13/151 (8.6)

Chemotherapy /immunotherapy, n/N (%)	1/33 (3.0)	0	3/137 (2.2)	4/138 (2.9)	39/152 (25.7)	13/151 (8.6)
VEGF-R, n/N (%)	0	0	3/137 (2.2)	4/138 (2.9)	2/152 (1.3)	0
Other, n/N (%)	0	4/103 (3.9)	2/137 (1.5)	1/138 (0.7)	4/152 (2.6)	1/151 (0.7)

A14. 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 section B.2.9.3 it is argued that PH does hold for PFS in ALEX and ALTA-1L. Please compare the arguments against PH and the supporting plots presented in the documentation for TA536 and TA670 with those presented in B.2.9.3, explaining any reasons for the different conclusions.

Separate curves were fitted to crizotinib and brigatinib in TA670 due to "a potential violation of proportional hazards"; however, exponential curves were chosen as the most appropriate curve by the committee for both brigatinib and crizotinib which suggests the PH assumption was appropriate. Also the company used PHs methods for their ITC (anchored and unanchored MAIC).

The rationale for the selection of the exponential models in TA670 was informed by TA536 where despite also concluding PH was potentially violated based on February 2017 data cut, so curves were fitted separately. In TA536 the committee's preferred assumption was exponential tails fitted to Kaplan-Meier data which suggests that the PH assumption over time was accepted.

We also compared the arguments presented in B.2.9.3 with those within TA536 an TA670, which further suggest the conclusions within Section B.2.9.3 are appropriate.

In TA536 only a log-cumulative hazard plot was provided (TA536 Clarification Questions B2 response) which is aligned with Figure 15 in B.2.9.3. The difference between them is within TA536 it was presented on the log-time scale which has exaggerated the crossing of the curves which was the rationale for suggesting PH was potentially violated. However, as mentioned in B.2.9.3, 'the curves cross at the beginning of the plot, correlating with the separation of the Kaplan-Meier curves at

approximately 6 months. After this initial period, the log-cumulative hazards curves appear parallel. Since the crossing occurs within the first 6 months of the trial and is likely due to trial protocol rather than treatment effect, there is little evidence of non-proportional hazards.'

A Schoenfeld residual plot was not presented or discussed in TA536, however, one was presented in Figure 16 in B.2.9.3, which 'appears relatively straight and close to the constant log HR line' providing further evidence that assuming PH within ALEX is appropriate.

In TA670 Figure 26 of the company submission, the log-cumulative hazard is similar to that presented in Figure 17 in B.2.9.3. In TA670 it was concluded that 'early crossing between the curves, followed by some separation, indicating a potential violation of proportional hazards'. However, similar to TA536, the crossing of curves has not been considered in the context of the trial. In B.2.9.3 it was suggested 'the curves cross at the beginning of the figure. This correlates with the crossing of KM curves during the first 4 months (2 assessment visits) due to the assessment schedule for PFS and is likely due to trial protocol rather than treatment effect. Therefore, given that after this initial period, the log-cumulative hazards curves appear parallel, there is little evidence of non-proportional hazards.'

The Schoenfeld residual plot in TA670 Figure 26 has a much smaller y-axis scale than that of Figure 18 in B.2.9.3, so some fluctuation in the curve would be expected. In Figure 18 B.2.9.3 'the line plotting varying log HR versus time appears relatively straight and close to the constant log HR line (and very similar to that in the Schoenfeld residual plot for ALEX).' Even with the smaller scale there was no systematic trend away from the constant log HR line. In TA670 they also did not comment on the Schoenfeld test p-value which was greater than 0.05, which indicates that the proportional hazards assumption is valid.

Section C: Textual clarification and additional points

Literature searches

C1. The searches presented for EMBASE.com (D.1.1, Appendix D) contain study design restrictions to limit retrieval to RCTs and non-randomised

studies only, therefore may have missed relevant systematic reviews. Please could Epistimonikos https://www.epistemonikos.org/ be searched for any relevant systematic reviews, a search strategy provided, and for any relevant results to be included in the SLR.`

From the clarification meeting, it is understood that this is best practice, however the EAG and company agree that it is highly likely that all relevant studies have been captured.

C2. Please could the following sources be searched, providing a search strategy for each resource and including any relevant results in the SLR:

- **International HTA database https://database.inahta.org/ for HTA reports and ongoing studies**

- **ClinicalTrials.gov https://clinicaltrials.gov/ for ongoing or completed but unpublished studies**

Although CENTRAL was searched for identifying ongoing or completed but unpublished studies, a more comprehensive approach can be achieved by searching ClinicalTrials.gov and other trial registers directly.

As above, it is understood that this is best practice, however the EAG and company agree that it is highly likely that all relevant studies have been captured.

C3. Please clarify the source of the study design search filters used for MEDLINE and Embase (lines 25 and 26, Table 1, p. 12-13, and lines 25 and 26, Table 5, p. 17, Section D.1.1, Appendix D), giving a reference where available.

The study design filters were based on recommendations from ISSG Search Filter Group which is a is a collaborative venture to identify, assess and test search filters designed to retrieve research by study design or focus. The filters can be accessed from URL - https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home. Within this group, to search for RCTs and non-RCTs, search filters were based on recommendations from SIGN (https://www.sign.ac.uk/what-we-do/methodology/search-filters/), CADTH (https://www.cadth.ca/finding-evidence-literature-searching-tools-support-systematic-reviews-0), BMJ (https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/).

C4. Please clarify why the MeSH term for crizotinib was not included in the searches of CENTRAL (Table 3, p. 14 and Table 7, p.18, Section D.1.1, Appendix D) This MeSH term was available from 2019 onwards – see: https://meshb.nlm.nih.gov/record/ui?ui=D000077547

All the relevant free text, investigational, brand/generic names and keyword terms for crizotinib were comprehensively searched and it is highly unlikely that any relevant study might be missed since EMTREE terms (which includes MeSH) were already searched in Embase.com.

C5. Please clarify if the searches for the April 2021 SLR update were limited from November 2020 as stated on p.16, D.1.1, Appendix D.

The original search date was 31st October 2019 and the update SLR was conducted on 22 April 2021 from September 2019 onwards to ensure sufficient overlap. However, there was a typo for November 2020 and no searches were conducted on this date.

C6. There appears to be a line missing in the search strategy for Embase and MEDLINE (Table 5, D.1.1, Appendix D, p.17). It appears to be the date restriction line which would account for the low number of results at line 34. Please provide the full search strategy which shows the date restriction used.

The missing line is mentioned below along with the full searches for Table 5:

Table 5: Search strategy for MEDLINE® and Embase®, 22nd April 2021

S. No.	Search Term	No. of Hits
1.	'non small cell lung cancer'/exp OR nsclc:ab,ti	176,163
2.	'neoplasm'/exp OR 'squamous cell carcinoma'/exp OR 'adenocarcinoma'/exp	5,178,939
3.	'lung'/exp	342,260
4.	#2 AND #3	74,991
5.	((lung OR pulmon* OR bronchial) NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ab,ti	352,559
6.	#4 OR #5	397,977
7.	'non small cell':ab,ti OR 'non-small-cell':ab,ti OR 'nonsmall cell':ab,ti	109,341
8.	#6 AND #7	108,378
9.	#1 OR #8	183,866
10.	'lorlatinib'/syn OR lorlatinib:ab,ti OR 'pf-06463922'	819
11.	'crizotinib'/syn OR crizotinib:ab,ti OR xalkori:ab,ti OR 'pf-02341066' OR 'pf-2341066'	9,141

S. No.	Search Term	No. of Hits
12.	'ceritinib'/syn OR ceritinib:ab,ti OR zykadia:ab,ti OR 'ldk 378' OR 'ldk378'	2,128
13.	'alectinib'/syn OR alectinib:ab,ti OR alecensa:ab,ti OR 'af802' OR 'af-802' OR 'ch5424802' OR 'rg7853' OR 'ro5424802' OR 'unii-lij4ct1z3y'	2,096
14.	'brigatinib'/syn OR brigatinib:ab,ti OR 'ap26113'	1,045
15.	ensartinib:ab,ti OR 'x-396'	167
16.	'belizatinib'/syn OR belizatinib:ab,ti OR 'tsr-011'	61
17.	'asp3026' OR 'asp-3026'	116
18.	'x-376'	16
19.	'cep-28122'	38
20.	'cep-37440'	34
21.	'entrectinib'/syn OR entrectinib:ab,ti OR 'rxdx-101'	701
22.	'retaspimycin'/syn OR retaspimycin:ab,ti OR 'ipi-504'	474
23.	'pemetrexed'/syn OR pemetrexed:ab,ti OR alimta:ab,ti OR 'ly231514'	15,750
24.	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	25,329
25.	'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR (randomi?ed NEAR/2 'controlled trial*'):ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR ((allocated OR assign*) NEAR/2 random):ab,ti OR (single NEXT/1 blind*):ab,ti OR (double NEXT/1 blind*):ab,ti OR ((treble OR triple) NEAR/3 blind*):ab,ti OR placebo*:ab,ti OR 'prospective study'/de NOT ('case study'/de OR 'case report':ab,ti OR 'abstract report'/de OR 'letter'/de)	2,477,536
26.	'clinical study'/exp OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/exp) OR cohort:ab,ti OR 'cohort analysis'/de OR (cohort NEAR/1 (study OR studies)):ab,ti OR ('case control' NEAR/1 (study OR studies)):ab,ti OR ('follow up' NEAR/1 (study OR studies)):ab,ti OR (observational NEAR/1 (study OR studies)):ab,ti OR (epidemiologic* NEAR/1 (study OR studies)):ab,ti OR ('cross sectional' NEAR/1 (study OR studies)):ab,ti OR 'register'/exp OR regist*:ab,ti	11,312,679
27.	#25 OR #26	11,601,794
28.	#9 AND #24 AND #27	10,442
29.	letter:it OR editorial:it OR note:it	2,672,077
30.	review:it OR 'review literature as topic'/exp OR 'literature review':ti NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	2,858,082
31.	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5,579,673
32.	'case report*':ab,ti OR 'case series':ab,ti	642,817
33.	#29 OR #30 OR #31 OR #32	11,380,516
34.	#28 NOT #33	8,509
35.	**#34 AND [1-9-2019]/sd NOT [22-04-2021]/sd**	**1,733**

C7. Please clarify the type of date restriction used in the search strategy for Embase and MEDLINE (Table 5, D.1.1, Appendix D, p.17). Was it a limit by entry date or by publication year?

As mentioned above, search strategy for EMBASE and MEDLINE in Table 5 was limited by entry date (i.e. September 2019) to ensure sufficient overlap between the original search dates (i.e. October 2019) and the update.

C8. Retrieval of records in the searches of MEDLINE and Embase (line 25, Table 18, p. 55-56, Section G.1.1, Appendix G), were restricted to cost-effectiveness studies. Please clarify if a published search filter was used for this restriction, giving a reference where available.

The study design filters was based on recommendations from ISSG Search Filter Group which is a is a collaborative venture to identify, assess and test search filters designed to retrieve research by study design or focus. The filters can be accessed from URL - https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home. For economic evaluations, validated study design filters were adapted from CADTH (https://www.cadth.ca/media/pdf/H0490_Search_Filters_for_Economic_Evaluations_mg_e.pdf), SIGN (https://www.sign.ac.uk/what-we-do/methodology/search-filters/), Royle et al (https://www.journalslibrary.nihr.ac.uk/hta/hta7340/#/abstract), and NHS EED (https://www.york.ac.uk/crd/SysRev/!SSL!/WebHelp/5_3_IDENTIFYING_ECONOMIC_EVALUATIONS_FOR_A_REVIEW.htm)

C9. Retrieval of records in the searches of MEDLINE and Embase (line 14, Table 27, p. 90, Section H.1.1, Appendix H), and PubMed (lines 10-15, Table 28, p. 90, Section H.1.1, Appendix H) were restricted to studies reporting utility evidence. Please clarify if a published search filter was used for this restriction, giving a reference where available.

The study design filters were based on recommendations from ISSG Search Filter Group which is a is a collaborative venture to identify, assess and test search filters designed to retrieve research by study design or focus. The filters can be accessed from URL - https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home. Within this group, to search for utilities, search filters were adapted based on recommendations from Arber et al (https://pubmed.ncbi.nlm.nih.gov/29065942/) and

CADTH (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/health-state-utility-values?authuser=0).

C10. The searches in Section G.1.1, Appendix G, Section H.1.1, Appendix H and Section I.1.1, Appendix I were carried out in November 2019. Please clarify why the searches have not been updated to identify more recent studies.

The searches were not updated given the limited potential impact of any additional identified studies .

Figures

C11. In Document B, figures 20, 21, 25, 26, 28 and 29 display different extrapolation curves, however the colours used for some curves are very similar and in some cases curves overlap so it is hard to distinguish which curves belong to which distribution. Please provide revised representations of these figures to make distinguishing the curves possible, e.g. by using different colours, line types or by adding text/arrows to the graph to indicate which curve is which.

Overall survival curves have been removed from the updated version of the model following the inclusion of PPS from second-line studies. Updated figures for PFS and CNS-PFS extrapolations are provided below in Figure 2 to Figure 5 .

Figure 2:PFS for lorlatinib

Figure 3: PFS for crizotinib

Figure 4:CNS-PFS for crizotinib

Figure 5:CNS-PFS for lorlatinib (generalised gamma curve has been removed as the model did not converge)

C12. In Document B, in figures 27, 30 and 32, the line for alectinib is not clearly visible possibly because it overlaps with another curve. Please indicate clearly

in the figures which other curve this overlaps with, or otherwise ensure it is visible.

These figures will be provided with the updated version of the model.

Tables

C13. Please indicate why some of the outcomes in Table 3 (Document B) are highlighted in bold.

Outcomes highlighted in bold were included in the CEM as requested in the NICE template.

C14. In Table 21 (Document B) the last column for the ALEX trial has the percentage with prior chemotherapy as '0 (NR)'. Please clarify whether it was zero or not reported.

The percentage of patients receiving prior chemotherapy was not reported.

Unclear text

C15. In Document B, reference to figure and table numbers in the text are incorrect – links need to be updated. For example, in the second paragraph of page 82, references to Tables 39 and 40 should be to table 36 and 37, respectively. To avoid confusion please update references to the tables and figures in the text and check that they match the correct figure.

The table links have been updated, and a revised version of document B has been submitted.

C16. Table 39, column 1, line 1 states 'Weibull distribution', but the text on page 82 implies that these values should be for the exponential distribution: "Therefore, exponential curves were selected to model OS in the lorlatinib and crizotinib arms, based on the plausibility of the long-term extrapolation." Please clarify.

The text on page 82 is correct, the values are for the exponential distribution, however OS data from first-line trials are no longer used in the model.

C17. In Section B.3.3.2, page 82 (just before table 35) it is stated that "…the exponential curves provide conservative survival estimate in both treatment arms…". Please justify what is meant by "conservative" in this context given that the Gamma curves provide lower survival predictions than the exponential.

The exponential, Weibull and gamma curves were considered to be the most conservative compared to alternative curve selections as they give the lowest survival estimates, estimating 9.0%, 4.1% and 4.2% of patients alive at 30 years, respectively. However, following the clarification meeting between the company and the EAG, these extrapolations of OS data from first-line trials are no longer used in the model, in favour of using OS data from second-line trials to model post-progression survival.

C18. Please clarify that the percentages in Table 48 relate to yearly AE rates.

The percentages in Table 48 are yearly AE rates, annualised based on average treatment exposure.

References

C19. Please can the company check the reference for the Alectinib (ALEX) trial in Table 48 ('Adverse Event Proportions'). The reference refers to a conference abstract, with limited reference to the drug's safety.

The adverse event proportions for alectinib are available in 'Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study' (https://doi.org/10.1016/j.annonc.2020.04.478)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
Lorlatinib EAG clarification letter to PM	**FINAL**	**Yes**	**28.06.22**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section B: Clarification on cost-effectiveness data

The EAG has very significant concerns regarding the conceptualisation and parameterisation of the company's model. The EAG does not believe these key uncertainties can be resolved in the context of the model structure adopted by the company, which we consider to be inappropriate for decision making in terms of both methodological robustness, transparency, and its capacity to represent the trial data or the NHS treatment pathway.

The EAG recognises the difficulty in parameterising a partitioned survival model (PSM) given the challenges presented by the current trial data. However, the parametric models fitted to the CROWN data demonstrate that the data are too immature to generate even an approximation of the expected future outcomes in a way that can be meaningfully implemented in a PSM, particularly when also considering the confounding introduced by previous and subsequent TKIs in the trials. Moreover, the company's approach in several instances generates benefits in the economic model (in OS, PFS, and CNS-PFS) which are not compatible with the evidence from the trial data over equivalent timescales.

The crude means by which a relative OS benefit was estimated is not methodologically sound and, more importantly, does not allow the uncertainty around the point estimates or alternative parametric distributions to be represented in the

model. The structural imposition of this ***fixed*** OS benefit renders the model extremely inflexible, insofar as no alternative assumptions affecting mortality can be implemented without breaking the premise of the model structure. Furthermore, there is no meaningful way of capturing the uncertainty associated with the immaturity of the data, the claimed survival benefit, and the model structure itself.

It is the EAG's opinion that a state transition model would allow more transparent characterisation of the extreme decision uncertainty, the use of wider data sources, the explicit modelling of subsequent treatments, and the exploration of alternative assumptions. However, the EAG recognises that this may not be possible within the current timelines of the appraisal. Given the EAG's substantive concerns and the constraints of the current timeline, a range of additions and changes to the existing model have been requested that would allow more transparency around decision uncertainty and greater flexibility. These additional requested changes, however, do not address all the EAG's concerns with the model structure.

Model Structure

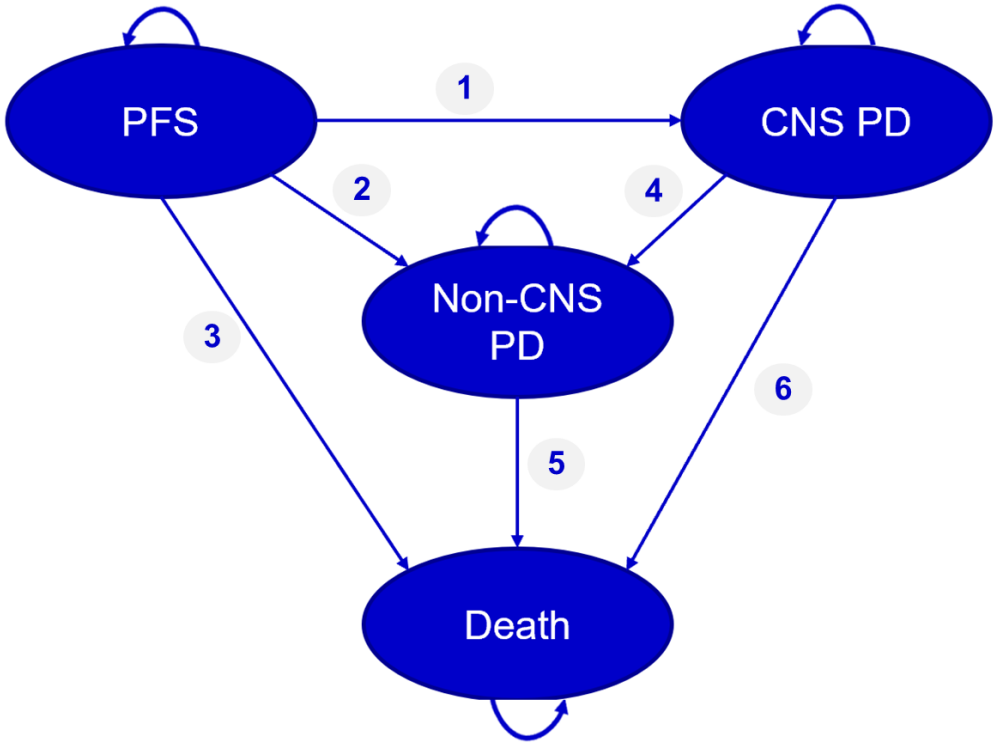
B1. Priority question: As outlined above the EAG has substantive concerns regarding the model structure and does not consider a PSM to be the most appropriate model structure given the limitations of the available survival data. Please revise the model structure to use a state transition approach using data appropriate to the structure and decision problem.

B2. Priority question: If it is not possible to fully revise the model (question B1), please include functionality for a pseudo-state-transition approach to post-progression survival. This should account for 2nd line use of lorlatinib, and use data appropriate to CNS-PD and PD respectively.

To address the EAG's concerns and following the discussion during the clarification meeting, we have updated the economic model to remove the fixed overall survival (OS) benefit and OS data from all first-line studies, given the concerns over the generalisability of data from ALEX/ALTA-1L to UK clinical practice and the current immaturity of OS in CROWN discussed in the meeting.

A pseudo state-transition model has been developed (see Figure 1), utilising second-line OS data from Study 1001 and PROFILE 1001/1005 (Ou et al. 2014; https://doi.org/10.1093/annonc/mdt572) to capture post-progression survival (PPS) following first-line treatment with an ALK-inhibitor.

Figure 1. Model structure



1. CNS-PFS; area under the curve (unchanged). Data source: CROWN & HR from NMA
2. PFS – CNS-PFS; area under the curve (unchanged). Data source: CROWN & HR from NMA
3. Proportion of PFS events that are deaths (unchanged). Data source: Assumption
4. PFS – CNS-PFS; area under the curve (unchanged). Data source: CROWN & HR from NMA
5. Constant PPS transition rate calculated from second-line OS. Data source: Study 1001 (lorlatinib) & PROFILE 1001/1005 (chemotherapy)
6. Same as 5

Two studies were utilised in line with the second-line lorlatinib submission (TA628) to represent PPS with second-line treatment of either lorlatinib or chemotherapy:

- Study 1001 (NCT01970865) is a Phase 1/2, multiple-dose, dose escalation, safety, PK, PD, and anti-tumour activity study of lorlatinib. The sample consisting of expansion cohorts EXP-3B, EXP-4 and EXP-5 (patients who have progressed after one or more prior ALK TKIs) is the most relevant population for this submission and is the data used to inform efficacy in the model.

- Ou et al. 2014 (PROFILE 1001/1005) was identified as the best source for chemotherapy as it was the only study that reported the OS of patients who received 'systemic therapy' following progression and discontinuation of crizotinib.

Data sources for the respective treatment pathways included in the model are shown in Table 1 below.

Table 1. Data sources for PFS and PPS

First-line		Second-line	
Treatment	**PFS data**	**Treatment**	**PPS data**
Lorlatinib	CROWN	Chemotherapy	PROFILE 1001/1005 Ou et al. (2014)
Alectinib	HR vs CROWN	Lorlatinib	Study 1001 (EXP3b:5)
Brigatinib	HR vs CROWN	Lorlatinib	Study 1001 (EXP3b:5)

Incorporation of time varying PPS would have required multiple tunnel states. Therefore, exponential curves using data from Study 1001 and Out et al. were used to model PPS. This was considered a minor limitation, given that although it does not allow for accurate overall survival landmark rates to be identified from the model for external validation. However, difference in the chemotherapy PPS are very minimal and for lorlatinib 2L PPS, alternative parametric extrapolations to the exponential were explored, to allow for the mean PPS to vary and reflect the uncertainty on the ICER. To incorporate this, the goal seek function was used to find the exponential rate to obtain the mean PPS for alternative distributions, which are presented in Table 2 below.

Table 2. Exponential rates to obtain the mean PPS for alternative distributions

Distribution	Mean PPS (months)	Exponential rates used in scenario analyses
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

For reference, all extrapolation, the mean, median and landmark values and AIC and BIC statistics for all second-line lorlatinib and chemotherapy OS parametric survival models are shown in Figure 2/Table 3 and Figure 3/Table 4 below.

Figure 2. OS parametric curves – lorlatinib

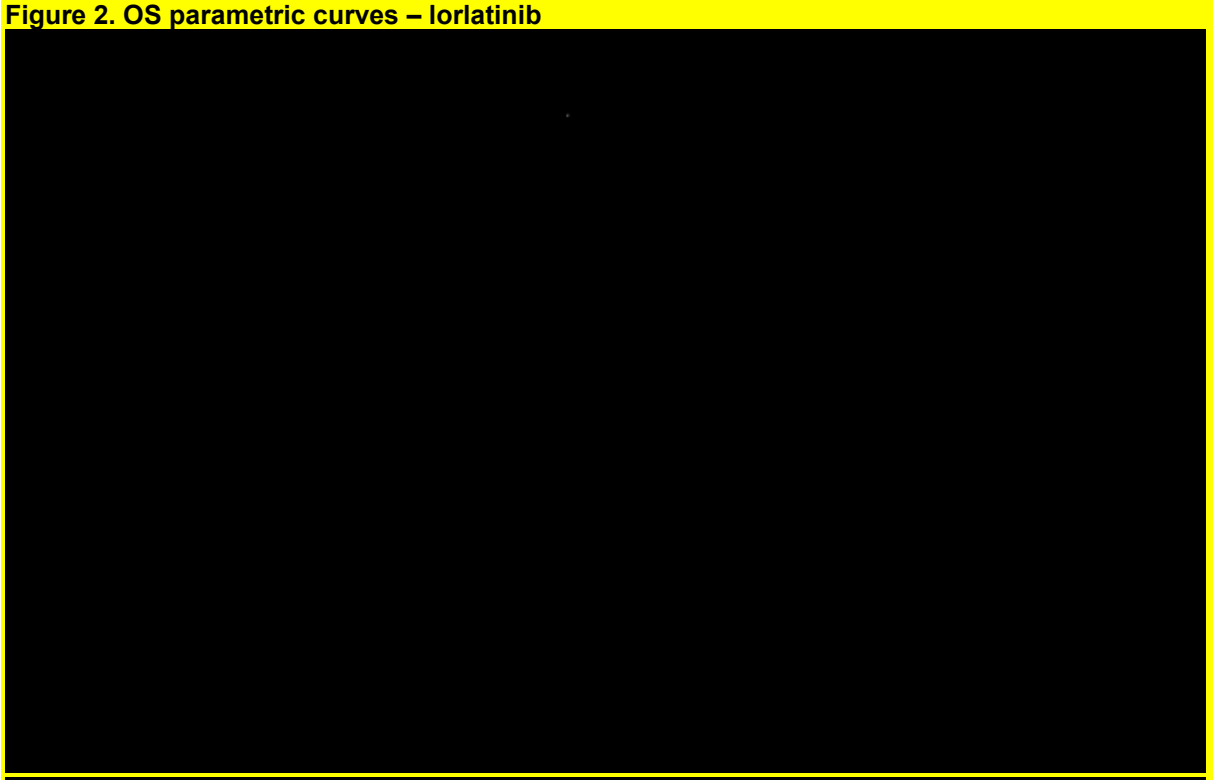


Table 3. Second-line lorlatinib OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)				
					6 months	1 year	2 years	3 years	5 years
Generalised gamma									
Exponential									
Weibull									
Log-normal									
Log-logistic									
Gompertz									

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion, OS = overall survival

Figure 3. OS parametric curves – PDC (derived from PROFILE 1001/1005 KM data for chemotherapy)

Abbreviations: KM = Kaplan–Meier; OS = overall survival; PDC = platinum doublet chemotherapy

Table 4. Second-line chemotherapy (PDC) OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)				
					6 months	1 year	2 years	3 years	5 years
Generalised gamma									
Exponential									
Weibull									
Log-normal									
Log-logistic									
Gompertz									

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion, OS = overall survival; PDC = platinum doublet chemotherapy

The updated model structure allows for alternative parametric distributions to be explored to extrapolate PFS and also alternative PPS as discussed above. All key assumptions have been explored in scenario analyses which are presented in Table 5 below to quantify the uncertainty around PFS and OS from the first line. The ICER range obtained by varying the PFS parametric distributions is [redacted] to [redacted] and [redacted] to [redacted] by varying mean lorlatinib PPS.

Table 5. Scenario analysis results

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER	NHB
	Base-case	[redacted]	[redacted]	[redacted]	[redacted]
1	Discounting set to 6%	[redacted]	[redacted]	[redacted]	[redacted]
2	Discounting set to 0%	[redacted]	[redacted]	[redacted]	[redacted]
3	Time horizon set to 20 years	[redacted]	[redacted]	[redacted]	[redacted]
4	Time horizon set to 40 years	[redacted]	[redacted]	[redacted]	[redacted]
5	Do not use detailed lorlatinib dosing	[redacted]	[redacted]	[redacted]	[redacted]
6	Include all RDI savings	[redacted]	[redacted]	[redacted]	[redacted]
7	Exclude RDI	[redacted]	[redacted]	[redacted]	[redacted]
8	TA670 EOL cost source	[redacted]	[redacted]	[redacted]	[redacted]
9	Utility source: TA670 (ALTA-1L)	[redacted]	[redacted]	[redacted]	[redacted]
10	Exclude AE disutility values	[redacted]	[redacted]	[redacted]	[redacted]
11	Treatment waning at 10 years	[redacted]	[redacted]	[redacted]	[redacted]
12	Treatment waning at 20 years	[redacted]	[redacted]	[redacted]	[redacted]
13	Societal perspective	[redacted]	[redacted]	[redacted]	[redacted]
14	Investigator assessed PFS	[redacted]	[redacted]	[redacted]	[redacted]
15	Mean PPS after alectinib/brigatinib based on generalised gamma distribution from 2L model	[redacted]	[redacted]	[redacted]	[redacted]
16	Mean PPS after alectinib/brigatinib based on Weibull distribution from 2L model	[redacted]	[redacted]	[redacted]	[redacted]
17	Mean PPS after alectinib/brigatinib based on log-normal distribution from 2L model	[redacted]	[redacted]	[redacted]	[redacted]
18	Mean PPS after alectinib/brigatinib based on log-logistic distribution from 2L model	[redacted]	[redacted]	[redacted]	[redacted]
19	Mean PPS after alectinib/brigatinib based on gompertz distribution from 2L model	[redacted]	[redacted]	[redacted]	[redacted]
20	Duration of AEs sourced from CROWN	[redacted]	[redacted]	[redacted]	[redacted]
21	PFS - Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
22	PFS - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
23	PFS - Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
24	PFS - Log normal	[redacted]	[redacted]	[redacted]	[redacted]
25	PFS - Weibull	[redacted]	[redacted]	[redacted]	[redacted]
26	PFS - Gamma	[redacted]	[redacted]	[redacted]	[redacted]
27	ITT NMA (including ALESIA)	[redacted]	[redacted]	[redacted]	[redacted]
28	10% of alectinib/brigatinib patients receiving 2L chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
29	20% of alectinib/brigatinib patients receiving 2L chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
30	Disutility for lorlatinib AE of special interest equals -0.037	[redacted]	[redacted]	[redacted]	[redacted]

How uncertainty will be addressed with additional data from CROWN

The data available for CROWN are currently immature, with median PFS not yet reached and very limited OS data. To reduce the uncertainty around long-term PFS and OS estimates, ongoing data collection from CROWN is planned. Lorlatinib is considered to be a suitable CDF candidate to allow for ongoing data collection and reduce the uncertainty around the survival estimates. Table 6**Error! Reference source not found.** below shows planned future CROWN data cuts, however given that PFS and OS endpoints are events driven, these dates are subject to change. Additional data collection will allow for an alternative four/five state partitioned survival model structure to be explored in the future, including post-progression outcomes after lorlatinib from CROWN (PFS, PFS2 and OS).

Table 6. Planned future CROWN data cuts

PFS; CNS-PFS	[redacted]
PFS2	[redacted]
OS [redacted]	[redacted]
OS [redacted]	[redacted]

B3. The current model structure implies that post-progression survival is the same following treatment with lorlatinib in either a 1st or 2nd line position. Please justify this assumption and comment on the clinical plausibility of this assumption. If possible please provide evidence from CROWN and Study 1001 comparing PPS.

The survival data from CROWN is too immature to ascertain whether PPS is the same following treatment with lorlatinib in either a first- or second-line position. The scenarios provided around PFS and PPS with the updated model structure have attempted to quantify the impact of this on the ICER.

B4. Priority question: Please amend the model to explicitly capture uncertainty in the data used to derive the relative effectiveness of lorlatinib. In the current model lorlatinib can only generate [redacted] LYs in the probabilistic sensitivity analysis (PSA). The model should calculate the 'live' difference in PFS such that the PSA reflects the uncertainty in the underlying data used to generate

the relative benefit of lorlatinib, as well as uncertainty around the parametric extrapolations and hazard ratios used to produce the curves in the PSM. This must be implemented for all extrapolations, see also question B5.

This question has been addressed in the updated model in response to B1 and B2 above.

B5. Priority question: Please fit standard parametric function to CROWN and STUDY 1001 PFS and OS data. Please use these to operationalise alternative parametric extrapolations using the approach taken in the base case for the exponential curve, calculating additional LYG on lorlatinib for each. This should include exploring alternative parametric models for PFS for all 1st line treatments as well as 2nd lorlatinib.

Alternative parametric extrapolations for PFS and PPS have been explored and results are presented in Table 5 above.

B6. Priority question: The exponential extrapolation of PFS substantially overestimates observed data for much of the duration of the KM curve likely due to overfitting to the tail where there are very low numbers at risk. The exponential model also assumes proportional hazards which is inconsistent with Document B where it is stated that the proportional hazards assumption does not hold for PFS in CROWN. Please validate the parametric model selection, considering committee preferences in previous TAs and justify the choice of an exponential curve in the base case analysis.

Parametric survival curves were fitted independently to lorlatinib and crizotinib data from CROWN, case as it is generally considered unnecessary to rely on the proportional hazards assumption when patient-level data are available. HRs for alectinib and brigatinib were applied to the crizotinib data from CROWN.

Feedback from a UK clinician was sought, who advised that Weibull, gamma or exponential curves would be appropriate to extrapolate PFS data. In TA536 and TA670, exponential curves or Kaplan-Meier data with exponential tails were selected in the base case across all treatment arms. The exponential extrapolation of PFS was considered appropriate on the basis of feedback from a UK clinician.

Given the uncertainty around the selection of the most appropriate PFS curve, all possible models have been explored to quantify the uncertainty around PFS and the results of these scenario analyses are presented in Table 5.

B7. Priority question: The model predictions for alectinib CNS-PFS do not appear to match the observed data in the ALEX and ALTA-1 study at key time points.

a) **Please present tables comparing the predictions of the model with trial data for PFS, CNS-PFS, and OS for alectinib, brigatinib, and lorlatinib at key time points and justify any departure from the observed data.**

OS has not been considered following the concerns raised by the EAG in the clarification meeting that OS data from ALTA-1L and ALEX no longer represent clinical practice, and CROWN is too immature. Exponential survival curves were selected in TA670, and the modelled median PFS (BICR) for alectinib and brigatinib are aligned with the reported data, as shown in Table 7, indicating that this aligns with previous assumptions.

Table 7. Validation of PFS

Treatment	Modelled median PFS	Reported median PFS (Source)
Alectinib	25.63 months	25.7 months (ALEX; Peters 2017)
Brigatinib	23.66 months	24 months (ALTA-1L; Camidge 2020)

b) **Please provide digitised KM data for ALEX and ALTA-1 and plot them against the Markov trace from the model.**

The independent review committee PFS KM curve from ALEX (Figure 4) was digitised and plotted against the Markov trace as shown in Figure 5.

Figure 4. Kaplan–Meier of independent review committee-assessed PFS in ALEX

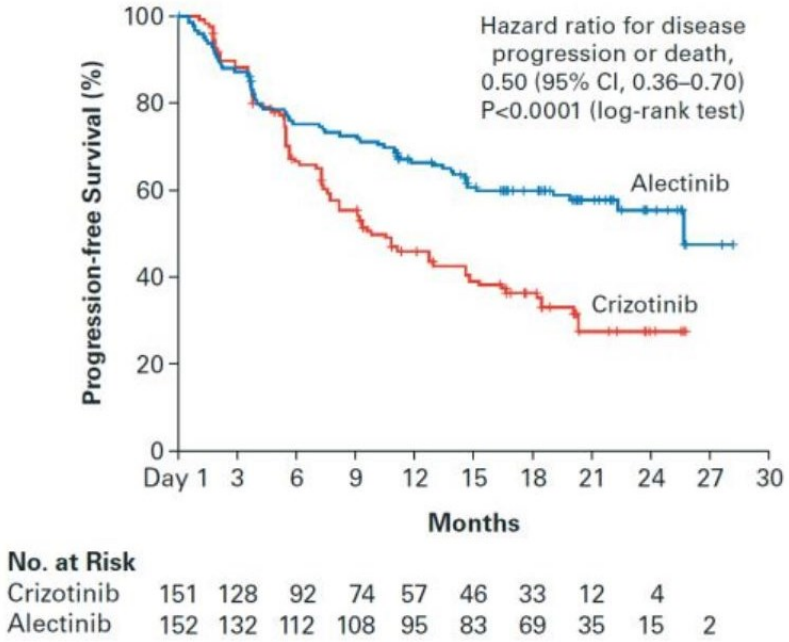
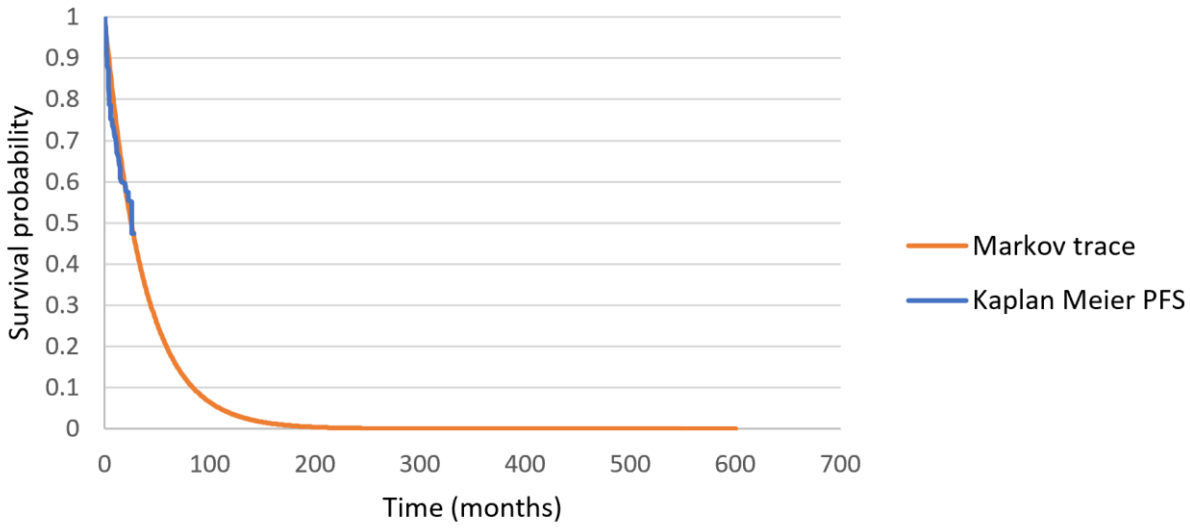


Figure 5. Independent review committee PFS alectinib (BICR)



The independent review committee PFS KM curve from ALTA-1L (Figure 6) was digitised and plotted against the Markov trace as shown in Figure 7

Figure 6. Kaplan–Meier of independent review committee-assessed PFS in ALTA-1L

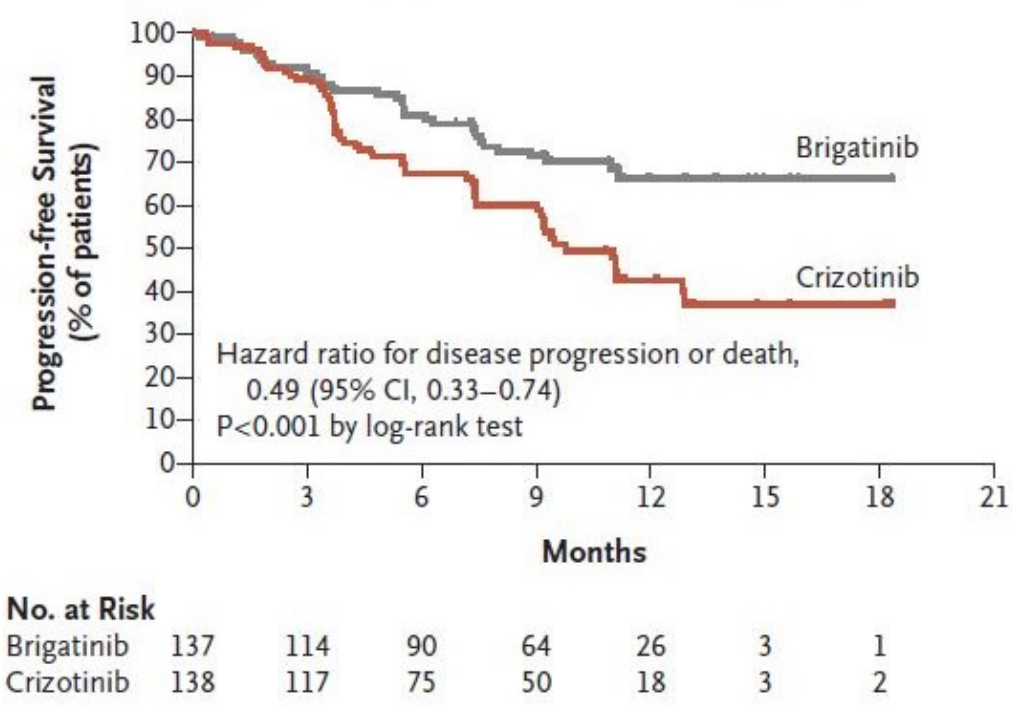
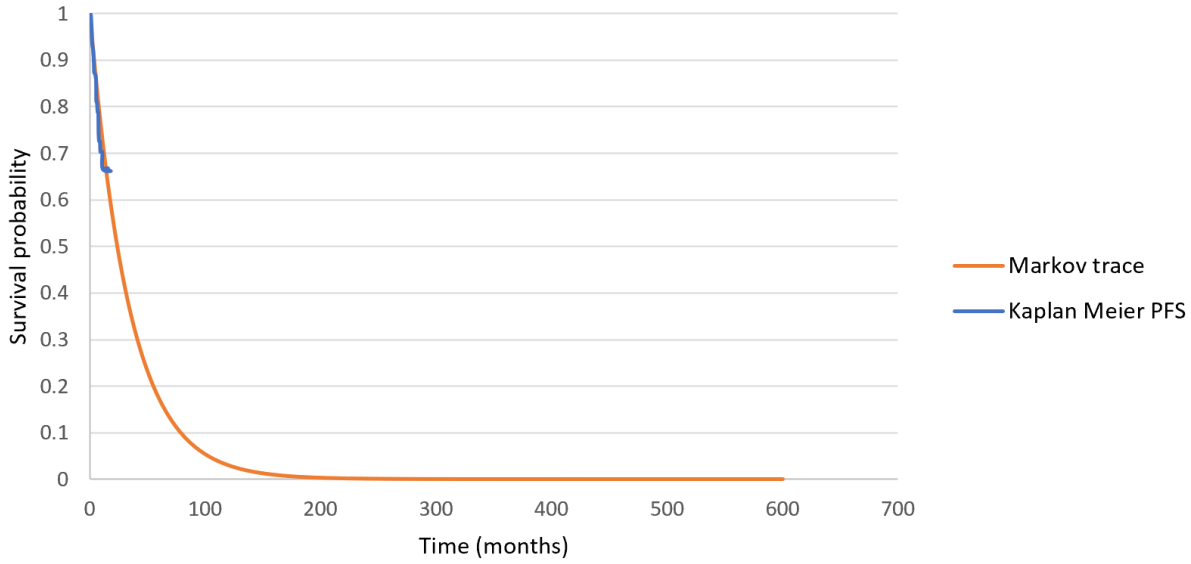
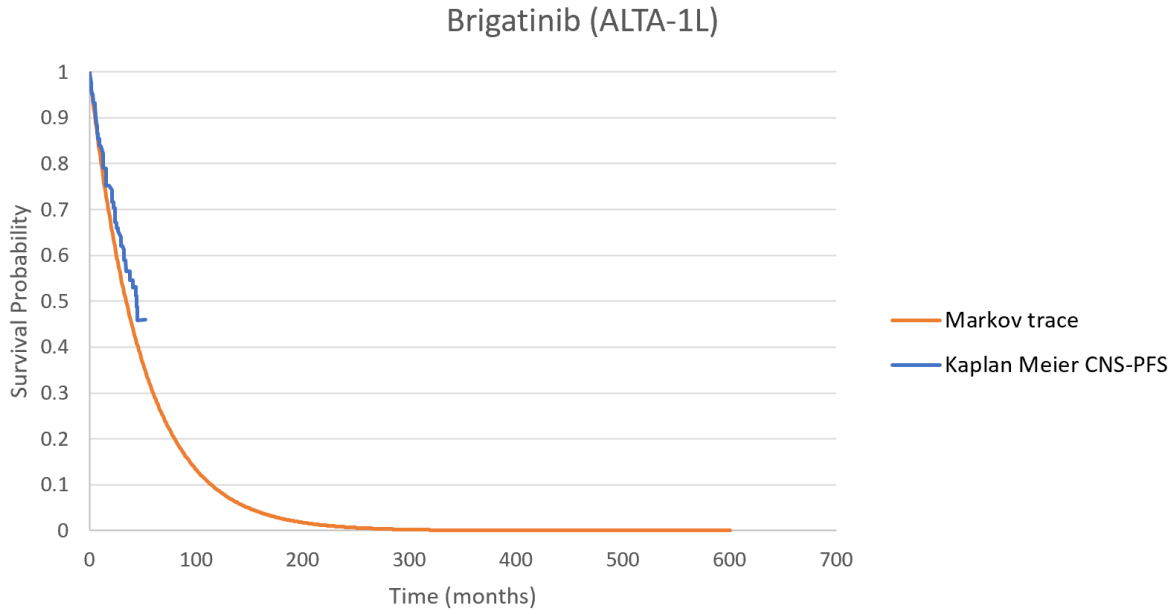


Figure 7. PFS brigatinib (BICR)



The digitised KM curve (Figure F; https://doi.org/10.1016/j.jtho.2021.07.035) plotted against the Markov trace for CNS-PFS for brigatinib is shown in Figure 8.

Figure 8. BICR-assessed Intracranial PFS (ITT population) versus Markov trace for brigatinib

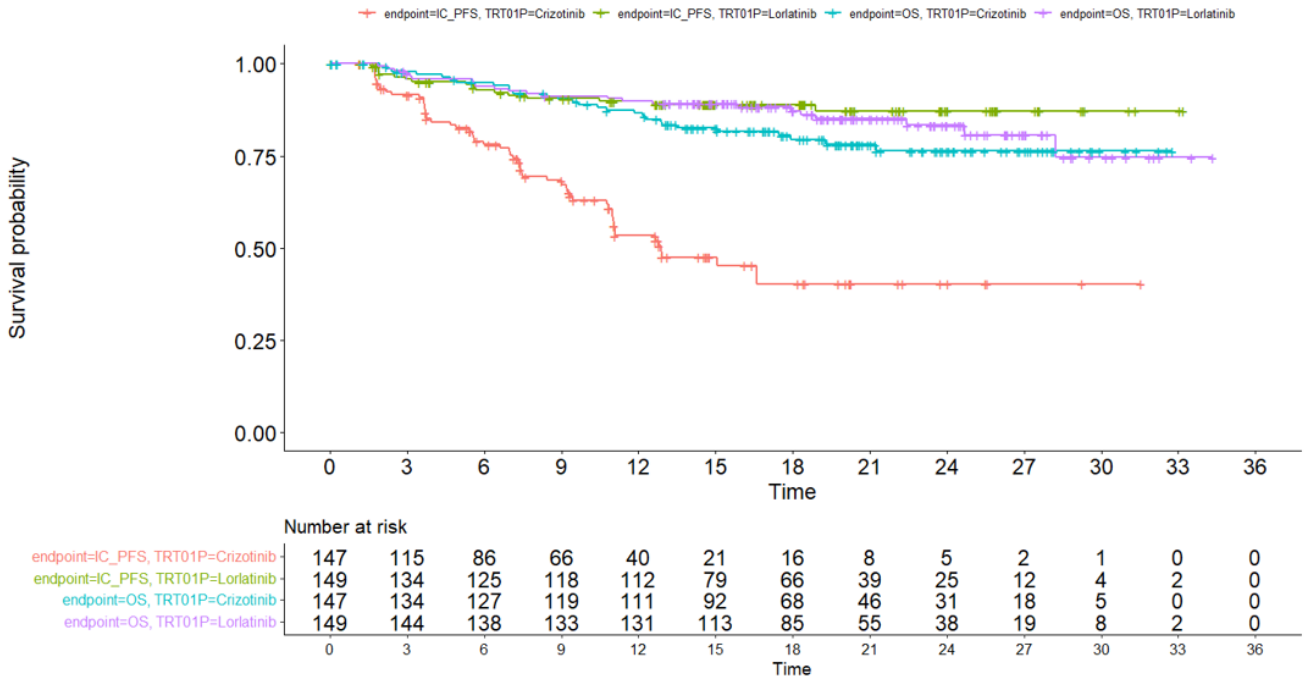


The KM data for CNS-progression for alectinib in ALEX are unpublished and redacted in TA536.

B8. The extrapolations of the survival analyses performed on lorlatinib CROWN CNS-PFS data mean that lorlatinib patients cannot experience CNS progression events in the model, despite CNS-progression events being observed in CROWN (see Figure 5 of Document B). Please add model functionality that allows lorlatinib patients to experience CNS events in line with the observed data.

In the previous model, OS and IC PFS for lorlatinib are very similar and after 18 months IC PFS appears higher than OS (as shown in Figure 9). This led to the phenomenon of lorlatinib patients being unable to experience CNS events. With th inclusion of PPS in the updated model, patients can now experience CNS progression events to reflect the CROWN data. Lorlatinib is highly effective in terms of preventing CNS progression. In CROWN, n=1 (0.9%) patient without brain metastases at baseline receiving lorlatinib had IC progression, and n=8 (21.6%) patients with brain metastases at baseline receiving lorlatinib had IC progression.

Figure 9: Kaplan-Meier estimates for overall survival and IC progression from CROWN overlaid



Treatment Effectiveness

B9. Following treatment with first-line lorlatinib in the CROWN trial, 63.6% of patients go on to receive a second-line ALK-TKI.

a) Do you expect to see similar post-progression survival outcomes for patients treated in the NHS, who will not receive a 2nd line TKI following progression on lorlatinib?

33 (22.1%) patients in CROWN received subsequent treatment due to disease progression, and of these 21 (63.6%) received a subsequent ALK TKI. Given the small number of patients progressing in CROWN, the data are too immature to compare PPS outcomes to NHS clinical practice.

b) How is the difference accounted for in the model?

Functionality has been built into the model to allow patients who progress after alectinib and brigatinib to receive chemotherapy instead of a 2nd line TKI (lorlatinib). A proportional split of patients receiving second-line lorlatinib or chemotherapy is applied to transition probability of death per cycle. This is discussed further in the response to question B23.

B10. Priority question: Please perform a scenario analysis in which the final data cuts from ALTA-1L and ALEX are used for brigatinib and alectinib respectively. If the latest available data cut is based on investigator-assessed PFS, use this for all treatments. Please ensure consistency of the data and model with question A11.

Investigator assessed PFS is explored in the scenario analyses in Table 5.

B11. Please perform scenario analysis to incorporate the PFS results from additional NMA analysis in which the ALESIA trial is included in the network (see question A10).

The NMA including ALESIA is explored in the scenario analysis in Table 5.

B12. Priority question: Please provide a table clearly listing the source and data-cut used for each outcome (including adverse events) used in the NMA and in the economic model for lorlatinib, brigatinib, alectinib and lorlatinib at 2nd line. This should be presented for each outcome and include clear information on the data cut used.

Data sources for all endpoints and treatments are presented in Table 8 below.

Table 8. Data sources used in the NMA

	PFS (BICR)	PFS (INV)	IC TTP	PPS	Adverse events
Lorlatinib	CROWN (September 2021 DCO)	CROWN (September 2021 DCO)	CROWN (September 2021 DCO)	PROFILE 1001/1005 (Ou et al.)	CROWN (September 2021 DCO)
Alectinib	ALEX (Camidge 2019; December 2017 DCO)	ALEX (Camidge 2019; December 2017 DCO)	ALEX (Camidge 2019; December 2017 DCO)	Study 1001	ALEX (Camidge 2019; December 2017 DCO)
Brigatinib	ALTA-1L (Camidge 2018; February 2018 DCO)	ALTA-1L (Camidge 2018; February 2018 DCO)	ALTA-1L (Camidge 2018; February 2018 DCO)	Study 1001	ALTA-1L (Camidge 2018; February 2018 DCO)

Abbreviations: CNS-PFS, central nervous system progression-free survival; DCO, data cutoff; PFS, progression-free survival; PPS, post-progression survival

B13. Please amend the current approach to modelling AEs to account for all AEs of special interest, regardless of grading, in terms of costs and utility effects.

The incidence of grade 1-4 AEs for peripheral neuropathy, cognitive effects and mood effects have been included in the updated model. For each AE, 2 additional oncology outpatient visits have been assumed. The management of peripheral neuropathy is anticipated to be managed by dose reduction (Bauer et al. 2019; https://doi.org/10.1634/theoncologist.2018-0380). For cognitive and mood effects, additional mental health assessments for cognitive impairment and common mental health problems have been included in the model.

Table 9. Adverse event costs per event

AE	Cost	Source	Resource assumption
Peripheral neuropathy	£272.71	NHS Reference Costs (2019/20)	2 oncology outpatient visits
Cognitive effects	£527.46	NHS Reference Costs (2019/20)	2 oncology outpatient visits; Cognitive impairment (MHCC18)
Mood effects	£697.76	NHS Reference Costs (2019/20)	2 oncology outpatient visits; Common mental health problems (low severity) (MHCC01)

B14. Priority question: Please present data on the duration of adverse events by type and grade in CROWN. Please provide a scenario in which duration of adverse events is informed by evidence from CROWN.

The duration of adverse events from CROWN are provided as an addendum to the CSR with this response. The duration of AE included in the model are summarised in Table 10.

Table 10. Duration of adverse events in CROWN

Adverse event	Median duration of AE in CROWN (lorlatinib arm), days
Hypertriglyceridemia	[redacted]
Weight increased	[redacted]
Hypercholesterolemia	[redacted]
Peripheral neuropathy	[redacted]
Cognitive effects	[redacted]
Mood effects	[redacted]

The duration of adverse events informed by the evidence from CROWN is presented as a scenario analysis in Table 5, using the assumption that the median duration of AEs reported in Table 10 is equivalent to the duration of AEs in the Utilities sheet.

Health-related Quality of Life

B15. Priority question: Please update the model to use utilities mapped to EQ-5D-3L using the Hernández-Alava algorithm as stipulated in the NICE reference case.

Utilities mapped to EQ-5D-3L using the Hernández-Alava algorithm have been included in the model. An updated statistical report is included in response to the clarification letter.

B16. Priority question: Please provide a comparison of post-progression utilities applied in the model with utilities observed on lorlatinib/chemotherapy in Study 1001.

Utilities calculated from Study 1001 are already applied in the model upon primary progression to account for progression-free on 2L treatment with lorlatinib. Annual post-progression utilities are calculated utilising subsequent treatment duration and the difference between on and off treatment utilities in the non-CNS progressed health state.

B17. Priority question: The committee for brigatinib (TA670) did not consider the Roughley et al. (2014, DOI: 10.1016/j.jval.2014.08.2364) abstract to be a reliable source to calculate the CNS-multiplier (it was accepted by the committee due to no alternative data being available). This was 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 with the addition of CNS metastases as a covariate.**

A substantial proportion of records in CROWN occur pre-progression. Overall, patients have a slight decrease in utility after progression, with the greatest difference between pre- and post-progression seen in the crizotinib arm. Post-progression HRQoL data for patients who received lorlatinib were collected on a

small number of patients (n=36) as shown in Table 11. HRQoL records post IC-progression were collected for n=65 patients across both treatment arms. Of the post-progression utilities, most were close to the date of progression, indicating that the post-progression utility in the trial may not be reflective of the true value of post-progression utility over time after the progression event.

Table 11. Summary of mean utility by treatment and progression status (BICR)

Health state	Treatment	N patients	N post baseline records	Mean utility (EEPRU)	Mean utility (crosswalk)
Pre-progression	Lorlatinib	146	3,902	[redacted]	[redacted]
	Crizotinib	135	1,520	[redacted]	[redacted]
Post-progression	Lorlatinib	36	377	[redacted]	[redacted]
	Crizotinib	85	336	[redacted]	[redacted]
Unknown health state	Lorlatinib	77	137	[redacted]	[redacted]
	Crizotinib	45	98	[redacted]	[redacted]

b) Please also present a comparison of observed disutilities associated with different types of metastases.

QoL data on the progression of extracranial sites were not collected in CROWN.

B18. Priority question: 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. Please provide further details of the regression methods used to estimate utilities.

Mixed effects regression models were used including univariate mixed effects and final fixed effects models. The variables explored in exploratory analyses were considered for mixed effects regression analysis. The model selection process initially explored simple univariate models fitted separately for each covariate identified as being potentially relevant. Additionally, to explore the explicit effect of treatment above the effect of these covariates, their interaction with treatment was investigated. Stepwise covariate selection was used to pragmatically identify the covariates to be included in the final models. Mixed effects regression models were performed using the lme function from the package ‘nlme’ in R. AIC and BIC values

were used to compare the fit of the models and were calculated using the AIC and BIC functions in the ‘stats’ package.

The models included a random effect for patient to adjust for the correlation between multiple observations from the same patient. It is believed that the observations for a single patient were distributed (clustered) around the mean for that patient. A random intercept value was estimated for each patient.

a) **Please provide further information on the patients contributing QoL data, including baseline characteristics and the number of patients. Please also provide the number of observations included in the analyses at each time point.**

There were 6,370 EQ-5D-5L questionnaires collected in the CROWN study (September 2021 DCO). The number of patients contributing to QoL data are available in the CSR, as outlined in Table 12. Baseline characteristics of patients who cease to report at each time point were not collected.

Table 12. Table in CSR of patients contributing to QoL data

QoL assessment	Treatment group	
	Lorlatinib	Crizotinib
EORTC QLQ-C30 Global QoL Physical functioning Role functioning Emotional functioning Cognitive functioning Social functioning Fatigue Nausea and vomiting Pain Dyspnoea (C30) Insomnia Appetite loss Constipation Diarrhea Financial difficulties	Table 14.5.1.1	Table 14.5.1.1
EORTC QLQ-LC13 Dyspnoea (LC13) Coughing Haemoptysis Sore mouth Dysphagia Peripheral neuropathy Alopecia Pain in chest Pain in arm or shoulder Pain in other parts	Table 14.5.1.2	Table 14.5.1.2

EQ-VAS	Table 14.5.1.3	Table 14.5.1.3
EQ-5D-5L	Table 14.5.1.4	Table 14.5.1.4

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.

QoL data for specific AEs are presented in Tables 14.5.1.1 (cognitive and emotional functioning) and 14.5.2.2 (peripheral neuropathy). However, QoL data specific to psychotic effects or speech were not collected.

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).

The utility analysis datasets were derived using the following assumptions:

- Only patients from the CROWN study who were randomised to receive study treatment were included in this analysis (intention-to-treat [ITT] population)
- All complete observations were included in the mixed effects regression models; observations that were not complete (i.e. the patient did not answer all questions in the questionnaire) were excluded
    - No imputation methods were used
- Baseline flags in the datasets 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 three-state structure of the economic model and the survival analysis outcomes: pre-progression and post-progression

- Pre-progression includes all observations prior to the date of objective progression of disease
- Post-progression includes observations on and after the date of objective progression of disease
- Observations recorded after a censored progression date were not included in the mixed effects regression models, as it is unknown which health state they are in at that time
- Health state was defined based on PFS assessed by BICR
- The health states further split by CNS progression were also investigated

Based on this derivation method and the September 2021 CROWN data cut, there were 6,370 EQ-5D-5L questionnaires collected in CROWN. Of the 149 patients randomised to the lorlatinib treatment arm, 148 patients out had at least one derived utility value. Of the 147 patients randomised to the crizotinib treatment arm, 140 patients out had at least one derived utility value. The lorlatinib arm had 29.8 records per patient on average, and the crizotinib arm had 14.0 records per patient on average.

d) Please provide the coefficients for each of the covariates included in the analysis, including mean, SE, p value, and 95% CI.

The coefficients for each of the covariates included in the analysis are presented in Table 13.

Table 13. Univariate naïve mean utility and mixed effects least square mean utility score results from CROWN (using the van Hout crosswalk algorithm)

Category	N patients	N records	Naïve mean (SD)	LS mean (95% CI)	p-value
Age – continuous	288	6370	[redacted]	[redacted]	<0.001
Age – years					<0.001
18–44	60	1372			
45–64	129	3151			
≥65	99	1847			
Baseline ECOG PS					<0.001
0	119	2884			
1	157	3430			
2	12	56			
Baseline brain metastases					0.69
No	212	4947			
Yes	76	1423			

Category	N patients	N records	Naïve mean (SD)	LS mean (95% CI)	p-value
Heath state (BICR)					<0.001
Pre-progression	281	5422	[redacted]	[redacted]	
Post-progression	121	713	[redacted]	[redacted]	
Unknown	122	235	[redacted]	[redacted]	
Heath state (INV)					<0.001
Pre-progression	280	5621	[redacted]	[redacted]	
Post-progression	137	509	[redacted]	[redacted]	
Unknown	106	240	[redacted]	[redacted]	
Health state (IC progression)					<0.001
Pre-prog & pre-IC-prog	282	5450	[redacted]	[redacted]	
Post-prog & pre-IC-prog	10	10	[redacted]	[redacted]	
Post-prog & post-IC-prog	59	266	[redacted]	[redacted]	
Post-prog & unknown	63	438	[redacted]	[redacted]	
Unknown & post-IC-prog	6	11	[redacted]	[redacted]	
Both unknown	104	195	[redacted]	[redacted]	
Race					0.0448
Asian	128	2900	[redacted]	[redacted]	
Non-Asian or unknown	160	3470	[redacted]	[redacted]	
Sex					0.222
Female	170	3,823	[redacted]	[redacted]	
Male	118	2,547	[redacted]	[redacted]	
Smoking status (1)					0.939
Current	22	432	[redacted]	[redacted]	
Former	94	2191	[redacted]	[redacted]	
Never	171	3746	[redacted]	[redacted]	
Treatment					0.331
Crizotinib	140	1,954	[redacted]	[redacted]	
Lorlatinib	148	4,416	[redacted]	[redacted]	
On/off treatment					<0.001
Off	148	255	[redacted]	[redacted]	
On	279	6115	[redacted]	[redacted]	
Key: CI, confidence interval; LS, least-squares; SD, standard deviation.					

B19. Priority question: Clinical advisers to the EAG described how the adverse events associated with lorlatinib (specifically cognitive adverse events) can have an impact on patients' quality of life. The EAG is concerned that the HRQoL data do not reflect the disutilities associated with adverse events associated with lorlatinib. Please source AE-related disutilities and include

these in the economic model over an evidence-based duration. This should be consistent with questions B13 and B14.

The disutility for neutropenia is -0.090, sourced from Nafees et al. 2017 (https://doi.org/10.1111/ajco.12477). 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. Adverse event utilities have also been sourced from TA670. The duration of adverse events for patients receiving lorlatinib in CROWN have been provided as part of this response and incorporated into the model (see response to B14). The inclusion of the duration of AEs and resource use for cognitive and mood effects is expected to capture the impact of AEs associated with lorlatinib. Furthermore this is a conservative assumption against lorlatinib as we have not considered relevant AE of special interest for alectinib and brigatinib. Given that there is uncertainty around the adverse event disutilities for peripheral neuropathy, cognitive and mood effects, a scenario has been explored in which the disutility associated with each of these AEs is -0.037 (aligned with the AE disutilities from TA670) and results are presented in Table 5.

B20. The economic model discusses progression-free (off-treatment) utilities.

a) **Please provide an explanation of your understanding of why the progression free off-treatment utility is so low relative to other health states.**

b) **Please clarify where this utility is applied in the model.**

Off-treatment records were associated with a 0.07 decrement in LS mean compared to records taken on-treatment. 255 off-treatment records were collected for n=148 patients. A high proportion of these records were taken close to the point of treatment cessation, which is likely to reflect the impact of adverse events or disease progression. Off-treatment utilities were therefore not applied in the model.

Resource Use

B21. In Figure 31 of Document B ('Observed time on treatment compared to PFS for lorlatinib'), the proportion of patients who are on-treatment undercuts

the proportion of patients who were progression-free. Please can the company provide an explanation for this pattern in the KM curve.

The time on treatment curve undercuts the progression-free survival curve likely due to the number of patients who have stopped treatment for reasons other than progression, for example toxicity.

B22. Priority question: Clinical advice to the EAG suggests that many patients on lorlatinib (~30%) would be expected to continue treatment beyond progression, as this is permitted in the MHRA licence.

a) **Please present a scenario based on available evidence on anticipated lorlatinib maintenance treatment in practice in terms of costs and effects.**

b) **Please clarify what proportion of patients the company anticipates will be treated beyond progression, and for how long.**

The MHRA license states that:

"Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity."

It is anticipated that a clause will be inserted into the Blueteq criteria, for example stating that the patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner. Therefore, the company does not anticipate that patients will continue to receive treatment with lorlatinib post-progression. Patients will be treated until loss of clinical benefit, excessive toxicity or patient choice to discontinue treatment, whichever is sooner. As discussed in question B21, the observed trend in CROWN is for the ToT curve to undercut the PFS curve. Whilst some patients may be treated beyond lorlatinib progression as discussed by Ou et al. 2021 (https://doi.org/10.1016/j.jtho.2021.12.011), data from CROWN are not mature enough to predict what proportion of patients will be treated beyond progression. However the company anticipates that this will be addressed with future data cuts.

B23. Priority question: Clinical advice to the EAG suggests that some patients currently treated with alectinib/brigatinib do not receive lorlatinib following

progression. Instead, some patients receive no further treatment as their performance status and rapid disease progression may preclude this. Please include a model scenario in which not all comparator patients receive 2nd line lorlatinib, referencing evidence from NHS practice or clinical opinion.

The model has been updated to include functionality for patients progressing on alectinib or brigatinib to receive either lorlatinib or chemotherapy as a second line treatment. In the base case, a [redacted] split of chemotherapy to lorlatinib has been assumed, and the transition probabilities of death for second-line treatment after alectinib/brigatinib have been weighted by this split. Market share data indicates that [redacted] of patients receive an ALK TKI as second line treatment, and [redacted] receive I/Os / Other. The impact of [redacted] and [redacted] of patients progressing from first-line alectinib or brigatinib to second-line chemotherapy is explored in the scenario analyses in Table 5.

B24. Please include the cost of treatment with statins for all patients with treatment related dyslipidemia of any grade, i.e. hypercholesterolaemia, hypertriglyceridemia, hyperlipidaemia. Please add resource use reflecting blood testing and clinician time for Grade 1/2 treatment related dyslipidemia events.

All adverse events (grades 1-4) in the September 2021 CROWN DCO have been modelled for hypercholesterolaemia, hypertriglyceridemia, hyperlipidaemia. In addition, the annual costs of statins (generic atorvastatin 10 mg; annual cost £8.87) has been included for hypertriglyceridemia and hypercholesterolemia AEs (sourced from the British National Formulary).

Presentation of cost-effectiveness results

B25. Priority question: Please reproduce all cost-effectiveness results with inclusion of net health benefit (NHB) at a QALY gain of £20,000 and £30,000 as stipulated in Section 4.2.16 of the NICE Methods Guide. The results of any additional analyses or changes to the model requested in the EAG's questions should also be presented in terms of NHB.

Pairwise results are presented in the tables below including incremental net health benefit (INHB) at a £30,000 threshold.

Table 14. Deterministic base case results versus alectinib including NHB

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)	INHB (QALYs)
Alectinib	[redacted]	5.09	3.30					
Lorlatinib	[redacted]	7.19	4.70	-£16,849	2.10	1.39	Dominant	1.96

Table 15. Deterministic base case results versus brigatinib including NHB

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)	INHB (QALYs)
Brigatinib	[redacted]	5.15	3.24					
Lorlatinib	[redacted]	7.19	4.70	-£7,655	2.04	1.46	Dominant	1.71

Table 16. Probabilistic base case results versus alectinib including NHB

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)	INHB (QALYs)
Alectinib	[redacted]	5.16	3.35					
Lorlatinib	[redacted]	7.23	4.71	-£26,683	2.07	1.36	Dominant	2.25

Table 17. Probabilistic base case results versus brigatinib including NHB

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£ per QALY)	INHB (QALYs)
Brigatinib	[redacted]	5.22	3.29					
Lorlatinib	[redacted]	7.23	4.71	-£16,983	2.01	1.42	Dominant	1.99

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

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About you

Your name	[redacted]
Name of your organisation	ALK Positive UK
Please indicate your position in the organisation	Department of Health and Social Care or Welsh Government in general? • Commissioning services for the Department of Health and Social Care or Welsh Government specific to the condition for which NICE is considering this technology? • Responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)? • A specialist in the treatment of people with the condition for which NICE is considering this technology? • A specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)? • Other (please specify):
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	No

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion	The current 1st line treatment option for ALK-positive lung cancer is Alectinib, although since the NICE approval for 1st line use of Brigatinib we are seeing some newly diagnosed patients being prescribed this as their first TKI. The use of Brigatinib as a first line treatment is primarily at teaching hospitals with large cancer centres. ALK Positive UK has asked the question which TKI should be 1st line to several oncologists experienced in treating ALK-positive LC patients and there doesn't seem to be a consensus. The charity has flagged the need

between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?	for a guideline as patients being treated at small DGHs (District General Hospital), where the oncologist might not even specialise in lung cancer, let alone have experience with ALK-positive LC, are very likely to be disadvantaged. We are already seeing this with access to CT scans, MRI scans and the treatment of bone mets and blood clots amongst ALK-positive patients across the UK. We can provide evidence of this if requested. [The only alternative to TKI's as a 1st line treatment option is chemotherapy, which everyone will be aware comes with significant side effects and has a poor Overall survival figure for ALK-positive LC patients. Chemotherapy has a significant impact on a patients Quality of Life as it causes significant fatigue (sometimes requiring long periods spent in bed) and horrendous sickness again rendering the patient incapable of little else. This not only has a significant impact on the patient but on their whole family and is distressing for all. The discovery of TKIs has revolutionised the treatment of ALK-positive LC and patients across the UK are immensely grateful for their availability.] Each TKI has advantages and disadvantages, and side effects vary widely (again we can provide real world data from our member survey on frequency of side effects). Alectinib, currently the most widely Rxed TKI for 1st line use, can cause significant fatigue. I would like to emphasise that this doesn't mean feeling tired, this fatigue has a significant effect on QoL as people feel washed out, with heavy limbs and with the feeling of wading through treacle on a permanent basis. This makes doing just everyday tasks extremely hard. The other significant side effect of Alectinib is sun sensitivity. This is not like sunburn; this is like having a kettle of boiling water poured on any part of your body exposed to the sun – even winter sun. This results in patients needing to use Factor50 sun protection and having all limbs covered and wearing a hat whenever the sun shines. I speak from personal experience on the painfulness of this – this isn't to be underestimated. Brigatinib users tend to experience diarrhoea as their primary side effect, with nausea and raised blood pressure in equal frequency (in our patient survey of 93 patients) occurring less frequently. The overall side effect frequency seems to be less with Brigatinib vs Alectinib with our members. From my understanding they have similar efficacy in the brain which is very important as 70% of ALK-positive patients develop brain mets hence the need for good blood-brain coverage.

To what extent and in which population(s) is the technology being used in your local health economy?	Lorlatinib is currently being used as the 2nd line treatment for all ALK-positive LC patients across the UK so clinicians have experience in its efficacy and side effects. From our member survey, it would seem to be the most tolerated from a side effect perspective, although neurological side effects are frequently mentioned.
Is there variation in how it is being used in your local health economy?	
Is it always used within its licensed indications? If not, under what circumstances does this occur?	ALK Positive UK believe it is always used within its current license.
What is the impact of the current use of the technology on resources? **What is the outcome of any evaluations or audits of the use of the technology?**	TKI's are expensive, we recognise this, however they give patients in most cases, the opportunity to live life to the maximum. This means they can keep being mum or dad, who is up before the kids in the mornings getting them off to school and being ready to play in the park when the kids want to. It means patients can continue to work, ensuring their families are fed well and can continue (as much as possible) to live the way they did before the diagnosis. It means they remain contributors to the UK economy. It means life can be as normal as possible.
What is your opinion on the appropriate use of the technology?	Lorlatinib we believe has superior activity in the brain vs both Alectinib and Brigatinib which is extremely important for ALK-positive patients. It is important to minimise the risk of developing brain mets, as patients with brain mets have a reduced overall survival due to the complications they bring with them. Some patients will present with brain mets which is then an important factor in what treatment plan is agreed between the oncologist and patient. Lorlatinib from the studies we have seen offers the best protection from brain mets. It is important that oncologists have a choice in order to ensure the most appropriate TKI is prescribed giving each patient the best possible chance of maintaining a good QoL for as long as possible.

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Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	The approval of Lorlatinib for 1st line use would give oncologists more choice to choose the most appropriate treatment for each patient. This will hopefully result in patients tolerating it well and it working for as long as possible which should result in a longer overall survival which is what all patients want.
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	The prescribing of TKIs will continue to be the sole responsibility of oncologists so no changes to current practice would be required.
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	ALK Positive UK doesn't believe this will have an increased impact on the NHS drugs budget should NICE approve Lorlatinib and oncologists start prescribing it as a first line hence replacing the current TKI options.
Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes	We don't foresee any resource implications should Lorlatinib been approved for 1st line use.

nurses versus more insulin pumps, or the loss of funds to other programmes)?	
Would there be any need for education and training of NHS staff?	Oncologists would continue to be the only prescribers of TKIs so no training would be required.

Equality

Please let us know if you think that this appraisal: **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced** **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology** **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**	In our opinion this appraisal would have no impact on people protected by the equality legislation.
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technology	Should the committee approve the use of Lorlatinib for use as a 1st line treatment for ALK-positive LC, which ALK Positive UK supports, there should be guidance developed on when and where each of the then 3 choices should be used in the 1st line setting. This will ensure patients being treated in smaller centres, without significant knowledge of ALK-positive LC receive the same treatment and overall survival odds.

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]
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.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- 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, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). 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 ALK positive advanced Non Small Cell Lung Cancer (NSCLC).
4b. 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?	As a result of the COVID pandemic, our contact with patients and carers has become mainly virtual. The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, 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?	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are 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. Lorlatiib has previously been approved for ALK positive patients, whose disease has progressed after - Alectinib or Ceritinib as the first ALK TKI or - Crizotinib and at least one other ALK TKI. 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 results of the CROWN trial, published in the NEJM, which compared Lorlatinib and Crizotinib, in untreated ALK positive patients. This showed an improvement in progression free survival with Lorlatinib. Of note, central nervous system involvement was assessed. Amongst the patients with measurable lesions on baseline brain scans, an intracranial response was noted in 82% in the Lorlatinib arm and 23% in the Crizotinib arm. 71% of the patients who received Lorlatinib had an intracranial complete response. This therapy is given orally (therefore, ease of administration) and in the anecdotal patient experience available to us, it appears to be generally well tolerated.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Side effects of the treatment. As above, there are several ALK inhibitors already in regular practice in this indication and Lorlatinib has been available after progression on treatment. As such, experience in use and side effect management is now commonplace. We understand that common side effects associated with Lorlatinib include oedema, peripheral neuropathy, weight gain, dyspnoea, arthralgia, diarrhea, hypercholesterolemia and cough. As above. 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:

- ALK positive NSCLC is known to often spread to the brain. As such, it is important to have treatment options which demonstrate both overall and intracranial effectiveness.
- Despite progress in therapies for ALK positive lung cancer in recent years, there is a need for additional and more effective treatments in this segmented patient group.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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Professional organisation submission

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

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.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Oncology Group (BTOG)**

3. Job title or position	[redacted]
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
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 stakeholder list.]	

If so, please state the name of manufacturer, amount, and purpose of funding.	
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 the survival (delay progression) of ALK positive lung cancer patients
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A response rate of greater than 60% A progression free survival of greater than 2 years Response in central nervous system disease

x cm, or a reduction in disease activity by a certain amount.)	
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?	First line options for this group of patients include Crizotinib, Ceritinib, Alectinib or Brigatinib In current practice Alectinib and Brigatinib would be the most commonly used
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO guidelines Also treatment is guided by NICE reimbursement
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway is well defined with most Health professional in England using Alectinib or Brigatinib as a first line treatment in this area

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It will provide a further treatment option in the first line setting that may have better efficacy than the current treatment options
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would feed into the first line treatment algorithm, which is already in place
• How does healthcare resource use differ between the technology and current care?	No difference. This would be a third oral treatment option that would be available for patients.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In secondary care / cancer specialist centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment required as the ALK testing / treatment pathway is already fully established

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Potentially yes Difficult to be certain as the drug was not trialled against what would be regarded as the standard of care drugs in current practice
• Do you expect the technology to increase health-related quality of life more than current care?	I expect it to be equivalent
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This will be aimed at ALK positive non small cell lung cancer patients
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 or additional tests or monitoring needed.)	It has a different toxicity profile to the other ALK inhibitors available. All ALK inhibitors have their own unique toxicity profiles that require some form of additional monitoring and potentially concomitant medication. There is a feeling that Lorlatinib is slightly more toxic than Alectinib and Brigatinib and hence may require closer monitoring or clinician input into toxicity management.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would continue as long as the agent is being tolerated and the patient is gaining clinical benefit (which will be determined by regular scanning and clinical assessments)
15. Do you consider that the use of the technology will result in any substantial health-	n/a

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
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?	Yes There are already effective treatment options in the ALK treatment naïve population. However if Lorlatinib provides a further survival benefit then it is a substantial and significant benefit. Also if it is better at controlling CNS disease – then again this is a significant improvment
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Potentially will provide a greater survival benefit as well as better CNS disease control

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?	The toxicity profile as per the trial is well recognised and manageable
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The standard of care drug (Crizotinib) in the trial is no longer commonly used as a first line agent – but was standard of care when the trial was set up. All other parameters reflect UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS, OS, ORR, intracranial ORR, quality of life They were measured, but the data is not all mature yet
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	n/a
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?	n/a
21. How do data on real-world experience compare with the trial data?	There is no published real-world data
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

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Still high unmet need for ALK positive NSCLC patients to improve clinical outcomes
- Lorlatinib is demonstrating impressive efficacy data and would be a useful addition to the first line treatment options
- It has a unique side effect profile – but these are manageable
-
-

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CONFIDENTIAL UNTIL PUBLISHED
External Assessment Report
Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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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.

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Contributions of authors
Lucy Beresford wrote the critique of the indirect treatment comparisons. Mark Corbett wrote the critique of the decision problem and clinical effectiveness evidence. Sofia Dias supported the critical appraisal of the evidence and takes responsibility for the report as a whole. Melissa Harden critiqued the search strategies, wrote the search strategy sections and provided editorial support. Robert Hodgson supported the critical appraisal of the economic evidence submitted by the company. Martin Njoroge co-authored the critique of the economic evidence submitted by the company. Matt Walton wrote the critique of the economic evidence submitted by the company.

Note on the text
All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
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)
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
FTA	Fast track appraisal
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IC-TTP	Intracranial time to progression
INHB	Incremental net health benefit
KM	Kaplan–Meier
LY	Life years
MAIC	Matched adjusted indirect comparisons
MHRA	Medicines and Healthcare products Regulatory Agency
NHB	Net health benefit
NMA	Network meta-analysis
NR	Nor reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PFS	Progression-free survival
PPS	Post-progression survival
PSM	Partitioned survival model
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumour
RR	Relative risk
SLR	Systematic Literature Review
SmPC	Summary of product characteristics
STM	State transition model
TA	Technology Appraisal
TKI	Tyrosine Kinase Inhibitor
ToT	Time on treatment

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 the EAG's Key Issues

ID	Summary of issue	Report sections
1	The anaplastic lymphoma kinase (ALK) inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE.	3.2.1.1
2	Nearly all patients in the CROWN trial had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS.	3.2.1.1 & Table 8
3	Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	3.2.1.2
4	Grade 3 or 4 adverse events occur more frequently with lorlatinib than with alectinib.	3.2.1.2
5	Baseline central nervous system (CNS) metastases as a potential treatment effect modifier.	3.4, 4.2.3
6	The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate.	3.4.1, 4.2.3
7	Immaturity of PFS outcome leading to lack of alternative extrapolations.	4.2.6
8	Death was not modelled as a PFS event.	4.2.2
9	There are insufficient data available to model CNS progressed disease (PD) health state appropriately.	4.2.2, 4.2.6.4, 4.2.6.5, 4.2.7
10	Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	4.2.6.5, 4.2.8
11	Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities.	4.2.7
12	Dosing calculations and proportion of patients receiving subsequent treatment.	4.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company prefers a four-state model which accounts for the effect of treatment on CNS metastases, the EAG prefers that this be removed;
- The company prefers to use utilities derived from the CROWN study, the EAG prefers to use the value set accepted by the committee in TA670;
- The company prefers the use of market share data to inform the use of second-line lorlatinib in the comparator arm, the EAG prefers to use subsequent treatment data from the CROWN study.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival;
- Increasing overall survival;
- Reducing the proportion of patients who develop intracranial metastases.

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 size of the progression-free survival benefit for lorlatinib (i.e. PFS extrapolation and effect waning assumptions)
- The size of the central nervous system progression free survival benefit for lorlatinib
- The utility value set selected

1.3 The decision problem: summary of the EAG's key issues

None

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Obsolete ALK inhibitor treatment sequences used in the CROWN trial

Report section	3.2.1.1
Description of issue and why the EAG has identified it as important	The second-line use of alectinib after lorlatinib, together with the obsolete comparator treatment sequence of first-line crizotinib followed by second-line alectinib or brigatinib (or another ALK inhibitor), limits the applicability of the CROWN trial results to both current NHS practice and to future practice (were first-line lorlatinib to be recommended by NICE).
What alternative approach has the EAG suggested?	No alternative trial data currently exist.
What is the expected effect on the cost-effectiveness estimates?	This has been accounted for in the updated model by using external data to model post-progression survival.
What additional evidence or analyses might help to resolve this key issue?	A trial which compares first-line lorlatinib (with some patients continuing on lorlatinib after progression) with first-line alectinib (or brigatinib) followed by lorlatinib at second-line (such a trial is not currently available).

Issue 2 Very few participants with an ECOG performance status score of 2 were recruited into the CROWN trial

Report section	3.2.1.1 & Table 8
Description of issue and why the EAG has identified it as important	Although participants with an ECOG PS score of 2 were eligible for inclusion in the CROWN trial, 96% of the recruited cohort had an ECOG PS score of 0 or 1. Nevertheless, lorlatinib's marketing authorisation is not restricted by ECOG PS score. Given that ECOG PS score is thought to be a prognostic indicator of PFS and OS – with higher scores associated with worse outcomes – lorlatinib may be less effective in the marketing authorisation population, compared with the narrower trial population.
What alternative approach has the EAG suggested?	Not applicable.
What is the expected effect on the cost-effectiveness estimates?	The limited evidence adds uncertainty to the cost-effectiveness estimates. The EAG does not consider it appropriate to extrapolate results of the presented economic analysis to an ECOG 2 population.
What additional evidence or analyses might help to resolve this key issue?	A randomised trial of first-line lorlatinib versus alectinib or brigatinib, which includes enough patients with an ECOG PS score of 2 to allow PFS and OS to be evaluated in this subgroup (such a trial is not currently available).

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	OS data from the CROWN trial are immature with the median OS not being estimable in either treatment arm. There is currently no evidence that increased PFS from lorlatinib leads to increased OS. This means that appropriate methods must be used for extrapolating and estimating longer-term OS data.
What alternative approach has the EAG suggested?	Not applicable.
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in the cost-effectiveness estimates. Extrapolations of PFS results in wide range of predictions many of which lack clinical plausibility, see Issue 7. The economic analysis assumes PFS is a surrogate for OS and that gains in PFS map 1:1 with gains OS.
What additional evidence or analyses might help to resolve this key issue?	The CROWN trial final analysis for OS is anticipated in [redacted].

Issue 4 Incidence of grade ≥ 3 adverse events with lorlatinib compared to other ALK inhibitors

Report section	3.2.1.2
Description of issue and why the EAG has identified it as important	The submission states that lorlatinib is tolerable, with an acceptable adverse event profile. Although published NMAs have reported a significantly greater risk of Grade ≥ 3 adverse events (AEs) with lorlatinib compared with alectinib, this was not mentioned in the company's submission and a relevant NMA was not presented. Given lorlatinib's [redacted] improvement in PFS compared to other ALK inhibitors, it is important to ensure that analyses comparing the relative safety of the ALK inhibitors is also presented.
What alternative approach has the EAG suggested?	The EAG has summarised key results from the published NMAs which compare the incidence of grade ≥ 3 AEs across ALK inhibitors.
What is the expected effect on the cost-effectiveness estimates?	The consideration of AEs of special interest in the model using CROWN AE durations reduces total QALYs by [redacted] on lorlatinib, although no equivalent data on AE duration were available for alectinib and brigatinib.
What additional evidence or analyses might help to resolve this key issue?	The EAG utilised published NMAs to partially resolve the issue.

Issue 5 Baseline CNS metastases as a potential treatment effect modifier

Report section	3.4, 4.2.3
Description of issue and why the EAG has identified it as important	There is some evidence that the presence of CNS metastases at baseline is a modifier of the PFS treatment effect. The alectinib and brigatinib trials recruited a larger population of patients with CNS metastases at baseline than in CROWN. If the presence of CNS metastases at baseline is indicative of a poor prognosis and/or a reduction in the treatment effect associated with Tyrosine Kinase Inhibitors (TKIs), the lower proportion of these patients in CROWN vs ALEX may inflate the apparent efficacy of lorlatinib.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	The evidence available is not sufficiently mature to resolve this issue. Sample sizes are currently too small to meaningfully inform subgroup analysis.

Issue 6 Exclusion of the ALESIA study from the NMA used in the economic model

Report section	3.3, 4.2.3, 4.2.6
Description of issue and why the EAG has identified it as important	The ALESIA study of alectinib was excluded from the company's NMA on the basis that it was conducted in Asian centres and thus was not applicable to the UK population. The company also argue that ALESIA was not considered relevant the appraisal committee in TA670. The EAG considers these arguments less relevant in the current appraisal. Many sites in the CROWN trial were in Asia, and OS outcomes (most affected by subsequent treatments) are not directly used in the model. The EAG also notes there is no evidence to suggest ethnicity is an effect modifier. Inclusion of the ALESIA study makes the alectinib evidence base more comparable to that of lorlatinib, and also reduces the apparent efficacy of lorlatinib relative to alectinib, and thus its cost-effectiveness.
What alternative approach has the EAG suggested?	The EAG's preferred approach is to use the 'Global NMA' results, which includes the ALESIA study.
What is the expected effect on the cost-effectiveness estimates?	Inclusion of the ALESIA study increased the total QALYs generated by alectinib [redacted]
What additional evidence or analyses might help to resolve this key issue?	Clinical and/or expert opinion on the biological plausibility of a differential treatment effect in terms of PFS in Asian patients. Clear evidence of a (pre-specified) subgroup effect from randomised controlled trials or meta-analyses. If the company maintain the position that evidence from Asian patients should not be considered, then the NMA should be

	repeated excluding both ALESIA *and* patients from Asian centres in CROWN.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 7 Immaturity of PFS outcome leading to lack of alternative extrapolations

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The immaturity of lorlatinib PFS data from CROWN (with respect to the number of events) resulted in a lack of clinically plausible extrapolations for use in the model. The PFS extrapolation selected for lorlatinib in the company's base case analysis appears optimistic and has a poor visual fit to observed data. Alternative projections of PFS on lorlatinib cannot be explored in the usual way due to the failure of other distributions to generate plausible extrapolations. The impact of uncertainty around long-term maintenance of PFS cannot be quantified.
What alternative approach has the EAG suggested?	The EAG consider treatment waning a potentially useful means of exploring alternative PFS projections beyond the exponential function previously described. This allows varying limits on the duration of the efficacy of lorlatinib according to previous appraisals and clinical input. The use of more flexible survival analysis techniques (spline models or two-piece models) could also be explored and may produce more plausible estimates of effectiveness.
What is the expected effect on the cost-effectiveness estimates?	Treatment effect waning at 7-, 10-, and 15-years [redacted]. Lorlatinib becomes less cost-effective if effect waning is considered.[redacted]
What additional evidence or analyses might help to resolve this key issue?	Due to the design of the CROWN trial, PFS is the sole outcome which is sufficiently generalisable to the NHS setting and treatment pathway to meaningfully inform a decision between lorlatinib and its comparators. Improved maturity of this outcome will serve to reduce much of the resolvable uncertainty associated with the duration of the treatment effect and the comparative effectiveness of lorlatinib. The EAG suggests the use of more sophisticated survival analysis techniques to assess whether these generate more plausible PFS projections.

Issue 8 Death was not modelled as a PFS event

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The company did not adjust health state transitions to reflect the proportion of PFS events that were death in CROWN. A substantial proportion of PFS events in CROWN were death, but the model treats all PFS events as progression. This results in the overestimation of the number of patients remaining alive in the model and inflates QALY outcomes accordingly. The EAG also disagreed with the pooling of deaths and progression events across treatment arms from CROWN to calculate the proportion of deaths as PFS events, as the observed rates in lorlatinib and crizotinib differed significantly.
What alternative approach has the EAG suggested?	The EAG assumed the omission of death events to be a modelling error, and corrected the model in line with the company's approach to estimating subsequent treatment costs. The EAG prefers the use of arm-specific death proportions from CROWN to adjust transitions out of the progression-free health state.
What is the expected effect on the cost-effectiveness estimates?	This issue represents the only correction made to the company's model. The effect upon cost-effectiveness is the difference between the company's base-case and the EAG-corrected company base-case analysis. This correction leads to a small reduction in the incremental QALY gain on lorlatinib versus both comparators. Lorlatinib becomes marginally less cost-effective in this scenario, but [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG's preferred approach assumes the proportion of deaths prior to progression will be the same for lorlatinib, alectinib, and brigatinib. It is unclear if this assumption is appropriate. Further, comparative analysis of the causes of death prior to progression may help substantiate this assumption.

Issue 9 Insufficient data available to model CNS-PD health state appropriately

Report section	4.2.2, 4.2.6.4, 4.2.6.5, 4.2.7
Description of issue and why the EAG has identified it as important	A number of issues with the parameterisation and modelling of central nervous system progressed disease (CNS-PD) render its inclusion inappropriate and potentially misleading. i) Highly immature data means uncertainty associated with very optimistic CNS-PFS outcomes cannot be evaluated; ii) intracranial outcomes are not comparable between trials and are confounded by subsequent treatments received i.e. there is no reliable basis to assess comparative effectiveness; iii) the link between non-CNS PD and CNS-PD has not been modelled and cannot be informed by CROWN data due to censoring of secondary CNS progression events; iv) differential prognosis of patients with intracranial metastases is not reflected in modelled post-progression survival data. The model generates significant but clinically unsubstantiated QALY benefits of lorlatinib compared to alectinib and brigatinib. This is based on an incomplete representation of the CNS-PD health state and the prognosis of patients with intracranial metastases.
What alternative approach has the EAG suggested?	The EAG has suggested the CNS-PD health state be removed from the model.
What is the expected effect on the cost-effectiveness estimates?	The removal of the CNS-PD health state has a number of effects which impact the cost-effectiveness of lorlatinib in different directions. Total QALYs are increased for all technologies by the removal of the CNS PD health state, however, this increase is only [redacted] for lorlatinib compared to [redacted] for alectinib and brigatinib. The removal of this health state also results in a modest and relatively equal reduction of costs for all technologies. Overall, lorlatinib becomes less cost-effective, but [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider it possible to accurately model CNS progressions given the currently available evidence. Further comparative evidence on CNS-progression is required.

Issue 10 Treatment beyond progression on lorlatinib is likely

Report section	4.2.6.5, 4.2.8
Description of issue and why the EAG has identified it as important	Treatment beyond the point of progression is anticipated on lorlatinib, but this is not permitted in the model. The model assumed that time on treatment will be equal to PFS, but the Medicines and Healthcare products Regulatory Agency (MHRA) license allows treatment for as long as a patient is deriving clinical benefit. The CROWN study enforced discontinuation at the point of progression, and studies in which treatment was continued beyond progression demonstrated no conclusive benefits. However, in the absence of further treatment options, it is likely that many patients will continue on lorlatinib following clinical progression. Whilst potential benefits cannot be captured in the model, acquisition costs for lorlatinib are likely to be higher than modelled when accounting for this.
What alternative approach has the EAG suggested?	The EAG has presented an exploratory scenario which uses a second-line study on lorlatinib (i.e. in whom there are few further therapies available), where 75.6% of patients continued to receive lorlatinib following progression, for a median additional duration of 5.7 months. The EAG implement this in a simplistic way, which assumes the duration of treatment to be equal to PFS + 5.7 months. This scenario only considers the cost implications for continued treatment, as appropriate data are not available to the EAG to support modifying post progression survival (PPS) to reflect any continuing benefit of treatment.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of the cost of post-progression treatment for first-line lorlatinib increases total costs by [redacted].
What additional evidence or analyses might help to resolve this key issue?	Current evidence only allows cost-effectiveness to be consistently assessed assuming no treatment beyond progression. It is necessary to balance the uncertainty in cost-effectiveness estimates resulting from treatment beyond progression against the desirability of a more restrictive stopping rule in which treatment beyond progression is not permitted. Further analysis incorporating external evidence on post-progression use of lorlatinib could be used to inform both costs and benefits of continuing treatment beyond progression.

Issue 11 HRQoL data from CROWN not reflective of real-world utilities

Report section	4.2.7
Description of issue and why the EAG has identified it as important	The difference in pre- and post-progression utilities collected in CROWN are small and clinically implausible. Post-progression utility data were collected at or near the point of clinical progression in CROWN, so cannot reflect HRQoL associated with progressed disease. The progressed disease utility is much higher than that preferred by committees in previous appraisals. This results in very little benefit associated with preventing progression in the model. The division of utilities by treatment status in the company's regression analysis of CROWN data also meant that patients experiencing a treatment-related adverse event (TRAE) did not contribute to the utility values applied in the model. As a result, reported toxicities associated with lorlatinib were not reflected in the modelled utilities.
What alternative approach has the EAG suggested?	The EAG's preference is to use the utility set from TA670 (brigatinib), noting the discussion in the Technical Report which led to the committee dismissing trial-derived utilities suffering similar issues to those from CROWN. The EAG considers this alternative utility set to more appropriately reflect the impact of progression on HRQoL. To reflect the differential impact of AEs on individual treatment utilities, the EAG also explores the application of AE-related disutilities as proposed in the company's clarification response.
What is the expected effect on the cost-effectiveness estimates?	The use of the TA670 utility set reduces total QALYs for all technologies by ~[redacted] compared to the EAG-corrected company base-case, with an approximately neutral effect upon the cost-effectiveness of lorlatinib. Using the EAG's suggested approach to modelling AE-related disutilities, the total QALYs for lorlatinib are reduced by 0.39 relative to the EAG-corrected company base-case analysis. This reduces its cost-effectiveness relative to alectinib and brigatinib, [redacted].
What additional evidence or analyses might help to resolve this key issue?	The uncertainty related to this issue is largely resolved through the use of the TA670 utility set. Further, evidence on HRQoL of life may however, be of benefit and reduce remaining uncertainty. A consistent approach to modelling AEs with regards to the use of AE durations from comparator trials, and all disutilities taken from the literature may result in a fairer comparison. This was not possible in the timescales of this report.

Issue 12 Dosing calculations and proportion of patients receiving subsequent treatment

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The ERG identified several issues relating to resource use. Detailed dosing information from CROWN was used to estimate the proportion of patients receiving a lower dose of lorlatinib. This approach is inconsistent with the approach used for alectinib and brigatinib where relative dose intensity (RDI) is used to account for dose reductions. For consistency the EAG prefers to use RDI to model acquisition costs for all treatments. The cost of lorlatinib does not scale pro rata with dose. The acquisition costs associated with lorlatinib are therefore dependent on the pack size used. This may be particularly relevant for patients receiving a lower dose of lorlatinib and may increase overall acquisition costs. The company assumes that all patients will receive 2nd line treatment following discontinuation of a 1st line TKI. This is not supported by evidence from CROWN. Clinical advice received by the EAG suggests that the majority of patients (> 80%) would receive further subsequent treatment but not all.
What alternative approach has the EAG suggested?	For consistency the EAG prefers to use RDI to model acquisition costs for all treatments. The EAG prefers to use evidence from CROWN to inform the proportion of patients receiving subsequent treatment following alectinib and brigatinib. This also has an effect on modelled benefits, as the proportion of patients who do not progress onto lorlatinib following alectinib and brigatinib receive PPS outcomes equivalent to the chemotherapy data from PROFILE 1001/1005.
What is the expected effect on the cost-effectiveness estimates?	Using RDI to calculate acquisition costs for lorlatinib increases total costs by [redacted]. By using CROWN to inform the proportion of comparator patients who receive second line lorlatinib, total comparator QALYs are reduced by approximately [redacted], with a reduction in total costs of around [redacted]. This scenario results in a moderate increase in the relative cost-effectiveness of lorlatinib.
What additional evidence or analyses might help to resolve this key issue?	The EAG's preferred approach assumes that all patients will use the 120 x 25 mg pack size. Clinical advice on the use of lorlatinib in current practice, and plausibility of this assumption, would be useful. The EAG's preferred approach assumes that the proportion of patients moving to subsequent treatment will be the same regardless of the first line TKI received (i.e. based on CROWN data). Clinical advice on this assumption would be helpful.

1.6 Other key issues: summary of the EAG's view

None.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Given the high level of uncertainty associated with available trial evidence for lorlatinib, particular consideration has been given to the exploration of the impact of uncertainty upon the estimates of cost-effectiveness. The EAG therefore explore two sets of alternative assumptions which both represent plausible interpretations of the available data and its associated uncertainty. The first is a plausible but reasonably optimistic set of assumptions, while the second represents a more conservative (but still plausible) scenario which places limits on the potential PFS benefits of lorlatinib, better reflects the potentially significant toxicities associated with lorlatinib, and includes the potential costs of treatment beyond progression. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.1.

The results of the EAG's exploratory analyses including the EAG's preferred base case are presented in Table 2 with probabilistic results for the EAG's preferred based case presented in Table 3. The results of the 'conservative' alternative analysis are presented in Table 4 and Table 5.

Table 2 Summary of EAG's preferred assumptions and ICERs

Scenario	Incremental cost (vs brigatinib)	Incremental QALYs (vs brigatinib)	ICER (change from company base-case)
Company's base-case	[redacted]	[redacted]	[redacted]
EAG-corrected company base-case	[redacted]	[redacted]	[redacted]
Scenario 1: Global NMA HRs (including ALESIA)	[redacted]	[redacted]	[redacted]
Scenario 5: Removal of CNS PD health state	[redacted]	[redacted]	[redacted]
Scenario 6: TA670 utilities	[redacted]	[redacted]	[redacted]
Scenario 9: RDI costing method used consistently for all treatments	[redacted]	[redacted]	[redacted]
Scenario 10: Comparator patients progressing onto chemo vs lorlatinib based on CROWN	[redacted]	[redacted]	[redacted]

Table 3 EAG's alternative base-case analysis results (probabilistic)

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

Table 4 Summary of EAG's alternative (conservative) assumptions and ICERs

Preferred assumption	Incremental cost (vs brigatinib)	Incremental QALYs (vs brigatinib)	Cumulative ICER (vs brigatinib)
Company's base-case	[redacted]	[redacted]	[redacted]
EAG-corrected company base-case	[redacted]	[redacted]	[redacted]
Scenario 1: Global NMA HRs (including ALESIA)	[redacted]	[redacted]	[redacted]
Scenario 3b: Treatment effect waning: 10 years	[redacted]	[redacted]	[redacted]
Scenario 4: Arm-specific deaths as proportion of PFS events	[redacted]	[redacted]	[redacted]
Scenario 5: Removal of CNS PD health state	[redacted]	[redacted]	[redacted]
Scenario 6: TA670 utilities	[redacted]	[redacted]	[redacted]
Scenario 7: AE disutility correction & CROWN duration data	[redacted]	[redacted]	[redacted]
Scenario 8: Treatment beyond progression	[redacted]	[redacted]	[redacted]
Scenario 9: RDI costing method used consistently for all treatments	[redacted]	[redacted]	[redacted]
Scenario 10: Comparator patients progressing onto chemo vs lorlatinib based on CROWN	[redacted]	[redacted]	[redacted]

Table 5 EAG's conservative alternative base-case analysis results (probabilistic)

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

EXTERNAL ASSESSMENT REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report the EAG has reviewed the clinical and cost-effectiveness evidence submitted by Pfizer in support of lorlatinib for untreated Anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC).

2.2 Background

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 treatment pathway is presented in Figure 1 of the company's submission Document B (CS). The newer (first-line) positioning of lorlatinib in the treatment pathway is in addition to the earlier marketing authorisation, which was for ALK-positive advanced NSCLC patients whose disease has progressed after prior treatment with an ALK inhibitor. The EAG's clinical adviser broadly agreed with the CS treatment pathway and the proposed positioning of lorlatinib. The Medicines and Healthcare products Regulatory Agency's (MHRA) summary of product characteristics (SmPC) for lorlatinib states that treatment is recommended as long as the patient is deriving clinical benefit without unacceptable toxicity. The EAG's clinical adviser anticipated that patients who experience progression on first-line lorlatinib would continue with lorlatinib if the progression was limited (e.g. to a single site); if progression occurs in multiple sites patients would probably switch to chemotherapy.

The EAG's adviser thought it likely that some clinicians would continue to use alectinib more frequently as a first-line treatment when compared with brigatinib and lorlatinib, considering:

- That alectinib was approved by NICE before brigatinib and lorlatinib
- That clinicians tend to use treatments they are more comfortable with in terms of efficacy and safety trade-offs
- The lack of direct head-to-head data comparing the three ALK inhibitors,
- And assuming that lorlatinib remained as a second-line treatment option

The EAG's adviser also thought that improved central nervous system (CNS) penetration is a key advantage of lorlatinib, so he might prefer lorlatinib as a first-line treatment in, for example, young patients with brain metastases. However, this may be countered by potential increased CNS toxicity with lorlatinib which will also be an important consideration, particularly for patients who may be working and/or have young families.

2.3 Critique of company's definition of decision problem

Population

The company's decision problem addressed a slightly broader population than NICE's final scope in terms of previous treatments received (see Table 6). The EAG's clinical adviser considered the slightly broader population proposed in the CS to be appropriate.

Although most patients (specifically non-squamous NSCLC patients) will receive ALK inhibitor treatment soon after diagnosis and genetic testing, a small number of squamous cell carcinoma patients may at first receive chemotherapy before ALK-positive NSCLC is identified (after which an ALK inhibitor can be started). However, the EAG notes that such patients were excluded from the lorlatinib CROWN trial: patients were not allowed to receive prior systemic NSCLC treatment, including molecularly targeted agents, angiogenesis inhibitors, immunotherapy or chemotherapy (see section 3.2.1.1).

Intervention

The recommended dose of lorlatinib is 100 mg taken orally once daily. ALK testing is routinely performed in the NHS during the diagnosis of NSCLC.

The CS stated that there remains a substantial unmet need for treatments that can penetrate the blood-brain barrier more effectively than currently available therapies (and so target CNS metastases) and that have low susceptibility to ALK resistance mutations.

Comparators

NICE's final scope included alectinib, brigatinib, ceritinib and crizotinib as comparators. The CS considered only alectinib and brigatinib as comparators and provided three main justifications:

- Alectinib and brigatinib are the two most effective and commonly used treatments in this indication in the UK
- TA670[1] excluded ceritinib from the NICE appraisal of brigatinib as first line therapy for ALK-positive advanced NSCLC
- Ceritinib and crizotinib have largely been replaced by more effective ALK inhibitors in this indication

The EAG's clinical adviser agreed that in the NHS first-line alectinib and brigatinib constitute current clinical practice and that ceritinib and crizotinib would very rarely be used to treat ALK-positive advanced NSCLC.

Outcomes

The outcomes reported in the CS covered all the outcomes listed in the NICE scope. The company noted that overall survival (OS) comparisons remain immature with only 18 months of follow-up data available for lorlatinib. The CS stated that OS data were not analysed as of the September 2021 data cut, with March 2020 OS data presented instead. The EAG noted that results for some outcomes were based on the September 2021 data cut, whereas other outcomes were analysed based on the March 2020 data cut. The EAG asked why this was so, in order to allay concerns about possible bias in the selection of reported results. The company supplied the EAG with the CROWN trial's statistical analysis plan which specified a maximum of three analyses for OS. The first analysis has been reported and the second analysis will occur once [redacted] have been reported. It is nevertheless unclear why not all AEs of special interest were reported in the September 2021 data cut.

Table 6 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 untreated ALK-positive advanced NSCLC	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	The population is aligned with the marketing authorisation for lorlatinib of 'adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor'	The EAG's clinical adviser considered the slightly broader population proposed in the CS to be appropriate, although patients who had received prior systemic NSCLC treatment were excluded from the CROWN trial.
Intervention	Lorlatinib	Lorlatinib	-	Lorlatinib's marketing authorisation recommends a once-daily100mg dose. This reflects how lorlatinib was studied in the CROWN trial.
Comparator(s)	Alectinib Brigatinib Ceritinib Crizotinib	Alectinib Brigatinib	• Alectinib and brigatinib represent the two most effective treatments currently available for patients with previously untreated ALK-positive NSCLC and the most commonly used therapies in this indication in the UK. • During the NICE evaluation of brigatinib as first-line therapy for ALK-positive advanced NSCLC (TA670), ceritinib was excluded from the evaluations as it was agreed by the EAG and clinical experts that ceritinib is rarely used (1–2%) in untreated ALK patients. It was concluded that patients with ALK-positive advanced NSCLC who have not had an ALK inhibitor before are usually offered alectinib. • Since receiving positive NICE guidance in 2016, crizotinib usage in this indication has	The EAG's clinical adviser agreed that in the NHS alectinib and brigatinib constitute current clinical practice and that ceritinib and crizotinib would very rarely be used to treat ALK-positive advanced NSCLC.

			predominantly been replaced by more effective second-generation ALK inhibitors. Crizotinib is therefore not considered to be a relevant comparator to lorlatinib in this evaluation; this again follows the precedent from TA670. • Following brigatinib's approval by NICE, which drew upon indirect comparative evidence that it is as effective as alectinib, the vast majority of patients in this setting are anticipated to receive either alectinib or brigatinib only. As such, these two therapies represent the most relevant comparators for this evaluation.	
Outcomes	Overal survival (OS) Progression-free survival (PFS) Response rates Adverse effects HRQoL	Overal survival (OS) Progression-free survival (PFS) Response rates Intracranial outcomes Adverse effects HRQoL	All outcomes listed are relevant in this patient population. However, OS comparisons remain immature at this time with only 18 months of follow-up data available for lorlatinib. Comparisons of OS at similar stages of trial evolution are included in this submission. Interim and final data cut-offs for OS are planned for [redacted] and [redacted].	OS data were particularly immature though the CROWN trial's statistical analysis plan did not permit another interim data cut.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison	Not reported.	Not reported.	The economic analysis aligns with the reference case. See Table 17 for details. Confidential commercial arrangements for all comparator treatments have not been accounted for in the company's analyses. The EAG presents analyses inclusive of available commercial arrangements in a separate confidential appendix to this report.

	may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	-	-	-	-
Special considerations	-	-	-	-

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify all relevant evidence regarding the clinical efficacy and safety of first-line treatments for patients with ALK-positive advanced NSCLC. Details of the review are reported in Appendix D of the CS. In the absence of direct evidence comparing lorlatinib with the relevant comparators, a network meta-analysis (NMA) was conducted (CS Section B.2.9).

3.1.1 Searches

The search strategies to identify studies of lorlatinib and comparator drugs for the treatment of ALK positive advanced NSCLC were included in Appendix D of the CS. Some weaknesses with the company searches were identified by the EAG which could have resulted in missing studies. In particular, searches to identify previous systematic reviews, health technology assessment (HTA) reports and ongoing or unpublished randomised controlled trials (RCTs) were not considered to be adequate for a systematic review.

The EAG also noted that the company searched for non-randomised studies although these studies were not included in the network meta-analysis and no other type of synthesis was undertaken. It is therefore unclear why the searches were restricted to non-randomised as well randomised studies, particularly since previous research has shown that search filters to limit to non-randomised study types are not sensitive enough for use in systematic reviews.[2] The EAG appraisal of the literature searching can be found in Table 7.

Table 7 EAG appraisal of evidence identification

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	A line was found to be missing in the search strategy for Embase and MEDLINE (Table 5, D.1.1, Appendix D, p.17) and it was not clear what date limit had been applied to the April 2021 update searches. Both issues were clarified in the company response to the points for clarification.
Were appropriate sources searched?	PARTLY	- Limited searching for previous systematic reviews. Although the company reported that the references of relevant systematic reviews were checked to identify any further relevant studies it did not report how the systematic reviews were identified. As the search of Embase and MEDLNE was restricted to RCTs and non-randomised studies only, it may have missed relevant systematic reviews. Epistimonikos, a source of systematic reviews, was not searched. - The HTA database and the INAHTA database were not searched. Both databases are key sources for identifying reports of studies from national and international HTA agencies.

		Searching of individual HTA agency websites was not reported. - Trial registers were not searched directly, but some relevant trial register records would have been identified through the search of CENTRAL. However, it is necessary to search trial registers directly for comprehensive identification of trials, including recent additions to the trial registers.[3]
Was the timespan of the searches appropriate?	YES	- The database searches covered the period from inception to 22nd April 2021. - Conference proceedings were searched for the years 2018 - 2021.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	- NSCLC (P) AND (lorlatinib (I) OR relevant comparators (C)) AND (RCTs OR non-randomised/observational studies (S)) - several comparators in addition to alectinib, brigatinib, ceritinib and crizotinib were included in the search strategy. - it was not clear why the searches were limited to non-randomised studies.
Were appropriate search terms used?	PARTLY	Trade names for lorlatinib (Lorbena and Lorviqua), and brigatinib (Alunbrig) were missing from the search strategies.
Were any search restrictions applied appropriate?	PARTLY	See comments below on the study design search filters used to restrict to RCTs and non-randomised/observational studies.
Were any search filters used validated and referenced?	UNCLEAR	- It appears that study design search filters were used to limit to RCTs and non-randomised/observational studies in MEDLINE and Embase. However, no references to particular study design search filters were reported in the submission. -Several search filters were referenced in the response to clarification, therefore it was unclear if the final filters used in the search strategies were validated. In addition, the combining and adapting of several search filters in the search strategies presented is not considered an optimal method of searching comprehensively to identify studies for a systematic review. - The company reported in the response to clarification that the source of the search filters used was the ISSG search filter resource. This resource does not provide recommendations for search filters and includes both validated and unvalidated search filters.

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the SLR of treatment effectiveness were presented in Table 9 of Appendix D. This table indicated that some treatments which were outside of the NICE scope were eligible (e.g. ensartinib). Non-randomised studies were also eligible; it was unclear why non-randomised studies were included in the SLR, given that it was evident from previous STAs that RCT data for comparator treatments were available. Review-eligible non-randomised studies and studies of comparators which were outside of the NICE scope were then excluded from the NMA. The EAG considers it would have been useful for the CS to:

- Describe the need for including non-RCT evidence in the SLR, as it was not subsequently appraised or synthesised in the CS and
- More clearly distinguish between criteria for inclusion the SLR and criteria for inclusion in the NMA (10 RCTs were included in the SLR and 'considered for inclusion' in the NMA, CS Table 19).

Both titles and abstracts, and full-texts, were independently reviewed by two reviewers, with any disagreements resolved via a third independent reviewer. This will have minimised the possibility of errors or bias affecting the screening process.

3.1.3 Critique of data extraction

The data extraction process was performed by one reviewer and independently checked for errors by a second reviewer. This will have minimised the possibility of errors or bias affecting the data extraction process.

3.1.4 Quality assessment

Two independent reviewers assessed the quality of the included trials by evaluating the risk of five key biases: selection bias, performance bias, detection bias, attrition bias and reporting bias, based on NICE's quality assessment checklist (CS Appendix section D.1.8). The results are critiqued in section 3.3. No formal assessment was made of the applicability of the included trials to the NHS setting.

3.1.5 Evidence synthesis

The evidence synthesis presented in the CS was an NMA. Details and further commentary on this analysis and the results are given in Section 3.4.

3.2 Critique of trials of the technology of interest and the company's analysis and interpretation

The company's submission documented one RCT of lorlatinib: the phase 3 CROWN trial (NCT03052608), sometimes referred to as Study 1006 in regulatory documents.

3.2.1 The CROWN trial

3.2.1.1 Methods

Lorlatinib (100mg, oral once daily) was compared to crizotinib (250 mg, oral twice daily) in the randomised CROWN trial, an ongoing phase 3, multicentre, open-label trial of 296 patients with previously untreated advanced ALK-positive NSCLC. Design details and eligibility criteria were reported in the CS in Tables 4 and 5, respectively. The primary outcome was progression free survival (PFS), assessed using blinded independent central review (BICR).

Risk of bias

The quality assessment of the CROWN trial was reported in Section B.2.5 of the CS. The submission stated that the CROWN trial was considered to be at low risk of bias. Although the methodology used appears likely to have minimised the impacts of most biases, the EAG disagrees with this low risk judgement with respect to the possible impact of the open-label (i.e. unblinded) design. More specifically, knowledge of the trial treatment received may influence investigator or patient judgements on subjective outcome measures such as (investigator-assessed) PFS, quality of life and (some) adverse events.

Baseline characteristics of the CROWN trial cohort were reported in Table 6 of the CS, which is reproduced below in Table 8. The EAG's clinical adviser thought that disease stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS), CNS metastases, age and burden of disease (single or multiple sites, volume of disease) might plausibly be considered as possible effect modifier candidates for ALK inhibitors (i.e. within each characteristic, outcomes might differ between subgroups). The CROWN trial stratified randomisation by presence of brain metastases and by ethnic origin (Asian versus non-Asian) to avoid chance imbalances in these characteristics. There were no notable imbalances in the other baseline characteristics, other than the lorlatinib group (median age 61 years) being somewhat older than the crizotinib group (median age 56) and a small difference in the distributions of ECOG PS scores; the lorlatinib group had both slightly more ECOG PS 0 patients (45% vs 39%) and slightly fewer ECOG PS 2 patients (2% vs 6%) than the crizotinib group.

Table 8 Baseline characteristics of patients in the CROWN trial (reproduced from the CS)

Characteristic	Lorlatinib (N=149)	Crizotinib (N=147)
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		
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		
0, n (%)	67 (45)	57 (39)
1, n (%)	79 (53)	81 (55)
2, n (%)	3 (2)	9 (6)
Smoking status		

Characteristic	Lorlatinib (N=149)	Crizotinib (N=147)
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		
IIIA, n (%)	1 (1)	0
IIIB, n (%)	12 (8)	8 (5)
IV, n (%)	135 (91)	139 (95)
Other, n (%)	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 anticancer drug therapy		
n (%)	12 (8)	9 (6)
Previous brain radiotherapy		
n (%)	9 (6)	10 (7)
Brain metastases at baseline		
n (%)	38 (26)	40 (27)

Applicability of the CROWN trial results to the NHS setting

No formal appraisal of applicability (or external validity) was reported 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, although the drug's license is broader, covering patients who have not been previously treated with an ALK inhibitor (i.e. prior chemotherapy is allowed). Although the CROWN trial will not provide efficacy data on the subgroup of patients who have received prior chemotherapy, the EAG's clinical adviser estimated this would constitute <5% of the ALK Tyrosine Kinase Inhibitor (TKI)-eligible population. He also thought that the post-ALK inhibitor outcomes for the prior chemotherapy patients were unlikely to differ from patients who have not received chemotherapy prior to taking an ALK inhibitor. The other trial eligibility criteria appeared largely appropriate and relevant.

Although participants with an ECOG PS score of 0-2 were eligible for inclusion in CROWN, more than 95% of the recruited patients had ECOG PS scores of 0 or 1, so CROWN provides very little data on the efficacy of lorlatinib in patients with an ECOG PS of 2. The EAG's clinical adviser considered that the proportion of patients with an Asian background (44%) is higher than would be

seen in the NHS and that the proportion with adenocarcinoma histology would be higher than 94% in the NHS.

At the September 2021 data cut, [redacted] of patients in the crizotinib arm had received a subsequent treatment, mostly [redacted] (Table 57 of the CS appendices) and [redacted] of patients in the lorlatinib arm had received a subsequent treatment – mostly [redacted]. These treatment sequences seriously limit the applicability of the CROWN trial results to the NHS setting. Firstly, crizotinib is very rarely used to treat this population in the NHS, so the CROWN trial's comparator is obsolete. Secondly, the second-line use of alectinib after lorlatinib falls outside of alectinib's marketing authorisation and thirdly the EAG's clinical adviser considered that a significant proportion of first-line lorlatinib patients would continue to receive lorlatinib after progression, rather than a different ALK inhibitor (see Section 2).

Current and anticipated NHS practice would be to use:

- Alectinib or brigatinib as first-line treatment, followed by lorlatinib at second-line and chemotherapy at third-line (which is current practice). Some patients may continue on lorlatinib after progression. Or
- Lorlatinib as first-line treatment, followed by chemotherapy at second line. Some patients may continue on lorlatinib after progression (and some may receive chemotherapy)

Although 147 patients were randomised to receive crizotinib, five of these patients were not treated with crizotinib (in contrast, all patients randomised to lorlatinib received lorlatinib); in a clarification question the EAG asked the company to state the reasons for this. The company stated that four patients withdrew and one patient was not eligible, was randomised by mistake, and received crizotinib outside of the study. Given the lack of data on subsequent treatments for all five patients, it is unclear whether this small imbalance (likely a consequence of the lack of blinding) would have biased results to slightly favour lorlatinib.

3.2.1.2 Results

Efficacy

Clinical efficacy results for CROWN were presented in Section B.2.6 of the CS. Lorlatinib was statistically significantly more effective than crizotinib for BICR-assessed PFS at the September 2021 data-cut; hazard ratio ([redacted]). The Kaplan-Meier plot is reproduced from the CS below in Figure 1. Intracranial time-to-progression was significantly longer in the lorlatinib arm compared with the crizotinib arm ([redacted]); only first progression events were counted in this analyses – if a patient experienced non-CNS progression and started a new anticancer therapy they were censored, so all patients who experienced a CNS progression event after progression by any other definition were excluded.

No significant difference between groups was found for OS (HR 0.72, 95%: CI 0.41 to 1.25) although these data were immature, being derived from the March 2020 data-cut. The median OS was not estimable in either treatment arm. At the September 2021 data-cut, the BICR-assessed median duration of response was [redacted] in the lorlatinib arm, with around [redacted] of patients continuing to respond at the data cut-off date. The median duration of response in the crizotinib arm was [redacted] months (95% CI: [redacted]).

Lorlatinib was statistically significantly more effective than crizotinib for objective response rate (based on BICR assessment, page 37 CS) and global quality of life (assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]). However, for the EORTC QLQ-C30 the result (a mean difference of [redacted]) was not considered to be a clinically-meaningful difference (CS page 44 – a change from baseline of ≥ 10 points is considered clinically-meaningful).[4] Moreover, it is also possible that the small difference of [redacted] may have been inflated by the impact of detection bias; patients were not blinded to their randomised treatment and may have anticipated feeling greater benefit from lorlatinib. Most of the positive objective responses (based on BICR assessment) were partial responses, with few patients achieving a complete response (CS, Table 13). Partial response was defined as a ≥ 30% decrease in the sum of the longest dimensions of the target lesions (when compared with the baseline sum of the longest dimensions).[4]

Figure 1 Kaplan–Meier plot of PFS based on BICR assessment (September 2021 data cut), reproduced from Figure 3 of the CS

Subgroup results for PFS were reported in section B.2.7 of the CS (page 46). These showed lorlatinib to have [redacted], although there was a suggestion that lorlatinib might be [redacted]. The EAG requested the result of the test for interaction for this analysis, which was [redacted]. A subgroup analysis for ECOG PS (0/1 versus 2) could not be performed as too few participants were recruited with an ECOG PS of 2.

When asked at the clarification stage about the possibility of ethnicity being an effect modifier, the company cited an analysis of lorlatinib pharmacokinetics which found no inherent differences in lorlatinib pharmacokinetics between Asian and non-Asian patients.[5] The EAG notes that the CROWN trial randomisation was stratified according to ethnic origin (Asian versus non-Asian) because a trend for lower activity in non-Asian patients was reported in Study 1001 (which was of lorlatinib for ALK-positive advanced NSCLC patients previously treated with one or more ALK-TKIs – see Section 3.2.2.1).[6] The EAG therefore considers that the current evidence for an ethnicity subgroup effect in patients taking lorlatinib is not compelling. Subgroup analyses comparing patients with an ECOG PS of 0 with those with an ECOG of 1 were not available.

Safety

Data on adverse events (AEs) were presented in section B.2.10 of the CS (page 63). In the CROWN trial (September 2021 data-cut), grade 3 or 4 adverse events occurred [redacted] ([redacted]) than in patients receiving [redacted] ([redacted]). There were also [redacted] serious AEs in the [redacted] arm than in the [redacted] arm ([redacted] vs [redacted]). There were [redacted] all-causality AEs leading to permanent treatment discontinuation in the [redacted]) than the [redacted] ([redacted]). The frequency of all-causality AEs leading to dose reduction or temporary treatment discontinuation was [redacted] for the lorlatinib arm and [redacted] for the crizotinib arm.

'Adverse Events of Special Interest' were reported in section B.2.10.4. of the CS, although the data presented in that section related to the March 2020 data-cut. However, September 2021 data were reported for *some* AEs of special interest in Table 27 of the CS (adapted here in Table 9, where the AEs of special interest are shaded in grey). The following events were graded only up to Grade 3: oedema, weight gain, speech effects and sleep effects.[7] For the following events, there was a notably [redacted] with lorlatinib in the rates of Grade 3 or 4 AEs of special interest, and any grade AEs of special interest: hypercholesterolaemia, hypertriglyceridemia, increased weight and cognitive effects (Table 9).

When evaluating the CROWN trial data, the MHRA noted that hypertension and hyperglycaemia were new lorlatinib safety findings which are now considered as adverse drug reactions (i.e. a causal relationship is either known or strongly suspected).[7] September 2021 data were not presented in the CS for the following AEs of special interest: pneumonitis, QT prolongation, atrioventricular block,

pancreatitis, speech effects, and psychotic effects; examination of the CROWN clinical study report revealed that [redacted].

The EAG asked their clinical adviser about the clinical importance of the AEs of special interest and how lorlatinib's safety profile compares with those of alectinib and brigatinib. The clinical advisor stated that lorlatinib had a different side effect profile to alectinib and brigatinib, and that choosing which ALK inhibitor to use as a first-line treatment would involve a discussion with the patient around the available data to reach a decision, including possible better PFS outcomes with lorlatinib that might not necessarily translate into better OS, set against the different safety profiles. For some patients, the risk of neurotoxicity including risk of peripheral neuropathy or impact on memory, cognitive function and mood may favour alecitnib or brigatinib as first-line treatment.

Table 9 Summary of adverse events (September 2021 data cut) adapted from the CS Table 27

Event, n (%)	Lorlatinib (N=149)			Crizotinib (N=142)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	[redacted]					
Hypercholesterolaemia	[redacted]					
Hypertriglyceridemia	[redacted]					
Oedema	[redacted]					
Increased weight	[redacted]					
Peripheral neuropathy	[redacted]					
Cognitive effects	[redacted]					
Diarrhoea	[redacted]					
Anaemia	[redacted]					
Fatigue	[redacted]					
Hypertension	[redacted]					
Vision	[redacted]					
Increased ALT level	[redacted]					
Constipation	[redacted]					

Mood effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased AST level	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperlipidaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: oedema and increased weight were graded only up to Grade 3[7]

The EAG's adviser added that the management of neurotoxic side effects might be by dose reduction (or discontinuation, if severe). In the CROWN study dose reductions were seen for lorlatinib for [redacted] patients due to peripheral neuropathy, [redacted] patients due to cognitive effects, [redacted] patients due to mood effects and [redacted] due to psychotic effects. [redacted] crizotinib patients had dose reductions for any of these reasons).

In a clarification question, the EAG requested a summary table of rates of AEs of special interest for all other lorlatinib studies. The company responded with a table of event rates for a pooled cohort of lorlatinib CROWN and study 1001 patients (total N=476). However, this table only included a limited number of relevant AEs; the EAG identified the more complete dataset in the lorlatinib MHRA report (see Table 10)[7] which noted that the incidence of (any grade) cognitive, mood, speech and psychotic effects were slightly lower in the CROWN trial than in the study of second-line lorlatinib (Study 1001): 22% vs 29%; 16% vs 24% and 5% vs 14%, respectively. Possible reasons for this were that there was no formal assessment of cognition required in CROWN and that CROWN studied patients at an earlier line of therapy so the patient cohort may have been healthier.

Table 10 Adverse events of special interest reported for a pooled lorlatinib cohort (N=476) in the MHRA Public assessment report[7]

Adverse events of special interest	All Grades n (%)	Grades 3-4 n (%)
Metabolism & nutrition disorders		
Hypercholesterolaemia	386 (81.1)	87 (18.3)
Hypertriglyceridaemia	320 (67.2)	92 (19.3)

Psychiatric disorders		
Mood effects	100 (21.0)	7 (1.5)
Psychotic effects	33 (6.9)	3 (0.6)
Mental status changes	6 (1.3)	5 (1.1)
Nervous system disorders		
Cognitive effects	132 (27.7)	14 (2.9)
Peripheral neuropathy	208 (43.7)	13 (2.7)
Speech effects	39 (8.2)	3 (0.6)
Vision disorder	82 (17.2)	1 (0.2)
Pneumonitis	9 (1.9)	3 (0.6)
Oedema	265 (55.7)	13 (2.7)
Fatigue	130 (27.3)	6 (1.3)
Weight increased	147 (30.9)	48 (10.1)

3.2.2 Other clinical studies used in the cost-effectiveness modelling

3.2.2.1 Study 1001 (informing survival with lorlatinib after progression on alectinib/brigatinib)

Lorlatinib study 1001 data were reported in a published paper by Solomon et al 2018[8] and in the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) report;[6] the published paper did not report OS results. Analyses were based on phase 1 and phase 2 data split into different cohorts. The cohorts differed by previous treatments (ALK inhibitors and chemotherapy) and by the proportion of patients with brain metastases at baseline (see Table 11). In response to clarification question B2 the company stated that they used data from cohorts EXP-3b, EXP-4 and EXP-5. In this pooled cohort the proportion of patients with brain metastases at baseline was high, as was the number of prior ALK inhibitors – most patients will have received two or three prior ALK-inhibitors before receiving lorlatinib, which does not reflect current NHS practice. Given that the OS data from this pooled cohort is used to represent part of the comparator treatment sequence in the cost-effectiveness modelling, it will result in a bias against alectinib and brigatinib. The EAG considers the EXP-3B cohort to be more appropriate, although only 27 patients were included in this group.

The EMA reported that in cohort EXP-3B, the median OS was 21.1 months (95% CI: 12.3 to not reached [NR]) and 60.7% patients were still censored for OS. The survival probability for EXP-3B at 12 months was 69.8% (95% CI: 48.5 to 83.6) and at 18 months was 61.6% (95% CI: 40.2 to 77.2). In pooled cohort EXP-4:EXP-5, the median OS for the 111 ALK-positive NSCLC patients was 19.2 months (95% CI: 15.4 to NR). The survival probability for EXP-4:EXP-5 at 12 months was 67.3% (95% CI: 57.6 to 75.4) and at 18 months was 54.2% (95% CI: 44.0 to 63.2).[6]

Table 11 Efficacy Cohorts of ALK-Positive NSCLC Patients in lorlatinib study 1001 (adapted from Table 27 of lorlatinib EMA CHMP report)[6]

Study Phase	Cohort Name	Cohort Description	Total N	N with Brain Metastases at Baseline (%)
Phase 1*	N/A	Treatment-naïve or pre-treated with 1 or more ALK inhibitor	41	34 (83)
Phase 2**	EXP-3B	1 prior non-crizotinib ALK inhibitor ± chemotherapy	27	12 (44)
	EXP-4:EXP-5	2 (n=65) or 3 (n=46) prior ALK inhibitors ± chemotherapy	111	83 (75)
	EXP-2:3A	Prior crizotinib only ± prior chemotherapy	59	37 (63)

* Dose escalation, ** 100mg once a day

3.2.2.2 PROFILE studies (informing post-progression survival after progression on lorlatinib)

The company stated (in response to clarification question B2) that Ou et al. 2014 (PROFILE 1001/1005)[9] was identified as the best source for chemotherapy as it was the only study that reported the OS of patients who received 'systemic therapy' following progression and discontinuation of crizotinib. However, the ERG report for TA628 (which evaluated second-line lorlatinib) stated that "*The company report that the ALUR and ASCEND5 did not provide any data for OS. However, Appendix D and the publications for ALUR and ASCEND5 indicate that data for overall survival appeared to be available. It is not clear to the ERG why these data were not used by the company*". It is therefore unclear whether the data from Ou et al 2014[9] were the most appropriate data, given that the merits and problems of ALUR and ASCEND5 relative to Ou et al 2014 were not discussed by the company.

Ou et al 2014[9] reports a Pfizer-funded retrospective analysis of a pooled cohort of two single-arm trials of crizotinib: PROFILE 1001 (phase I) and PROFILE 1005 (phase II). Patients who were allowed to continue crizotinib beyond RECIST-defined progression (i.e. those who continued to derive clinical benefit, n=120) were compared with patients who did not continue with crizotinib after progression (n=74). The authors carried out an analysis of the sites of progressed disease. In the absence of standard minimum tumour growth criteria defining individual sites of progressed disease when there are multiple sites of progressing target lesions, they analysed the subset of patients who had progressed disease involving new lesions and/or non-target lesions (n=60 for patients not continuing with crizotinib). The liver (37%) and brain (28%) were the most common sites of progressed disease. By comparison, in CROWN (September 2021 data-cut) 35% of crizotinib patients experienced intracranial progression compared with 6% of lorlatinib patients (CS, Table 16).

The median OS post-progressed disease among patients who did not continue crizotinib but received subsequent systemic therapy (n=37; 5.4 months, 95% CI 3.8 to 12.3) was longer than that of those

who did not continue crizotinib and received no subsequent systemic therapy (n=37; 2.2 months, 95% CI 1.1 to 3.8).

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 evaluate the comparative efficacy of lorlatinib against alectinib and brigatinib.

The company considered ten RCTs identified in the SLR for inclusion in the NMA, six of which were initially deemed not relevant to the decision problem for this appraisal. This included five studies with irrelevant comparators, and one study evaluating a treatment at an unlicensed dose (Table 19, CS).

The ALESIA[10] study of alectinib versus crizotinib was excluded following the feasibility assessment. The company argued this study should be excluded because it only included Asian patients and because it was excluded from the NMA conducted to inform the brigatinib NICE appraisal.[1] Although the ERG for the brigatinib appraisal argued for inclusion of the ALESIA trial, the NICE committee concluded it should be excluded. The Final Appraisal Document (FAD) stated that differences in healthcare systems and subsequent treatment options meant that data from the ALESIA trial were not applicable to the UK population.[1]

The EAG agrees with the company's exclusion of the six studies initially deemed not relevant to the decision problem for this appraisal. However, the EAG and their clinical adviser had several concerns with the exclusion of ALESIA from the NMA in the current lorlatinib appraisal. First, if this assumption was applied consistently across the submission, 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, Section 2.9.1 Table 4). Many sites were conducted in healthcare systems different from the UK such as Japan (17 sites), China (9 sites), Taiwan (4 sites), Hong Kong (3 sites) and Russia (4 sites). Second, PFS is unlikely to be impacted by differences in subsequent treatment options between healthcare systems offered post-progression, even though these factors may impact on the validity of OS estimates (but no NMA was conducted for OS).

At the clarification stage, the EAG requested that the PFS NMA was rerun to include the ALESIA trial. In response, the company repeated that they considered ALESIA to not be generalisable to the UK population, as ALESIA only included Asian patients. Despite this, the company did conduct an NMA including ALESIA as a scenario analysis to provide a 'global perspective' on the effectiveness of lorlatinib against alectinib. The results of the NMA are detailed in the section 3.4.3.

The ALTA-1L trial allowed patients in the brigatinib arm to continue on treatment beyond progression at the discretion of the investigator if there was still evidence of clinical benefit. The ALTA-1L trial of brigatinib versus crizotinib allowed treatment crossover, meaning patients who progressed on crizotinib could go on to receive brigatinib. This crossover, and allowance of treatment beyond progression can confound the OS estimates of brigatinib against crizotinib. Removing ALTA-1L from the OS network would prevent the evaluation of brigatinib against lorlatinib. The EAG consider the inclusion of ALTA-1L to be acceptable, but there is considerable uncertainty with regards to the impact of including data from patients who crossed over from crizotinib to brigatinib.

Risk of bias of studies included in the NMA

The methods used in the company's systematic review have been summarised in Section 3.1. Risk of bias assessments for the comparator RCTs included in the SLR were reported in Table 17 of the CS appendices document. The results showed that none of the included trials used methods to blind patients or caregivers, and so all were at high risk of performance or detection bias (for some outcomes). The ALTA-1L trial was reported as not having adequate allocation concealment; the EAG checked the brigatinib ERG report and found that the risk of selection bias relating to allocation concealment in ALTA-1L was found to be low, although this was unclear from the study publication. The trials included in the NMA therefore all had similar risks of bias.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Overall, the EAG had a number of concerns regarding the transparency and reporting of the NMAs that were conducted as part of this technology appraisal. First, the company provided a number of different inputs for the NMA between the main document and the appendix of the original submission, and in their response to clarification, most of which used different sources that were not adequately cited. In addition, despite EAG's request for full data, inputs and source code used to run all the NMAs, these were not provided. Therefore, it was difficult for the EAG to identify where the NMA inputs were obtained from, which population they were associated with and to validate the results.

3.4.1 Consistency and similarity of trials included in the company NMA

It was not possible to statistically assess the consistency of direct and indirect evidence as there were no loops in the networks, i.e. there were no trials directly comparing lorlatinib, alectinib and brigatinib.

The company's NMA feasibility assessment is summarised in section B.2.9.2 of the CS. Disease stage and ECOG PS were similar in the four (including ALESIA) included trials. The maturity of data included in the NMA was also relatively similar. Data used for the CROWN, ALEX and ALESIA

trials had not yet reached median PFS for lorlatinib and alectinib respectively. Data from the first interim analysis of the ALTA-1L trial where approximately 50% of expected events of disease progression or death had occurred were used.

There were differences between trials in baseline prevalence of brain metastases and prior chemotherapy use. The proportion of patients with brain metastases (see CS Table 21) was higher in the ALEX trial (alectinib=42%, crizotinib=38%) and ALESIA (alectinib = 35%, crizotinib = 37%), than in CROWN (lorlatinib=26%, crizotinib=27%) or ALTA-1L trials (brigatinib=29%, crizotinib=30%). The brigatinib appraisal adjusted for these baseline differences using anchored and unanchored matched adjusted indirect comparisons (MAIC) but no baseline adjustments were conducted in the current appraisal. However, as reported in the FAD for brigatinib, the committee did not consider the indirect comparisons to be reliable, owing to differences in the baseline characteristics of the included population. The company acknowledge that the proportion of patients with brain metastases was low in the CROWN trial and suggest that the differences were considered unlikely to affect relative treatment effects, but do not provide any evidence or justification to support this claim. Clinical advice to the EAG and published evidence suggests that brain metastases are associated with a poorer prognosis and significant morbidities, but it is unclear whether it is an effect modifier. Although the ALEX trial[11] found that the PFS for alectinib did not differ between patients with and without baseline metastases, patients with brain metastases in the brigatinib trial did have a superior PFS (HR: 0.25 [95% CI 0.14 to 0.46]) compared to those without brain metastases at baseline (HR: 0.62 [95% CI 0.43 to 0.91]).[12]

While the CROWN and ALEX trials included only treatment-naïve patients, the ALTA-1L and ALESIA trials also included patients who received prior chemotherapy (ALTA-1L: brigatinib=26%, crizotinib=27%; ALESIA: alectinib = 6%, crizotinib = 15%). However, clinical advice to the EAG suggested that because chemotherapy is not a targeted ALK inhibitor, the impact of previous treatment in this situation is unlikely to impact substantially on effect estimates. This can be seen in the subgroup analysis in ALTA-1L, where the HRs for PFS in patients who had prior chemotherapy compared to no prior chemotherapy did not differ substantially.[12] However, uncertainty remains whether the effect of brigatinib and alectinib identified in the mixed population in ALTA-1L and ALESIA is similar to the efficacy seen when brigatinib or alectinib are given as a first-line TKI.

In the brigatinib appraisal (TA670), population adjustment was made to account for baseline differences between the populations in the ALTA-1L and ALEX trial. Unanchored, anchored and unweighted MAICs were used to compare the efficacy of brigatinib and alectinib, all of which provided similar estimates of PFS. The NMA results for OS varied more, owing to the immaturity of the data. However, the committee considered that it was reasonable to assume equivalence in OS,

based on similar mechanisms of action between brigatinib and alectinib, an increase in PFS and CNS-PFS by brigatinib could be associated with an improvement to OS.

3.4.2 Proportional Hazards Assumptions

In the CROWN study, the company consider that the proportional hazards assumption is violated for BICR assessed PFS, owing to the crossing of the curves in the log-cumulative hazard plot (Figure 11 in the CS), and a significant Schoenfeld individual p-value (p = 0.0181; Figure 12 in the CS). This is further illustrated in the smoothed hazard plot in Figure 14, where the risk of disease progression or death over time reduces for patients receiving lorlatinib but for crizotinib, the risk of progression or death increases before decreasing. The company conclude that is it therefore appropriate to fit separate parametric survival models. The EAG agrees with the company's approach.

For each of the other included trials, the company generated pseudo patient-level data from published Kaplan-Meier (KM) curves in order to assess the proportional hazards assumption. The company assessed the proportional hazard assumption for ALTA-1L and ALEX by inspecting log-cumulative hazard plots, and Schoenfeld residuals. For ALTA-1L, both the log-cumulative hazard plots and Schoenfeld residuals, there is little evidence to suggest that the proportional hazards assumption is violated. In the ALEX trial, the curves on the log-cumulative hazard plot do cross initially but remain relatively parallel after the first 6 months. The company consider that this is likely due to trial protocol, rather than treatment effect. The p-value from the Schoenfeld test is statistically significant, but the company argue that this is likely to be due to the crossing of the curves at the start of follow-up.

The company provided additional arguments for these conclusions in response to clarification question 14. The EAG agree with the company that for the ALTA-1L and ALEX trials, there is no evidence that the assumption of proportional hazards has been violated. The company do not comment on whether the proportional hazards assumption holds for ALESIA. Based on the Kaplan-Meier curves provided in the Zhou et al,[10] the EAG were unable to determine whether the proportional hazards assumption was violated, although the Kaplan-Meier lines do not cross.

3.4.3 NMA results

3.4.3.1 Overall Survival

The company NMA (see CS section B.9.4.2) found [redacted] in OS compared to alectinib (HR [redacted], 95% CrI [redacted]) and brigatinib (HR [redacted], 95% CrI [redacted]). The EAG were able to reproduce these findings (accounting for small simulation error) with the inputs provided to Question A8 at the clarification stage.

Table 12 Overall Survival Inputs

Study	Treatment	N	Inputs in the original CS	
			HR (95% CI)	Source
CROWN	Crizotinib	147	0.72 (0.41, 1.25)	Company Submission, Page 36 DCO: 20 March 2020
	Lorlatinib	149		
ALEX	Crizotinib	151	0.67 (0.46, 0.98)	Mok et al (2020). DCO: 29 November 2019
	Alectinib	152		
ALTA-1L	Crizotinib	138	0.92 (0.57, 1.47)	Camidge et al (2020) DCO: 28 June 2019
	Brigatinib	137		

The company argue that no conclusions should be drawn from these analyses owing to the immaturity of the OS data from the CROWN trial, with only 51 (26%) deaths occurring at the March 2020 data cut-off, meaning that the median OS cannot be estimated. Furthermore, the company highlighted some limitations of the ALTA-1L OS data, that were discussed during the NICE committee for the evaluation of brigatinib (TA670). First, the company consider that in the TA670 appraisal, the committee were concerned with the immaturity of the ALTA-1L trial, and the high crossover from the crizotinib to the brigatinib arm upon disease progression – the impact of which could not be fully analysed due to the immaturity of the data. The company consider that the same limitations apply to this appraisal. The EAG note that whilst additional data cuts for ALTA-1L have since been published,[12] which would have provided more mature OS estimates, the available data were not adjusted for treatment crossover.

Overall the EAG agrees that NMA results for OS suffer from several limitations. However, these results are not used in the economic model.

3.4.3.2 Progression Free Survival

The company provided a range of HRs for PFS that were used to conduct the NMAs, based on different data cut off points and different populations. At the clarification stage, the company said that the inputs provided in the original CS were wrong, as they included only a subgroup of patients who were treatment-naïve, and said that the correct values are shown on Page 29 of Appendix D. These inputs, however, do not correspond to the results provided in the original CS either.

At the clarification stage, the company also provided an additional set of inputs and results (Table 6 and 7 from the response to clarification document), which the EAG could reproduce. This included HRs from the most recent data cut from CROWN (September 2021) and the whole population from the ALTA-1L including previously treated and untreated patients. A summary of the inputs provided in the original company submission, and in the points for clarification response are provided in Table 13.

Table 13 Important BICR-PFS inputs used in the CS and clarification response

Study	Treatment	N	Inputs in the original CS		Inputs provided in Table 6 at clarification	
			HR (95% CI)	Source	HR (95% CI)	Source
CROWN	Crizotinib	147	0.28 (0.191, 0.413)	CROWN - March 2020 DCO	0.280 (0.195, 0.401)	CS Figure 8 – All patients (unstratified) Sept 2021 DCO
	Lorlatinib	149				
ALEX	Crizotinib	151	0.5 (0.36, 0.7)	Peters et al (2017) Supplementary Fig. 1	0.500 (0.360, 0.700)	Peters et al (2017) Supplementary Fig. 1
	Alectinib	152				
ALESIA	Crizotinib	62			0.37 (0.22, 0.61)	Zhou (2019) IRC assessed HR
	Alectinib	125				
ALTA-1L	Crizotinib	138	0.55 (0.34, 0.88)	Camidge et al (2018), Fig 2B (No Prev. Chemotherapy)	0.489 (0.350, 0.680)	TA670 committee papers (Table 12)
	Brigatinib	137				

CS, Company Submission; HR, Hazard Ratio; CI, Confidence Interval; DCO, data cut-off; BIRC, blinded independent review committee.

The company NMA of PFS (see response to clarification, Question A9) found that lorlatinib was associated with an improvement in BICR assessed PFS compared with alectinib (HR [redacted], 95% CrI [redacted] and brigatinib (HR [redacted]).

At the clarification stage, the EAG requested that the company re-run the PFS NMA to include the ALESIA trial. When this was included, lorlatinib still showed an improvement in BICR assessed PFS compared to alectinib, but the effect size had reduced slightly (HR [redacted], 95% CrI [redacted]).

The company also provide input data for investigator assessed PFS for the included studies (Table 14 Investigator assessed PFS inputs cited in the CS Appendix). When the EAG ran the NMA based on the investigator assessed PFS, lorlatinib was associated with an improvement in investigator assessed PFS compared to alectinib (HR 0.57, 95% CrI 0.36, 0.92) and brigatinib (HR 0.49, 95% CrI 0.29,.82).

Table 14 Investigator assessed PFS inputs cited in the CS Appendix

Study	Treatment	N	HR (95% CI)	Source
CROWN	Crizotinib	147	0.21 (0.14, 0.31)	CROWN trial March 2020 DCO
	Lorlatinib	149		
ALEX	Crizotinib	151	0.43 (0.32, 0.58)	Mok et al (2020), Figure 1(A) November 2019 DCO
	Alectinib	152		
ALESIA	Crizotinib	62	0.22 (0.13, 0.38)	Zhou et al, 2019 May 2018 DCO
	Alectinib	125		
ALTA-1L	Crizotinib	138	0.43 (0.31, 0.61)	Camidge et al (2020) June 2019 DCO
	Brigatinib	137		

HR, Hazard Ratio; CI, Confidence Interval; DCO, data cut-off

3.4.3.3 Intracranial Progression Free Survival

The company did not conduct an NMA to evaluate the efficacy of lorlatinib for intracranial PFS compared to alectinib and brigatinib. However, in Appendix D.1.5, the company provide details of intracranial progression-free survival for brigatinib (ALTA-1L), alectinib (ALEX and ALESIA) and lorlatinib (CROWN). The intracranial PFS data provided by the company are based on a subgroup of patients who had baseline metastases and experienced PFS, so does not account for patients without baseline CNS metastases. Furthermore, the EAG consider that the PFS data provided in this section could relate to either systemic (non-CNS) progression or CNS progression. Therefore, the EAG do not consider these inputs to be an accurate representation of the intracranial efficacy of alectinib, brigatinib and lorlatinib.

It was not possible to conduct an NMA of intracranial PFS, owing to differences in the reporting of intracranial outcomes in the relevant studies. The CROWN trial measured intracranial outcomes using time to progression (which does not include deaths as events), compared to ALTA-1L and ALEX trial where intracranial outcomes were assessed using progression free survival (including deaths as events). This was raised by the company in the CS (Section B.2.12.2) as a limitation of the CROWN study and its comparability with the relevant trials. Therefore, the EAG consider the intracranial efficacy of lorlatinib compared to brigatinib and alectinib to be uncertain. Given that there is biological plausibility that lorlatinib could be more effective intracranially compared to older generations of TKIs, the benefits of lorlatinib could be underestimated.

3.4.3.4 Adverse Events

A recent systematic review and NMA of lorlatinib and alectinib found that the incidence of all-grade serious AEs was significantly higher for lorlatinib compared to alectinib.[13, 14] In the original CS, the company did not perform an NMA on the risk of adverse events for lorlatinib, compared to alectinib and brigatinib. At the clarification stage, the EAG requested an NMA on the risk of Grade 3+ AEs for

lorlatinib compared with alectinib and brigatinib. In response the company did not consider an NMA to be of value due to the heterogeneity in the type of adverse events included across the trials, but did provide the frequency of G3+ AEs for each trial, including ALESIA (see Table 10 in the clarification response document). Recently published NMAs that explored the difference in Grade 3+ adverse events between lorlatinib, alectinib and brigatinib are discussed in Section 3.4.4.

The EAG also requested an NMA on results of any grade AEs for peripheral neuropathy, cognitive and mood effects (which were judged to be key AEs by our clinical advisor). However, the company did not conduct an NMA owing to an absence of comparator data on peripheral neuropathy, cognitive and mood effects for brigatinib and alectinib.

3.4.4 Comparison with published NMAs

3.4.4.1 Included studies

There have been three published NMAs[13-15] in ALK-positive NSCLC. Table 15 compares the main results for these published NMAs with the company's NMAs.

Table 15 Comparing the trials included in the CS and published NMAs

Reference	Population	Included trials	NMA method
CS	Previously untreated* (CROWN, ALEX), ALK-inhibitor naïve ± prior chemotherapy (ALTA-1L))	CROWN ALEX ALTA-1L	Bayesian
Wang et al. 2021	Previously untreated*	CROWN ALEX ALTA-1L J-ALEX ALESIA	Bayesian
Wang et al. 2021	ALK inhibitor naïve	CROWN ALEX ALTA-1L J-ALEX ALESIA	Bayesian
Ando et al. 2021	Combination of trials with previously untreated* and ALK inhibitor naïve alone	CROWN ALEX ALTA-1L J-ALEX ALESIA PROFILE 1014 PROFILE 1019 ASCEND-4	Bayesian

Reference	Population	Included trials	NMA method
Chuang et al. 2021	Combination of trials with previously untreated* and ALK inhibitor naïve alone	CROWN ALEX ALTA-1L J-ALEX ALESIA Exalt3	Frequentist

* ALK inhibitor naïve and chemotherapy naïve. Sources: CS Table 20; Ando et al 2021; Chuang et al; Wang et al.

The NMA in Wang et al.[15] had a similar network structure to that reported in the CS but included two further trials (J-ALEX[16] and ALESIA[10]). Chuang et al.[14] included three further trials compared with the CS (J-ALEX,[16] ALESIA[10] and Exalt3[17] (ensartinib vs crizotinib)). Ando et al.[13] included a broader network structure that also included treatments not considered in the company's NMA (chemotherapy and ceritinib). Ando et al.[13] also included the J-ALEX[16] and ALESIA trials.[10]

The EAG believes that the inclusion of the ALESIA trial by both Wang et al. and Ando et al. provides additional relevant data to the decision problem that were not included in the company's NMA. However, the EAG believes that the inclusion of the J-ALEX trial in Wang et al. and Ando et al., where the effect of the lower dose of alectinib (300mg twice daily [BID]) used in J-ALEX was considered equivalent to the effect of the UK recommended dose (600mg BID) and the doses were combined, may contribute to bias or heterogeneity in these NMAs, making them less relevant to this appraisal. Although Chuang et al. also included J-ALEX, the lower dose of alectinib was treated as a separate node and separate relative effects were estimated for each dose, therefore there is no bias or additional heterogeneity due to combining across doses in this NMA.

The EAG judged the inclusion of chemotherapy and ceritinib in the Ando et al. [13 13 13 13 13] NMA would be unlikely to result in additional relevant data to inform NHS decision-making. However, the inclusion of these treatments does not impact the estimates comparing lorlatinib with alectinib and brigatinib due to the lack of loops in the network.

On balance, the EAG consider the Chuang et al.[14] NMA was likely to provide more valid estimates for this appraisal than the other two NMAs.

3.4.4.2 Results

Overall Survival

Chuang et al.[14] did not conduct an NMA for OS.

Progression Free Survival

Similar to the CS, the Chuang et al. NMA found that lorlatinib was more effective than brigatinib (HR 0.57, 95% CI 0.34 to 0.95). However, the published NMA found similar effect estimates for lorlatinib

compared to alectinib (HR: 0.82, 95% CI 0.45 to 1.51). The SUCRA ranking was highest for lorlatinib (93.3%), followed by alectinib (76.8%), brigatinib (38.9%) and crizotinib (0.00%). Differences in the NMA results are likely to be due to differences in the inputs used (for ALEX a more recent data cut-offs were used by Chuang et al.).

Adverse Events

Chuang et al. found that lorlatinib was associated with an increased risk of experiencing ≥ Grade 3 adverse events when compared with alectinib (relative risk [RR] 1.62, 95% credible interval [CrI] 1.24 to 2.12). There were limited differences between lorlatinib and brigatinib (RR 1.07, 95% CrI 0.84 to 1.37). Ando et al. [13 13 13 13 13] drew similar conclusions that lorlatinib was associated with greater risk compared with alectinib (RR 1.92, 95% CrI, 1.49 to 2.48) and similar risk compared with brigatinib (RR 1.18, 95% CrI 0.90 to 1.55) of experiencing ≥ Grade 3 adverse events. However, it is worth noting that in the Ando et al NMA, the J-ALEX trial (where a lower dose of alectinib was given) is included in the estimates of alectinib, and not separated into different treatment nodes.

3.4.4.3 Subgroup Analyses

Table 16 summarises the findings from subgroup analyses of the Wang et al.,[15] Ando et al.,[13] and Chuang et al.[14] NMAs. Potentially important subgroup differences were identified for race (Asian vs non-Asian) and presence of CNS metastases at baseline.

Table 16 Comparing subgroup analyses of PFS outcomes in published NMAs

Subgroup	**Wang et al 2021**[15] Effect estimate vs Lorlatinib (95% CrI)	**Ando et al 2021**[13] Effect estimate vs Lorlatinib (95% CrI)	**Chuang et al 2021**[14] Effect estimate vs Lorlatinib (95% CI)
Age	**Alectinib (300-600mg)**: ≥ 65 years HR 0.86 (0.37 to 1.98) < 65 years: HR 0.57 (0.31 to 1.03) **Brigatinib:** ≥ 65 years HR 0.58 (0.25 to 1.34) < 65 years: HR 0.51 (0.26 to 0.99)	-	-
Sex	**Alectinib(300-600mg)**: Female: HR 0.68 (0.36 to 1.29) Male: HR 0.78 (0.40 to 1.53) **Brigatinib:** Female: HR 0.53 (0.27 to 1.06) Male: HR 0.67 (0.33 to 1.39)	-	-

Subgroup	Wang et al 2021[15] Effect estimate vs Lorlatinib (95% CrI)	Ando et al 2021[13] Effect estimate vs Lorlatinib (95% CrI)	Chuang et al 2021[14] Effect estimate vs Lorlatinib (95% CI)
Ethnicity	**Alectinib(300-600mg)**: Asian: HR 1.39 (0.72 to 2.69) Non-Asian: HR 0.39 (0.20 to 0.77) **Brigatinib:** Asian: HR 0.39 (0.20 to 0.77) Non-Asian: HR 0.35 (0.18 to 0.69)	**Alectinib(300-600mg)**: Asian: HR 1.42 (0.75 to 2.71) Non-Asian: HR 0.39 (0.20 to 0.77) **Brigatinib:** Asian: HR 1.15 (0.46 to 2.86) Non-Asian: HR 0.35 (0.17 to 0.73)	-
Smoking status	**Alectinib(300-600mg)**: Current/Former smoker: HR 1.19 (0.49 to 2.91) Non-smoker: HR 0.61 (0.33 to 1.15) **Brigatinib:** Current/Former smoker: HR 0.80 (0.37 to 1.74) Non-smoker: HR 0.52 (0.26 to 1.05)	-	-
ECOG PS	**Alectinib(300-600mg):** ECOG PS 0/1: HR 0.72 (0.40 to 1.28) **Brigatinib:** ECOG PS 0/1: HR 0.49 (0.27 to 0.90)	**Alectinib(300-600mg):** ECOG PS 0/1: HR 0.77 (0.49 to 1.23) **Brigatinib:** ECOG PS 0/1: HR 0.56 (0.31 to 1.03)	-
CNS metastases	**Alectinib(300-600mg):** No: HR 0.72 (0.40 to 1.28) Yes: HR 0.67 (0.29 to 1.56) **Brigatinib:** No: HR 0.49 (0.27 to 0.90) Yes: HR 0.80 (0.31 to 2.06)	**Alectinib(300-600mg):** No: HR 0.71 (0.40 to 1.23) Yes: HR 0.54 (0.23 to 1.29) **Brigatinib:** No: HR 0.45 (0.23 to 0.86) Yes: HR 1.00 (0.33 to 2.98)	**Alectinib (600mg):** No: HR 0.74 (0.42 to 1.30) Yes: HR 0.75 (0.34 to 1.66) **Brigatinib:** No: HR 0.49 (0.27 to 0.91) Yes: HR 0.74 (0.42 to 1.30)

Ethnicity

In both NMAs comparing Asian and non-Asian subgroups, PFS was higher for alectinib compared with lorlatinib in Asian patients (Wang et al. [15 15 15 15 15]: HR 1.39, 95% CrI 0.72 to 2.69; Ando et al: HR 1.42, 95% CrI 0.75 to 2.71). In contrast, in non-Asian patients PFS estimates favoured lorlatinib over alectinib (Wang et al.: HR 0.39, 95% CrI 0.20 to 0.77; Ando et al.: HR 0.35, 95% CrI 0.18 to 0.69) (Table 16).

Findings from the subgroup analyses comparing PFS for lorlatinib and brigatinib differed between NMAs. Ando et al. found potentially important differences between Asian (HR 1.15, 95% CrI 0.46 to

2.86) and non-Asian patients (HR 0.35, 95% CrI 0.17 to 0.73). It was uncertain whether there were differences in PFS between lorlatinib and brigatinib in Asian patients but PFS was greater for lorlatinib in non-Asian patients. However, Wang et al. found similar effect estimates in Asian (HR 0.39, 95% CrI 0.20 to 0.77) and non-Asian patients (HR 0.35, 95% CrI 0.18 to 0.69). The EAG notes that the current evidence for an ethnicity subgroup effect in patients taking lorlatinib is not compelling (see section 3.2.1.2).

CNS Metastases

There was no evidence that CNS metastases at baseline impacted PFS estimates comparing lorlatinib with alectinib. Wang et al. and Chuang et al. found similar estimates for those with (Wang: HR 0.67, 95% CrI 0.29 to 1.56; Chuang: HR 0.75, 95% CI 0.34 to 1.66) or without (Wang: HR 0.72, 95% CrI 0.40 to 1.28; Chuang: HR 0.74, 95% CI 0.42 to 1.30) CNS metastases. Although Ando et al. reported differences in PFS between lorlatinib and alectinib which were larger in patients with CNS metastases (HR 0.54, 95% CrI 0.23 to 1.29) than in patients without CNS metastases (HR 0.71, 95% CrI 0.40 to 1.23) the 95% CrIs substantially overlap.

In contrast, PFS differences between lorlatinib and brigatinib were potentially impacted by the presence of CNS metastases at baseline. Lorlatinib was more effective than brigatinib in patients without CNS metastases (Wang et al.: [15 15 15 15 15] HR 0.49, 95% CrI 0.27 to 0.90; Ando et al.: [13 13 13 13 13] HR 0.45, 95% CrI 0.23 to 0.86; Chuang et al.: HR 0.49 95% CrI 0.27 to 0.91). However, there was more limited evidence of benefits for lorlatinib compared with brigatinib in patients with CNS metastases (Wang et al.: HR 0.80, 95% CrI 0.31 to 2.06; Ando et al.: [13 13 13 13 13] HR 1.00, 95% CrI 0.33 to 2.98; Chuang et al.: HR 0.74 95% CrI 0.42 to 1.30), although the 95% CrIs for this subgroup were very wide (Table 16).

3.5 Conclusions of the clinical effectiveness section

The evidence presented in the CS on the efficacy and safety of lorlatinib is based on the results of the CROWN RCT. Although this showed that lorlatinib produces statistically significant improvements in response and progression-free survival when compared to crizotinib, this did not translate into clinically meaningful improvements in health-related quality of life. Moreover, the CROWN results have limited applicability to the NHS setting; crizotinib is an obsolete comparator treatment and the ALK inhibitor treatment sequences used in both trial arms do not come close to reflecting either current NHS practice nor future practice (i.e. were first-line lorlatinib to be recommended by NICE). Furthermore, the overall survival data from the CROWN trial are immature and there is currently no evidence that the increased PFS derived from lorlatinib leads to increased overall survival benefit.

Lorlatinib appears to have an unfavourable safety profile when compared to other ALK inhibitors, with CNS toxicity events (any grade) being a particular concern.

Owing to the absence of direct evidence comparing lorlatinib against brigatinib and alectinib the company conduct indirect treatment comparisons. Three trials (CROWN [lorlatinib], ALEX [alectinib] and ALTA-1L [brigatinib]) were included in the company's NMAs. The company considered that a fourth trial, ALESIA (which only includes Asian patients), should be excluded from the NMA owing to differences in healthcare systems and subsequent treatment options. The EAG do not agree with this approach and consider that the ALESIA trial should be included in the PFS NMA, as the impact of subsequent treatment should not affect response to first-line treatment. There were some differences in the baseline characteristics included in the trials, namely the presence of CNS metastases at baseline, and proportion of patients who had received previous chemotherapy. The EAG are uncertain what – if any – impact these will have on the results.

The NMAs found [redacted] in overall survival for patients on lorlatinib compared to alectinib [redacted] and brigatinib [redacted] Owing to the immaturity of the data, no firm conclusions should be drawn from this NMA. Lorlatinib showed significant improvements in BICR assessed PFS compared to alectinib [redacted] and brigatinib [redacted] It was not possible to explore IC-PFS owing to differences in reporting of intracranial outcomes between trials. Finally, despite requesting an NMA on the incidence of grade 3-4 adverse events, the company did not provide an indirect treatment comparison, arguing that it would not be of value owing to heterogeneity in adverse events. The EAG identified a recent, published NMA which found that lorlatinib was associated with an increased risk of Grade 3+ adverse events compared to alectinib (RR 1.62, 95% CrI 1.24, 2.12), but not compared brigatinib (RR 1.07, 95% CrI 0.84 to 1.37).

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. These searches were conducted in August 2018 and were updated in November 2019. The company provide a detailed report of the methods and results of the SLRs in Appendix G, H, and I of the Company Submission.

4.1.1 Searches

The EAG was concerned that more recent evidence was missing from the systematic review. The last searches were carried out in November 2019 and several new economic evaluations may have been published since then. The EAG requested that the company clarify why the searches had not been updated to identify more recent studies. The company stated in their response that the searches were

not updated given the limited potential impact of additional identified studies. Given the pace of research in this area, the EAG considered it highly likely that relevant economic evaluations were missed.

The searches may also have missed potentially relevant economic evaluations due to the way that several study design search filters were adapted and incorporated into the strategies for MEDLINE and Embase. Validated search filters that have been designed and tested for use in the search strategies of systematic reviews of economic evaluations are available and would have been a more reliable method of limiting to economic evaluations, particularly for identifying those published since the NHS Economic Evaluations Database closed in 2015.

4.1.2 Study selection criteria

The criteria applied by the company to assess eligibility for inclusion were described in CS Appendix Table 23 for the review of cost-effectiveness studies, in CS Appendix Table 31 for the Health-related quality of life (HRQoL) review, and in Table 36 for the cost and resource review. Only studies published 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 first-line setting using various listed interventions (found in CS Appendix Tables 23) versus any chemotherapy. There were no specific inclusion criteria in terms of interventions and comparators received in the HRQoL 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 considered 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) was potentially overly restrictive and may have led to relevant studies being omitted from the reviews.

4.1.3 Studies included in the cost-effectiveness review

With regards to the cost-effectiveness review, 20 records were judged to meet the inclusion criteria 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. The company undertook quality assessment of the identified studies but did not provide the referenced 'qualitative synthesis' or discussion of the studies identified or their potential relevance to the decision problem. 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 there have been a number of

studies published between November 2021 and the submission date which assessed the cost-effectiveness of lorlatinib as a first-line therapy in this population.

Thirteen articles were included from the main searches of HRQoL 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 Table 32. The company only extracted data from full economic evaluations, rather than from trials and observational cohorts as stated in the selection criteria. The company did not validate the utility values adopted in their model against those identified in these searches, the EAG therefore provides a summary comparison in Section 4.2.7. However, the company includes a scenario analysis in which the utility values from the NICE appraisal of alectinib (TA536) were applied. It is unclear whether the omission of studies other than economic evaluations will have led to relevant utility data being missed.

Twenty-four unique studies were judged to meet the inclusion criteria, 15 of which were extracted in this review. The results are presented in full in CS Appendix Table 41. As with the HRQoL review, the company appeared only to extract data from full economic evaluations, rather than any studies reporting costs and/or resource use as stated in the selection criteria. The impact of the *post hoc* omission of other types of studies is unclear.

4.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

4.2.1 NICE reference case checklist

Table 17 summarises the EAG's assessment of whether the company's economic evaluation meets the NICE reference case and other methodological recommendations.

Table 17 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 adequately captured lifetime costs and benefits.
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.* mapping algorithm.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D data directly obtained from patients in the CROWN trial. Unlikely to adequately represented HRQoL 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.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

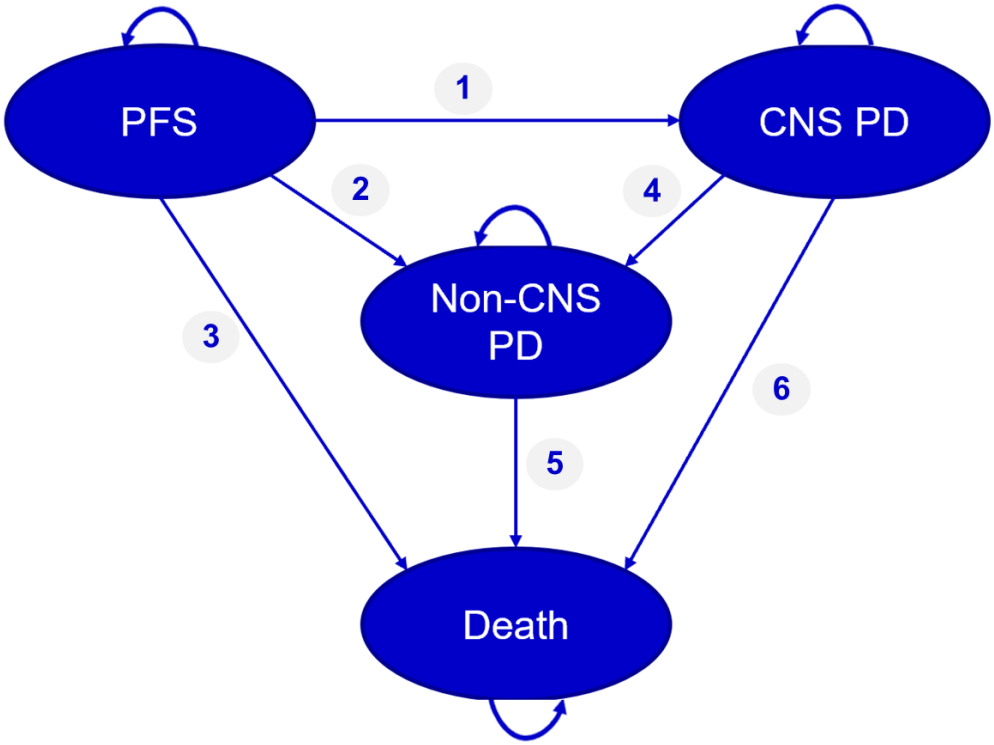
The model outlined in the CS was based on a four-state partitioned survival model (PSM) or "area under the curve" model to assess the cost-effectiveness of lorlatinib versus relevant comparators in untreated ALK-positive NSCLC. In this original PSM, four health states were defined: Progression free, non-CNS progressed disease (PD), CNS PD and death. Health state membership was determined from a set of non-mutually exclusive survival curves, derived from time-to-event data from the CROWN trial and adjusted using PFS hazard ratios derived from the NMA described in Section 3.4.3.2 for the comparators. In an exception to the broad approach lorlatinib OS rate was not estimated within the model or informed by an NMA, but instead calculated externally and imposed upon the model results retrospectively. The target life years achieved on each treatment was based on the use of median PFS from sources representing first line lorlatinib, and summed median PFS based on first-line alectinib/brigatinib followed by second-line lorlatinib. This calculation resulted in a target life years (LY) benefit of [redacted] over alectinib. An exponential function was then applied to model OS, with Excel's 'Goal Seek' function used to adjust the exponential rate until the model generated the appropriate LY increment for lorlatinib.

The EAG did not consider the original model methodologically robust. The model lacked transparency and any flexibility to explore alternative extrapolations of trial data. The model also did not fully reflect NHS practice and resulted in projections which were incompatible with the evidence from the trial data over equivalent timescales. Importantly, the model, could not probabilistically represent the uncertainty associated with the methods used to calculate OS benefits. The lack of a meaningful PSA or flexibility to undertake scenario analysis meant the model could not represent decision uncertainty, and specifically could not reflect the significant uncertainty generated as a consequence of the immature survival data available from CROWN.

These significant concerns with the company's approach were described to the company at the clarification step and the company responded by providing a heavily revised model. The revised model used a hybrid approach based on a PSM, but also included functionality for a pseudo-state-transition approach to modelling post-progression survival. In contrast with the original model, this approach leveraged more mature data from second-line studies Study 1001 and PROFILE 1001/1005 to estimate post-progression outcomes for alectinib/brigatinib, and lorlatinib, respectively. The use of these data represents an important change and helps to align the model with NHS practice, and better reflects the range of treatments receive post-progression.

The structure of the re-parameterised PSM (as described by the company) is depicted in Figure 2. It comprised four mutually exclusive health states: (i) progression free health state (including those on treatment but pre-progression), (ii) non-CNS PD, (iii) CNS PD, and (iv) death, which is an absorbing state. Note several of the transitions depicted in Figure 2 do not exist in the economic model submitted, and will be discussed below.

Figure 2 Model structure (Clarification Response Part B, Figure 1)



The transition probabilities between health states are labelled in the model schematic in Figure 2. For each transition as labelled, the following data were used:

(1) CNS-PFS estimated from parametric models fitted to CROWN trial data. For alectinib and brigatinib, the crizotinib curve was adjusted using the PFS HRs from the NMA.

(2) Using the PFS curve from parametric models fitted to CROWN trial data and as in (1), the NMA conducted by the company as discussed in Section 3.4.3;

(3) The transition representing death in progression-free patients was not accounted for in the model. Meaning patients were only at risk of death once they had transitioned into the CNS- and non-CNS PD state.

(4) This transition is conceptually backwards – patients with non-CNS PD should be able to develop CNS metastases and move to the CNS PD state. More importantly, this transition was not populated in the model, meaning that patients could not develop CNS metastases following disease progression elsewhere.

(5 & 6) An exponential transition rate based on survival analysis conducted on second-line OS data from Study 1001 (second-line lorlatinib) & PROFILE 1001/1005 (chemotherapy) to represent post-progression survival as explained in Section 4.2.6.5.

Points for critique

As outlined above, the original company model was based on PSM while the revised model introduces elements of a state-transition model (STM), specifically in the modelling of post-progression survival (PPS). This represents an important change to how state occupancy is determined and how transition probabilities are generated. In a PSM, transitions between health states are not explicitly modelled, with state occupancy instead determined directly by the trial-derived survival curves using an area under the curve approach. This contrasts within a STM, where state occupancy is a function of the transition probabilities applied to each health state, with explicit state transition probabilities modelled.

Economic evaluations in oncology typically do not adopt a STM approach as their implementation can be more complicated, and they typically require specific structural assumptions about the relationship between PFS and PPS, often imposing a surrogate relationship between PFS and OS. However, the STM approach offers a range of advantages over PSM in the current context, allowing for greater flexibility and to overcome several limitations of the current evidence base. Specifically, an STM approach offers two important advantages. Firstly, a weakness of the current evidence base is that OS data, from CROWN, ALEX and ALTA-1, are heavily confounded by the range of treatments received following progression, which do not reflect NHS practice. A STM allows for alternative, more representative data to be used to model PPS, and can therefore better reflect current NHS practice. Secondly, the flexibility offered by an STM can overcome inconsistencies in available survival evidence which are more likely when evidence is immature. A typical example of this would be the crossing of PFS and OS curves. This cannot occur in a STM, as OS data is not directly used in the model and instead a structural relationship is imposed between PFS and OS.

The EAG considers the additional functionality offered by a pseudo-STM to be a positive addition, that substantially increases transparency and overcomes several limitations associated with company's original model. More broadly, the EAG considers the use of an STM approach most appropriate given the limitations of the current evidence base. However, while this reparametrized model represented an improvement on the original company model, primarily because it allowed for an assessment of the structural uncertainty of the model and the claimed effects and benefits by the company, the EAG notes several issues.

Death PFS events not modelled

Progression-free survival is a composite endpoint, where an event can be either progression or death. In the company's resource use calculations, costs incurred following the point of progression were adjusted according to the proportion of PFS events that were death. That is to say, patients whose PFS event was death incurred none of the costs associated with treatment or management of the PD health state. The company did not, however, adjust the health state transitions in the same way, meaning that all PFS events were counted as progression, and no patients could die in the PFS health state. This is inconsistent with the model schematic and leads to an overestimation of QALY gain across all treatment arms as well as an underestimation of total costs.

The EAG assumed this to be a modelling error, and a correction was made in line with the company's approach to calculating deaths as a proportion of PFS events, with [redacted] of progression events assumed to be death across both arms. The EAG did not agree with this interpretation of the data observed in CROWN, which involved summing the death and progression events across both arms and applying the same proportion to both. The proportions differed markedly between treatment arms in CROWN, with [redacted] ([redacted]%) of events in the lorlatinib arm being death, compared to only [redacted] ([redacted]%) on crizotinib. The EAG notes that the value for crizotinib more closely resembles that on brigatinib in the ALTA-1L trial (5.1%), than does the lorlatinib value. The EAG therefore presents a scenario in which treatment arm specific values are instead used (Section 6.2).

The EAG further notes that the company assumed [redacted] of CNS-PFS events were death in the modelled resource use calculations. This figure could not be replicated by the EAG using the figures provided in the submission, and it was also unclear whether or not deaths were censored in the intracranial time to progression data applied in the model. Table 16 of the company submission lists death as a censoring condition in the analysis of IC-TTP, if this were the case, it would be inappropriate to further adjust costs and transition probabilities to account for death as an event, as deaths would already be accounted for in the underlying data.

Issues with the independent modelling of CNS-PD;
No link between non-CNS PD and CNS PD

The EAG agrees that conceptually there should be patients who experience disease progression which is later followed by the development of intracranial metastases. This transition is depicted in the model schematic and was described in the company submission (i.e. the reverse of transition 4 in Figure 2). However, such a link is not built into the model. The EAG does not consider the available data from CROWN appropriate to inform transitions between the non-CNS PD and CNS PD health states. Upon progression, patients in CROWN received a range of anticancer therapies. This means that data for patients who experienced CNS progression after a non-CNS progression will be confounded by the subsequent treatments received. Further, it is not clear if appropriate data were

captured in CROWN, as patients with non-CNS progression events appear to have been censored in the IC-TPP analysis, and therefore post non-CNS progression events are not captured in the company's CNS-PFS analysis.

This means that only first progression events were counted – if a patient experiences non-CNS progression they generally start a new anticancer therapy in the trial, and are then censored from the CNS-PFS analysis. This is methodologically correct as future outcomes would be contaminated by subsequent treatment lines. However, as a consequence, essentially all patients who experienced a CNS progression event after progression by any other definition were not included in this dataset.

Because of the HRQoL benefits of preventing the development of CNS metastases, and the biologically plausible mechanism for superior outcomes on lorlatinib, this is a significant gap in the model, but also the evidence base itself. This represents one of several fundamental flaws with the CNS-PD health state, and indeed the concept of a four-state model structure as adopted by the company. As will be further discussed below, the EAG prefers the removal of the CNS PD health state in the economic model. This has implications working both in favour of and against lorlatinib, however, assessment of the relative effectiveness of lorlatinib and the key comparators for reducing the development of CNS metastases in patients with non-CNS PD would be very challenging if not impossible given the differences in outcome assessment between the pivotal trials.

The time to development of CNS metastases is modelled using the CNS-PFS survival curve from CROWN. There was no flexibility to adopt alternative assumptions regarding the benefits of lorlatinib versus alectinib/brigatinib, despite scant evidence to support benefits of the magnitude modelled. The EAG has concerns about this modelling as there is little flexibility to evaluate uncertainty associated with the very optimistic CNS-PFS outcomes (see Table 18). The EAG further notes that the company's base-case analysis predicts that a significant proportion of lorlatinib patients will remain free from CNS-progression for the entire time horizon, while in the comparator treatments (alectinib and brigatinib) less than 1% of patients remain free from CNS-progression at 20 years in the exponential distribution adopted by the company. This represents both an optimistic interpretation of lorlatinib CNS-PFS and a pessimistic interpretation of CNS-PFS on alectinib and brigatinib, for which observed data is clearly more positive. As discussed in Section 4.2.6.4, the EAG does not consider the evidence presented to substantiate the modelled benefits, and for a number of reasons described in this section considers it appropriate to remove the CNS-PD health state from the model in its entirety.

Table 18. Lorlatinib modelled CNS-PFS from fitted parametric models

	Modelled landmarks					
Distribution	**1 year**	**5 years**	**10 years**	**15 years**	**20 years**	**30 years**
Exponential	93.4%	71.2%	50.4%	35.7%	25.3%	12.7%

Gompertz	89.5%	80.3%	79.7%	79.7%	79.6%	79.6%
Log-logistic	91.0%	75.6%	64.9%	57.8%	52.6%	45.1%
Log-normal	90.8%	76.2%	67.1%	61.2%	56.9%	50.7%
Weibull	91.2%	75.5%	63.2%	54.4%	47.5%	37.2%
Gamma	91.4%	75.3%	62.0%	52.0%	44.2%	32.4%

Incomplete depiction of CNS-progressed health state

The model assumes that all patients enter the model free of progression – intracranial or otherwise. Approximately one quarter of patients in CROWN had brain metastases at baseline, where in ALTA-1L this was 29% for brigatinib and 42% for alectinib patients in ALEX. In assuming no patients have CNS metastases upon entry into the model, potential differences in benefits for inducing remission in pre-existing intracranial involvement cannot be captured. As discussed previously, the model can only capture a CNS progression event if it occurs after entering the model and *before* any other progression event.

Inappropriate application of PPS data to CNS-PD health state

As discussed in greater detail in Section 4.2.6, the EAG does not consider the use of data from Study 1001 and PROFILE1001/1005 appropriate to estimate PPS outcomes for the CNS-PD population. These studies comprise a mixed population of patients with and without CNS metastases at study entry. The prognosis of patients with intracranial metastases is inferior to the general population of patients with progressed disease, thus the application of PPS outcomes from a population with a better average prognosis will serve to overestimate the QALY gain in these patients.

The studies used to estimate PPS outcomes adequately represent the cohort of patients who experience progression in the model with regards to site of progression. It therefore may be more appropriate to simply assume that the outcomes of patients in the non-CNS PD health state represent all modelled patients.

Whilst the EAG does not disagree in principle with the inclusion of the CNS PD health state, the EAG does not consider it possible to appropriately parameterise the transitions in or out of this health state given the data available. To model the CNS-PD health state with the data available is inappropriate and misleading. Whilst immaturity of data presents a key issue, this is unlikely to be resolvable with more mature data from CROWN due to the censoring of this outcome and the corruption of the treatment effect achieved by the study drug versus subsequent treatments received by progressed patients. The EAG therefore consider it most appropriate to remove the CNS PD health state in its entirety. This scenario is explored in Section 6.2.

4.2.3 Population

The modelled population considered in the base-case analysis was adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor. This population aligns with the marketing authorisation for lorlatinib and the NICE scope. The modelled population is based upon CROWN study data (n= 296).[4] The clinical effectiveness data used in the model were derived from the CROWN trial for lorlatinib, and from the ALEX and ALTA-1 trials for alectinib and brigatinib respectively (see Section 4.2.6). The baseline characteristics of the modelled population are presented in Table 19 and include age, sex, weight, height, percentage of patients on lorlatinib at baseline, percentage of patients with brain metastases at baseline, proportion of PFS events that are deaths, and proportion of CNS-PFS events that are deaths. Age and percentage of patients on lorlatinib at baseline were used to adjust the utility values for HRQoL in the model as explained in Section 4.2.7.

Table 19 Baseline patient characteristics of modelled population

Characteristic	Modelled population
Age	[redacted]
Sex	59.12% female
Weight	[redacted]
Height	[redacted]
Percentage of patients on lorlatinib at baseline	[redacted]
Percentage of patients with brain metastases at baseline	[redacted]
Proportion of PFS events that are deaths	[redacted]
Proportion of CNS-PFS events that are deaths	[redacted]

Points for critique

Consistency of trials included in the NMA

The EAG reiterates an issue raised in Section 3.3 regarding the exclusion of the ALESIA study to inform effectiveness estimates for alectinib in the NMA, on the basis of the population composition. As discussed in Section 3.4 and Section 4.2.6, the company did not consider the inclusion ALESIA appropriate, noting differences in care practices and subsequent treatments availability between Asian and European centres. The EAG acknowledges the potential for such differences, but notes that there is no evidence to suggest that these would impact on relative (as opposed to absolute) effectiveness, particularly for PFS which is the only outcome measure directly used in the economic analysis. The EAG further notes that a substantive proportion of sites in the CROWN study were based in Asia and this is in contrast with the ALTA-1 study. The inclusion of ALESIA may therefore act to make the evidence base for alectinib and lorlatinib more comparable. In Section 6.1 the EAG presents a scenario in which hazard ratios for PFS are drawn from the NMA which included both the ALESIA and ALEX studies to inform the effectiveness of alectinib.

The EAG also reiterates a further issue raised in Section 3.4.1 regarding the comparability of the baseline characteristics of the trial populations included in the NMA. Specifically, the EAG is

concerned that discrepancies in the proportion of patients with CNS metastases at baseline may be indicative of a different average prognosis and potential treatment effect between the populations. This is particularly relevant to the comparison of lorlatinib and alectinib. Reported baseline CNS metastases were substantively higher in the ALEX trial (alectinib=42%, crizotinib=38%) compared to the CROWN study (lorlatinib=26%, crizotinib=27%). It is widely accepted that CNS metastases are associated with poorer prognosis but it remains unclear whether CNS metastases are an effect modifier due to the small samples included in these trials.

4.2.4 Interventions and comparators

As described in Section 2.2 lorlatinib is a selective small molecule inhibitor of ALK and ROS1 RTKs, that is capable of crossing the blood-brain barrier.[18] The marketing authorisation granted on 23rd September 2021, permits the use of 100mg or 25mg film-coated tablets as a monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) not previously treated with an ALK inhibitor, or whose disease has progressed after prior treatment with an ALK inhibitor.

The recommended dose of lorlatinib in adults is 100 mg (as a single tablet or 4 x 25 mg), administered orally. Patients in the CROWN trial received 4 x 25 mg until confirmed disease progression assessed by blinded independent central review (BICR), patient refusal, patient lost to follow-up, or unacceptable toxicity, whichever comes first. Lorlatinib treatment is implemented in the economic model as per its use in CROWN trial, i.e.,100mg administered once daily.

The NICE scope identified several relevant first- and second-generation ALK inhibitor comparators following diagnosis of ALK-positive advanced NSCLC; crizotinib (TA406), ceritinib (TA500), alectinib (TA536) and brigatinib (TA670). In addition, lorlatinib is already offered within the NHS as a second-line ALK TKI following treatment with alectinib, brigatinib, or ceritinib, or as a third-line ALK TKI where crizotinib is used first line followed by either brigatinib or ceritinib as a second-line ALK TKI (TA628).

The company's submission did not include crizotinib or ceritinib as comparators in the economic analysis, reasoning that their use as a first-line therapy is now extremely limited in NHS practice. The company argued that in the UK, crizotinib has predominantly been displaced by more effective second-generation ALK inhibitors, and therefore it is not considered to be a relevant primary comparator for this evaluation. Similarly, the company cited clinical experts consulted during the NICE appraisal for brigatinib (TA670), who suggested that only 1–2% of patients with ALK-positive advanced NSCLC receive ceritinib in UK NHS practice.[1] The comparators as modelled by the company were therefore alectinib and brigatinib, which were also administered until confirmed disease progression or unacceptable toxicity, whichever comes first. Alectinib is modelled as a BID

dose of 600 mg (total daily dose of 1200 mg), and brigatinib is modelled at a once daily dose of 180 mg.

In all treatments, time on treatment (ToT) was assumed to be equal to PFS. This is somewhat inconsistent with CROWN and other relevant pivotal trials. Importantly, the model does not permit treatment beyond progression.

Lorlatinib and chemotherapy were assumed to comprise subsequent treatment after alectinib or brigatinib. In the model, chemotherapy comprised pemetrexed plus cisplatin for a duration of 6.30 weeks. 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[19] as described is Section 4.2.8.

Points for critique

Exclusion of ceritinib and crizotinib as primary comparators

The EAG considers the interventions and comparators included in the economic model to be broadly appropriate and consistent with the decision problem. The EAG's clinical advisor agreed with the exclusion of crizotinib and ceritinib as primary comparators as they are now rarely used in the UK. A small number of patients may still use crizotinib due to toxicity concerns, or if they have used crizotinib historically. Alectinib and brigatinib are the preferred first-line ALK TKIs for new patients presenting in current NHS practice. Clinical advice suggests that alectinib is much more widely used compared to brigatinib and may dominate the UK market.

Time on treatment

The EAG considers the company's use of PFS to determine ToT to be reasonable and the most appropriate assumption for use in the base case. The EAG, however, notes two points regarding this assumption.

Firstly, this assumption creates a disconnect between modelled costs and the treatment effects used in the model, which are inferred from the relevant pivotal trials. In this regard, it is worth noting that ToT does not perfectly align with PFS in CROWN, ALEX, or ALTA-1. In CROWN and ALEX, ToT undercuts PFS, reflecting that a proportion of patients discontinued treatment due to AEs and other tolerability issues. In ALTA-1, time on treatment exceeds PFS due to differences in trial design between CROWN, ALEX and ALTA-1, where ALTA-1 permitted treatment beyond progression but CROWN and ALEX did not.

Secondly, the company asserts that this assumption is conservative concerning lorlatinib. The EAG accepts that in terms of representing the underlying trial data, this assumption leads to an

overestimation of total costs for lorlatinib as time on treatment was on average shorter than PFS. However, this assumes that no patients will continue treatment beyond progression, which as described above, is likely to occur in practice given the licence phraseology. Furthermore, in relative terms the picture is more complicated, and the EAG does not consider this assumption to necessarily be conservative in the way described by the company. The impact of this assumption will be dependent on relative acquisition costs between the TKIs, and the degree to which ToT undercuts PFS. In this regard, the EAG notes that a higher proportion of patients in ALEX and ALTA-1 discontinue treatment due to AEs than in CROWN (7.4% lorlatinib, 11% alectinib, and 12.5 % brigatinib). The reason for this is unclear, and is arguably at odds with the AE profile associated with lorlatinib which may be worse than that of either alectinib and brigatinib, see Section 3.4.3.4. Nonetheless, the observed data indicate that more patients are likely to discontinue treatment prior to progression when receiving alectinib and brigatinib compared with lorlatinib. The assumption that ToT is equal to PFS therefore creates a disconnect between the trial efficacy data for alectinib and brigatinib, and the costs incurred in the model. This may result in the model overestimating the costs for the comparators, and inflating the relative cost-effectiveness of lorlatinib. Moreover, the availability of subsequent TKIs in patients receiving either alectinib or brigatinib in NHS clinical practice may further exaggerate this effect, as patients initiating 1st-line lorlatinib have fewer 2nd-line treatment options available. The net effect of this assumption on costs is uncertain, and it is plausible that this assumption underestimates incremental costs in favour of lorlatinib.

Treatment beyond progression

The company's base case analysis does not permit patients to be treated beyond progression. This aligns with the CROWN trial and therefore is consistent with the effectiveness data used in the economic analysis. This assumption is, however, inconsistent with the MHRA marketing authorisation for lorlatinib, which states that patients may continue to receive treatment "*as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity"*. Clinical advice received by the EAG stated an expectation that many patients would be treated beyond the point of clinical progression, and noted that this was consistent with historical practice for other TKIs used in the treatment of ALK-positive NSCLC. The EAG's clinical adviser noted that, in practice, the point of progression is essentially a technicality, and lorlatinib may continue to provide clinical benefit for many patients beyond this point. The EAG also notes that in the previous TAs for crizotinib, alectinib, and brigatinib treatment beyond progression was assumed to occur.

The EAG requested that the company comment on the plausibility of patients receiving treatment beyond progression. The company's response stated an expectation that patients will not be treated beyond progression and that Blueteq criteria may be developed to imply treatment should not continue beyond progression. The company also suggested that further information on the use of

lorlatinib beyond progression is likely to become available with time, citing the recent Ou *et al*. (2022) publication,[20] which showed that of 74 patients receiving lorlatinib at second-line (post one 2nd generation TKI), 56 continued to receive lorlatinib following progression, with a median additional duration of 5.7 months (95% CI 0.8 – 32.7). The clinical adviser to the EAG considered this a reasonable duration for treatment beyond progression in NHS practice. However, this study found no statistically significant difference between the OS of those who continued treatment beyond progression and those who did not.

While the EAG acknowledges that the modelled base-case analysis is consistent with stopping rules implemented in CROWN, the clinical advice received by the EAG and previous NICE precedent on this issue suggest that it is likely that treatment beyond progression would occur in clinical practice. The EAG recognises that Blueteq criteria could be worded in such a way to restrict access beyond progression, but consider that the marketing authorisation does indeed permit treatment beyond progression and patients may benefit from this. Given the available evidence, the EAG considers it important to consider the uncertainty associated with the current assumption, noting that the company failed to respond to a request to implement such a scenario. The EAG, therefore, presents additional scenario analysis in Section 6, in which treatment beyond progression is permitted. In interpreting these scenarios, the EAG notes there is no evidence to indicate how treatment beyond progression will impact the effectiveness of lorlatinib, and therefore this analysis explores only cost implications. It is therefore necessary to balance the uncertainty in cost-effectiveness estimates offered by these scenarios against the desirability of a more restrictive stopping rule in which treatment beyond progression is not permitted.

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide,[21] the company's analysis adopted an NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5%. The impact of alternative discount rates for costs and QALYs (6% & 0%) were explored in scenario analysis.

A lifetime horizon of 30 years was chosen to capture all relevant differences in costs and benefits between comparators. The impact of a shorter 20-year time horizon and longer 40-year time horizon were also explored in scenario analysis. 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. Although few patients are expected to be alive at this time, the extrapolation method adopted in the submitted company model results in improbable predictions. A conservative extrapolation of OS (Weibull) predicts that [redacted] of the population is alive at 30 years, and in the most

optimistic extrapolation (generalised gamma), [redacted] of the population is alive at 30 years. This is discussed further in section 4.2.6.

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 model provided by the company in their clarification response was a hybrid partitioned survival model informed by survival analysis undertaken on data from several sources. The model comprised four health states; progression-free survival, non-CNS progressed disease, CNS progressed disease, and death. This model represents a re-structure of that presented in the original submission, which is summarised in Section 4.2.2.

The primary source of PFS and CNS-PFS data for lorlatinib, alectinib, and brigatinib, was the CROWN trial, and the NMA described in Section 3.4. In the absence of sufficiently mature and unconfounded OS data on patients treated with lorlatinib at first line, post-progression survival was informed by data from two second-line studies – PROFILE 1001/1005 and Study 1001. The outcomes of patients who received chemotherapy following progression on first line lorlatinib were modelled using data from the former. The second-line Study 1001 was used to inform survival following progression on alectinib and brigatinib for patients receiving second-line lorlatinib.

The efficacy of the comparator treatments in terms of PFS and CNS-PFS was based on parametric survival curves fit to time-to-event endpoints from the crizotinib arm of the CROWN trial, which were then adjusted using hazard ratios generated from the NMA. As described in Section 3.4, the company did not include the ALESIA study for alectinib in the network.

4.2.6.2 Progression-free survival

Due to the immaturity of the PFS data available in CROWN, it was necessary to extrapolate the available BICR PFS data for lorlatinib and crizotinib using standard parametric models. Occupancy of the progression-free health state in the economic model was estimated directly from parametric curves fitted independently to each arm of the CROWN study. Progression-free survival on alectinib and brigatinib was calculated by adjusting the crizotinib curve using the hazard ratio between crizotinib and each drug from the NMA.

The company's base-case analysis used an exponential curve to extrapolate lorlatinib PFS. The exponential curve had the worst statistical fit in terms of AIC and BIC. However, the EAG notes that the exponential curve represents the most pessimistic extrapolation of available PFS data for lorlatinib. Table 20 presents a comparison of the predictions generated by each parametric model for PFS at time points between 1 and 30 years, i.e. the end of the base-case time horizon. Figure 3 compares these extrapolations graphically.

Table 20 Proportion of progression-free patients predicted by company's PFS extrapolation – lorlatinib (based on company's economic model)

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3 Comparison of PFS extrapolations – lorlatinib (based on company's economic model)

[redacted]

The exponential curve was also applied in the model for the crizotinib arm for consistency with lorlatinib and with NICE DSU recommendations to use a consistent distribution across treatment arms. Again, this distribution had a poor statistical fit to the data, ranking six out of the seven models used. As can be seen in Figure 4, BICR-assessed PFS data for crizotinib were much more complete than for lorlatinib, resulting in relatively minor differences in long-term predictions of each of the modelled distributions. Table 21 compares the proportion of patients remaining progression-free on crizotinib across each of the modelled distributions, the exponential distribution arguably results in

less pessimistic estimates of medium-term PFS compared to the Weibull and Gamma models for crizotinib, but the differences are relatively minor, as each of these three distributions has 0% of the population remaining by around ten years.

Table 21 Proportion of progression-free patients predicted by company's PFS extrapolation – crizotinib (based on company's economic model)

Distribution	Modelled landmarks					
	1 year	5 years	10 years	15 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 4 Comparison of PFS extrapolations – crizotinib (based on company's economic model)

[redacted]

The company applied hazard ratios to the crizotinib PFS curve to estimate residence of the PFS health state for patients on alectinib and brigatinib. A hazard ratio of [redacted] was

applied for brigatinib vs crizotinib, while a hazard ratio of [redacted] was used for alectinib vs crizotinib.

Points for critique

The EAG is concerned that the exploration of only simple parametric functions has led to the selection of the exponential as a 'least worst' option, rather than on the basis of good statistical fit or clinical plausibility. Whilst the exponential extrapolation produces the most pessimistic long-term predictions of the fitted models, the visual fit to the observed data is poor, and it overestimates the proportion of patients remaining progression-free over the period for which we have Kaplan-Meier data available (see Figure 5). For much of the first two years of the model, PFS is estimated at around 8% higher than the corresponding data from CROWN. As no such artefact appeared in the crizotinib model fits, it is likely that this introduces bias in favour of lorlatinib. In Section 6.2, the EAG presents a scenario in which PFS is set to equal the Kaplan-Meier data until approximately Month 30 before switching to the extrapolation. The poor fit over this period generates approximately [redacted] additional QALYs versus direct application of the KAPLAN-MEIER up to the point the curves cross.

Figure 5 Visual fit of exponential curve to lorlatinib PFS Kaplan-Meier

The EAG is concerned that due to small number of PFS events observed in CROWN, all alternative parametric curves fitted by the company generate clinically implausible long-term predictions of PFS. As a consequence, clinically meaningful alternative scenarios cannot be explored in the usual way. Four of seven extrapolations fitted by the company predict that over 20% of patients will remain

progression-free at the end of the modelled time horizon (30 years). Clinical advice received by the EAG suggested that 10-year survival on lorlatinib was more likely to be < 10% based on clinical understanding of relapse mechanisms observed on TKI treatment – less than half of the expected PFS predicted by the most pessimistic extrapolation implemented by the company. Given that relapse is considered more or less inevitable on available TKIs in this indication, the PFS predictions provided by the company appear to contradict the established paradigm of disease response, and thus cannot provide an informative exploration of alternative plausible PFS projections.

Taken together, the above issues indicate a failure in the survival analysis process, namely due to the immaturity of available PFS data, and models which may have over-fit to the 'plateau' in the tail. The EAG's preference would be for more flexible survival analysis techniques to be explored, which could have examined the fit and projections of spline models or two-piece models. This may have allowed a greater range of clinically plausible PFS projections to be explored, and gone some way to resolving the issue of the exponential function's poor fit to the observed data. Unfortunately, due to time constraints the EAG was unable to implement any alternative survival analysis methods, but recommends this be explored in the Technical Engagement. The EAG also suggests an alternative means of exploring less optimistic eventualities with regards to maintenance of progression-free survival (see below).

Due to the design of the CROWN trial, PFS is the sole outcome which is sufficiently generalisable to the NHS setting and treatment pathway to meaningfully inform a decision between lorlatinib and its comparators. Improved maturity of this outcome will serve to reduce much of the resolvable uncertainty associated with the duration of the treatment effect and the comparative effectiveness if lorlatinib were recommended for use through the Cancer Drugs Fund or other managed access arrangements.

4.2.6.3 Treatment effect waning

All PFS extrapolations assume that some patients continue to receive benefit from treatment with lorlatinib for many years, if not decades. It is unclear whether mechanisms of ALK-TKI resistance and relapse would allow such benefits to be realised. The company provided model functionality which switches hazards for PFS and CNS-PFS to the survival hazards estimated for crizotinib beyond a specified timepoint.

The appraisals of alectinib and brigatinib considered scenario analyses in which the treatment effect duration was capped at a range of time points between 3 and 20 years. In these appraisals, time on treatment was estimated independently using trial data, rather than assuming it is equal to time to progression as in the present model. As the proportion of patients remaining progression-free was lower than that of patients on treatment, waning was also used to approximate the effects of a loss of

treatment effect in patients who had discontinued. Treatment waning in the context of the lorlatinib model therefore only represents an increased rate of resistance and relapse. The company presented scenario analyses with the treatment effect on PFS and OS capped at 10- and 20- years.

Points for critique

The EAG's clinical adviser considered that even the most pessimistic of the PFS curves fitted to the lorlatinib arm of CROWN generated extremely optimistic long-term effectiveness estimates. Whilst there is limited evidence for treatment effect waning on TKIs in this indication, it has been considered in both TA536 and TA670. It may therefore present a potentially useful means of exploring alternative PFS projections beyond the exponential function previously described. The EAG presents a wider range of scenarios in Section 6.2 which examine the implications for cost-effectiveness of a waning effect at 7-, 10- and 15- years, essentially placing a limit on the potential benefits of treatment with TKIs.

4.2.6.4 CNS-progressed disease health state

The economic analysis presented in the CS fitted parametric models to intracranial-time to progression (IC-TTP) data for each arm of the CROWN population to estimate the rate of CNS-progression events. These data were immature for the lorlatinib arm (i.e. few events were observed), which led to all models predicting higher CNS-PFS than OS. The company proceeded to implement these curves directly to the model to calculate progression into the CNS-PD health state, and applied a cap to CNS-PFS to ensure it could not exceed OS. However, as CNS-PFS was essentially set equal to OS, this approach meant that no modelled patients ever experienced CNS progression events, despite [redacted] lorlatinib patients in CROWN experiencing intracranial progression by the September 2021 data cut. In the EAG's clarification letter, the company was asked to amend the model to apply a relative rate of CNS progression based on that observed in CROWN to patients in the PFS and non-CNS progressed health states. This issue was partially resolved with the updated model provided following clarification. However, as discussed in Section 4.2.2, due to the censoring of patients who experienced an intracranial progression event secondary to any other type of progression and the initiation of further lines of therapy, CNS-TTP data from CROWN cannot represent clinical practice on the NHS, and will underestimate the true proportion of treated patients who develop CNS metastases following treatment with lorlatinib. As discussed in Section 4.2.2 the EAG again highlights that patients could not move into the CNS PD health state from the non-CNS PD health state, reflecting the lack of data to inform this transition from CROWN.

As previously discussed in Section 3.4, there was insufficient appropriate data to perform indirect comparison with alectinib and brigatinib for the CNS-PFS endpoint. The model therefore applied the PFS HR for each treatment to the crizotinib CNS-PFS curve derived from CROWN. That is, the relative effectiveness of alectinib and brigatinib versus crizotinib with regards to prevention of

intracranial progression is equal to the effectiveness of these drugs for the prevention of non-CNS progression events. This led to an underestimation of CNS progression events observed in the source trials in the economic model.

Points for critique

The use of survival curves based on immature data in the PSM framework led to predictions which did not align with the data observed in the CROWN study, and to the underestimation of the rate of CNS-PFS events on lorlatinib and the overestimation of the rate observed on alectinib and brigatinib. Around [redacted] of lorlatinib patients in CROWN experienced intracranial progression as their 'first' progression event.

A significant proportion of patients in this population have CNS metastases at baseline, and addressing this aspect of the condition is a key aim of treatment and overall management of the symptom burden. The model does not account for a potential differential effect of treatment in inducing remission in these patients (see Section 4.2.2).

As discussed in Section 4.2.2, the EAG does not consider it possible to inform the rate at which patients with progressed disease (without CNS metastases) develop CNS metastases given the censoring of this outcome in CROWN. Therefore, the EAG does not consider the PSM approach to modelling CNS-progression appropriate. At the clarification stage, the EAG requested that a relative progression rate based on that observed in CROWN was instead applied across both arms, to ensure the model predictions aligned with the observed trial data. However, this approach was not adopted by the company in their response.

The immaturity of the CNS-PFS data available led to the failure of survival analysis to produce plausible alternative extrapolations, resulting in a lack of flexibility to evaluate the uncertainty around the magnitude of CNS-PFS benefits on lorlatinib relative to the comparators. The application of the PFS HRs as a proxy for the CNS-PFS treatment effect results in a very large benefit of lorlatinib compared to alectinib and brigatinib in terms of delaying the development of CNS-metastases, but the company has provided no meaningful evidence to substantiate the existence of such an effect. The model generates highly optimistic predictions of long-term CNS-PFS on lorlatinib, with the company's base-case analysis predicting that 12.7% of lorlatinib patients will remain free from CNS-progression at 30 years, whereas for alectinib and brigatinib less than 1% of patients remain free from CNS-progression at 20 years. This represents both an optimistic interpretation of lorlatinib CNS-PFS and a pessimistic interpretation of CNS-PFS on alectinib and brigatinib, for which observed data is clearly more positive. The model increasingly overestimates intracranial progression events for brigatinib compared to the ALTA-1L trial at key time points. At 12 months observed CNS-PFS was ~[redacted] in the model, increasing to [redacted] at 24 months, and [redacted] at 30 months.

Whilst equivalent data is not publicly available for alectinib, it is likely that the model similarly overestimates the rate of progression events.

There is little evidence presented in support of such a significant benefit of lorlatinib relative to alectinib and brigatinib, and the inclusion of such very unclear and uncertain benefits may present a significant source of bias in favour of lorlatinib. The EAG does not consider the evidence presented to substantiate the modelled benefits. Due to the incompleteness of the data and only partial modelling of this health state, it is likely to be more appropriate to remove the CNS-PD health state from the model in its entirety.

In Section 6.2 the EAG presents an alternative to the company's base-case method for modelling the CNS-PD health state which aims to explore how the lack of directly comparable data and the assumptions adopted by the company affect estimates of the relative cost-effectiveness of each drug. The EAG examines the effect of removing benefits associated with the CNS-PFS health state in their entirety. In the absence of convincing evidence of superiority of lorlatinib over alectinib and brigatinib, it may be inappropriate to model QALY benefits associated with the prevention of CNS events on lorlatinib. Indeed, the modelling of differential CNS-PFS in this way means that lorlatinib generates net QALY benefits of [redacted] and [redacted] versus brigatinib and alectinib respectively under the company's base-case assumptions. This may be a conservative assumption, however, as benefits of this magnitude have not been appropriately evidenced or modelled, it is inappropriate to include them in the model.

As discussed in Section 4.2.6.5, the EAG considers the use of Study 1001 and PROFILE 1001/1005 used to inform post-progression survival inappropriate in a population comprising only patients with CNS metastases. Therefore, it is the EAG's preference that this health state be removed.

4.2.6.5 Post-progression survival

The company were unable to produce data on overall survival from the CROWN study which aligned with the most recent PFS data cut. The available OS data for lorlatinib are therefore immature, and unrepresentative of NHS practice due to the ubiquity of subsequent anticancer treatment following progression. These data were therefore considered unsuitable for direct use in a PSM.

In the original company submission, the company assumed that post-progression survival would be constant regardless of the number or type of therapies previously received by a patient. The company assumed that OS on lorlatinib would be equal to the difference between the median PFS predicted on lorlatinib and median PFS on alectinib plus second line lorlatinib ([redacted] in favour of lorlatinib). This benefit was then retrospectively imposed upon the model using an exponential function for

lorlatinib OS which was adjusted using the Excel 'Goal Seek' function, until total discounted LYs on lorlatinib exceeded that generated by alectinib by [redacted].

At the clarification stage, the EAG expressed a preference for a more flexible model which could explore different scenarios and data sources for post-progression survival without contamination from subsequent use of TKIs. In their updated model, the company removed this fixed OS benefit and all OS data derived from first-line studies, given the mismatch between subsequent therapies received with anticipated NHS practice. Instead, the company used OS data from Study 1001 and Profile 1001/1005 to estimate post-progression survival on lorlatinib and chemotherapy respectively, following first-line treatment with an ALK-inhibitor. This method allows for alterative extrapolations to be explored for both PFS and PPS, and to capture uncertainty associated with these data probabilistically. The same mortality rate is applied for patients with CNS progressed disease as for those with non-CNS progression.

Lorlatinib

The PROFILE 1001/1005 studies were said by the company to provide the only evidence on OS for patients who received chemotherapy following disease progression and discontinuation of a TKI, which in this study was crizotinib. Patients who progressed on crizotinib either continued to receive crizotinib (n=120), or did not continue to receive crizotinib (n=74). Of the 74 patients who switched to chemotherapy following progression, 17 (28%) had brain metastases. Kaplan-Meier OS data for this latter group were extracted from Ou *et al*. (2014),[9] to which the company fitted a range of simple parametric curves. As there was limited time available, the company used the 'goal seek' function in MS Excel to estimate the exponential rate parameter required to produce a curve which generated a similar mean OS prediction to each of the alternative parametric distributions. Table 22 presents a summary of the survival models applied to post-progression survival data for chemotherapy. As PPS KM data from this study is relatively complete, estimated OS did not differ significantly between extrapolations.

Table 22 Models applied to second-line chemotherapy data (PROFILE 1001/1005) (Company clarification response B, Table 4)

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)				
					6 months	1 year	2 years	3 years	5 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company applied the exponential model to estimate post-progression survival on chemotherapy after progression (of any type) on first-line lorlatinib. The rate of PPS was not adjusted according to whether patients had non-CNS PD or CNS PD. The EAG highlight that the listed distributions themselves were not implemented directly into the economic model, rather, an exponential function producing the mean OS predicted by each was used to approximate the effect of alternative parametric distributions. Figure 7 illustrates the visual fit of the parametric models to the observed PPS data in PROFILE 1001/1005.

Figure 6 PPS extrapolations approximated using exponential rate for chemotherapy arm of PROFILE 1001/1005 (Company clarification response B, Figure 3)

[redacted]

Alectinib/brigatinib followed by lorlatinib

Study 1001 (NCT01970865) is a single arm Phase 1/2 trial sponsored by the company, in which patients received lorlatinib after prior exposure to a TKI. The company fitted a number of simple parametric curves to OS data from Study 1001. As with the PROFILE 1001/1005 data, the company used the 'goal seek' function to approximate the OS estimated by alternative parametric functions. The basic exponential function was used in the company's updated base-case analysis to estimate post-progression survival on second-line lorlatinib following progression of any kind on alectinib and brigatinib.

Table 23 presents the mean PPS predicted for post-progression survival for second-line lorlatinib, i.e. following progression (of any type) on alectinib and brigatinib. Note again that the curves are implemented in the model as exponential functions with a mean OS equal to that of each of the fitted survival models. The approximated exponential curves are depicted in Figure 7. The company stated that market share data indicated that [redacted] of patients would not receive lorlatinib following progression, instead going on to receive chemotherapy instead.

Table 23 Models applied to Study 1001 data (2nd line lorlatinib (Company clarification response B, Table 3)

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)				
					6 months	1 year	2 years	3 years	5 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 7 PPS extrapolations approximated using exponential rate for lorlatinib arm of Study 1001 (Company clarification response B, Figure 2)

Points for critique

The company's amended model explicitly models post-progression survival using external data sources. The EAG highlights that whilst the recommendation to adopt a pseudo state-transition approach with regards to PPS was motivated by the immaturity of the data, it is unlikely that further data from CROWN will be able to inform OS. As has been described in previous sections, a substantial proportion of patients who progressed on lorlatinib in CROWN received further lines of TKIs. Data on survival after progression on lorlatinib is therefore not representative of NHS practice, and is likely to overestimate OS.

A significant issue with the approach taken by the company is the use of whole-population PPS data to reflect the survival of patients who experienced intracranial progression. The prognosis of these patients is likely to be worse than those with progression and metastases at other sites. The use of Study 1001/PROFILE 1001/1005 data in this way may therefore overestimate the survival of patients in the CNS-PD health state. Likewise, would the use of these data to estimate outcomes in a non-CNS PD population would underestimate OS. Given the mix of patients in the cohort who progress in

CROWN with the cohort entering Study 1001/PROFILE1001/1005 in terms of progression type, it may be more appropriate to model the outcomes of this cohort as a whole, as insufficient data are available to appropriately and fully model entry and exit of the CNS-PD health state.

The EAG notes the company's assumption that only 5% of patients would be expected to not receive lorlatinib following progression on alectinib and brigatinib. The EAG's clinical adviser suggested that the proportion may be higher. The EAG therefore presents a scenario in which the proportion of patients who receive second line lorlatinib is equal to the proportion of patients who received a subsequent anti-cancer therapy in CROWN after progression on lorlatinib. In CROWN, of [redacted] who experienced a progression event on lorlatinib, [redacted] received a subsequent active therapy [redacted], comprising TKIs and chemotherapy. The EAG considers that second line chemotherapy use may have been due to a lack of locally available alternatives, so has assumed that these patients would receive lorlatinib were it available. The remaining [redacted] of patients are assumed to receive no further treatment, and to receive outcomes equivalent to chemotherapy given the lack of alternative sources.

A further issue with the implementation of this model structure relates to the parameterisation of PPS curves in the model. As described above, the company approximated the effects of alternative curves in only terms of the mean survival estimates generated by each. By implementing different mean PPS durations as exponential functions, the particular skew of each parametric function is lost. The primary means by which this would affect cost-effectiveness estimates is through misrepresenting the discounting of costs and benefits accrued over the PPS period. For example, a parametric function in which a greater proportion of mean survival is accrued in the tail (i.e. where hazards decrease over time) would be more heavily discounted if implemented fully in the model, as opposed to the exponential function. The opposite would be the case for distributions with increasing hazards. The effect of this issue is likely to be minor, so has not been explored further.

A further key uncertainty is the unknown effects of continuing treatment beyond progression. As was discussed in TA670, the decision to continue treatment beyond progression depends on the availability of further lines of effective therapies. Clinicians may opt to continue treatment beyond progression if they consider the patient to be receiving some ongoing clinical benefit. This opinion was echoed by the EAG's clinical adviser, who disagreed with the company's assessment that the wording of the MHRA license meant that treatment should be stopped at progression. The point of clinical progression itself is not a signifier of complete loss of response, and patients may receive some continuing benefit. Continuing on first-line lorlatinib is particularly likely as there are no further oral targeted therapies available at this point in the treatment pathway. The EAG's clinical adviser also highlighted the a recent publication,[20] which showed that of 74 patients receiving lorlatinib at second-line (post one 2nd generation TKI), 56 continued to receive lorlatinib following progression, with a median additional duration of 5.7 months (95% CI 0.8 – 32.7). This was considered a

reasonable duration for treatment beyond progression. However, this study found no statistically significant difference between OS for those who continued treatment beyond progression and those who did not. Therefore, this is only explored with regards to the potential impact upon resource use (see Section 6.2 for details).

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. Each adverse event was associated with both an annualised incidence rate and a duration, which were then used to estimate per cycle disutilities and the costs associated with each event (see Table 24).

At the clarification stage, the EAG requested that the company include consideration of a number of additional AEs of special interest, and consider the management of some lower grade but high frequency events in their cost calculations. Clinical advice to the EAG indicated that lipidaemia events of any grade would require additional blood tests and statin treatment, and that patients experiencing peripheral neuropathy, cognitive effects, and mood effects whilst being treated with lorlatinib would have an effect upon quality of life, and would require additional management (see Section 4.2.7). The EAG notes that all AEs were assumed to be five days in duration. The application of AEs in the model is discussed in further detail in sections 4.2.7 and 4.2.8.

Table 24 Incidence and rate of AE by treatment arm (adapted from company's executable model)

Adverse Event	Lorlatinib (CROWN)		Alectinib (ALEX)		Brigatinib (ALTA-1L)	
	Proportion	Annual rate	Proportion	Annual rate	Proportion	Annual rate
Hypertriglyceridemia (Grade 1-4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased lipase level	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypercholesterolemia (Grade 1-4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral neuropathy (Grade 1-4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive effects (Grade 1-4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mood effects (Grade 1-4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Points for critique

The EAG considers the company's approach following changes made in their updated model to be broadly appropriate. The EAG note that whilst the company's approach following clarification is more consistent with TA670, the application of disutilities accrued over only five days for each AE is inconsistent with TA670 and contradicted by data available from CROWN. As described in Section 4.2.7 the mean durations of the AEs of special interest in CROWN was vastly longer than the five days assumed in the trials (See Table 28).

4.2.7 Health-related quality of life

4.2.7.1 Collection of utility data in CROWN

Health-related quality of life data were collected in the CROWN trial using the EQ-5D-5L questionnaire and were mapped to EQ-5D-3L using the algorithm derived from the EEPRU dataset by Hernández-Alava *et al.*[22] for use in the economic model. The September 2021 CROWN data cut was used for this analysis.

Patients were assessed using the EQ-5D-5L questionnaire on Day 1 of each 30-day treatment cycle. The company submission did not provide detail on attrition over time or by patient subgroup/health status. A report providing further details on the collection and analysis of EQ-5D-5L data was provided by the company at clarification.

Less than 12% of EQ-5D-5L responses were collected in patients who had experienced disease progression, and most of these were collected close to the date of clinical progression. Using the EEPRU mapping algorithm, the mean utility of lorlatinib patients was 0.86 both pre- and post-progression, whereas the mean utility of crizotinib patients was 0.86 prior to progression, and 0.83 post-progression.

The EAG note that other disease-specific PROs (namely EORTC QLQ-LC13) indicated no longitudinal difference in HRQoL between crizotinib and lorlatinib, despite significant differences in the proportions of patients remaining progression-free.

4.2.7.2 Health state utilities

Utility data from the CROWN study were analysed using a mixed-effects regression model with the final (statistically significant) covariates listed in Table 25 below. A detailed description of the methods used was not provided in the original submission, but was later provided upon request (Clarification Response Part B, Question 15).

Table 25 Company EQ-5D-5L regression model covariates

Parameter	Utility data from CROWN	Health state parameters			
		Progression-free (on treatment)	Progression-free (off treatment)	Progressed (on treatment)	Progressed (off treatment)
(Intercept)	[redacted]	[redacted]			
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline brain metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib: baseline brain metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age: post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib: post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

From this analysis the company derived the final utility values presented in Table 26. Utilities were assumed to be the same regardless of TKI received. 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 which evaluated the impact of brain metastases on HRQoL on patients with Stage IV NSCLC.[23] 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 CROWN utility for progressive disease to quantify the impact of CNS-metastases in the model, yielding a utility of 0.62 for modelled patients in the CNS-progressed health state. The final utilities applied in the model are presented in Table 25.

The modelled utilities imply a positive effect of receiving treatment on quality of life, regardless of which health state a patient resides in (see Table 26). The EAG asked the company to clarify why they believed such an effect might exist in practice. In their response, the company described how a high proportion of the off-treatment records were taken close to the point of treatment cessation, which was likely to reflect the impact of adverse events or disease progression. The company therefore do not use the 'off treatment' utility for patients in the progression-free health state in the base-case analysis, as patients are assumed to continue treatment until progression. Likewise, the 'on treatment' utility for progressed patients not used.

Table 26 Basic utility values used in company model

Progression-free		Progressed		CNS-progressed	
On treatment	Off treatment	On treatment	Off treatment	On treatment	Off treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* not applied in the company base-case

Points for critique

The EAG has a number of concerns with the utility set applied in the model which may mean it cannot adequately reflect the impact of HRQoL. The utilities derived from the CROWN study and applied in the present model were considerably higher than those accepted in the brigatinib appraisal (for comparison see Table 27). There are several factors which may have led to these apparent discrepancies, linked to both the collection of data in CROWN, and the regression methods used by the company to account for the effect of treatment status on HRQoL.

Division of utilities by treatment status

The EAG disagrees conceptually with the division of utility in the progression-free state into on- and off-treatment, and highlights the lack of precedent for such a division on previous appraisals. The EAG agrees use of on/off treatment utilities is appropriate in patients with progressed disease, which is consistent with previous appraisals. However, it appears counter-intuitive that patients with no symptomatic progression should have a lower utility when off treatment, as the toxicities associated with TKIs would be expected to lead to reductions in HRQoL. The EAG considers it likely that patients on- and off-treatment would indeed have had different utilities in the CROWN trial. The primary reason a patient would have been off-treatment whilst progression-free would be due to a treatment interruption to allow for the resolution of significant treatment-related adverse events. It therefore follows that any patients who are off-treatment in the PFS state would have a lower HRQoL due to an ongoing AE, thus generating the lower off-treatment utility observed in the company's regression model. However, it is clearly inappropriate to statistically segregate these patients whilst also claiming that the effect of adverse events on HRQoL is captured in the on-treatment utilities. The model does not apply this off-treatment utility for patients experiencing an adverse event leading to a dose interruption, thereby decoupling the modelled utilities from the overall effects of treatment with lorlatinib (i.e. benefits *and* safety). It therefore cannot be claimed that the modelled utilities encompass the effects of adverse events. In Section 6 the EAG explores a scenario in which a proportion of patients experience a utility decrement in line with the difference between on- and off-treatment utilities in the PFS arm, based on the duration of AEs of special interest observed in the trial.

Comparison of utilities with previous appraisals

It is clear that the utilities applied in the present model are consistently higher than those adopted in past appraisals, as illustrated in Table 27 which compares the utilities applied in the present model with those used in previous appraisals. This is particularly the case for the progressed disease health state, in which there is only a negligible reduction in utility versus PFS. In their clarification response, the company stated that the majority of EQ-5D-5L measurements in patients with progressed disease were taken close to the point of clinical progression. The EAG therefore does not consider the use of this utility value appropriate to represent the quality of life of patients with progressed disease. The EAG further highlights that in TA670 the trial-derived utilities were subject to the same issue. The committee therefore considered external data sources to inform the PD utility most relevant, noting that clinical progression does not immediately correspond to an increase in a patient's symptom burden – an issue reiterated by the EAG's clinical adviser in the current appraisal. Moreover, patients who experienced progression in CROWN on lorlatinib were likely to have been moved onto a subsequent TKI, offering greater symptom control for many patients before progression had a substantial effect on HRQoL. This would not be the case in NHS practice, as there are no further TKIs recommended following discontinuation of lorlatinib. The EAG therefore explores a scenario in Section 6.2 which instead applies utilities from TA670 of brigatinib to more appropriately reflect the impact of progression on HRQoL.

Table 27 Comparison of modelled utilities with previous appraisals

Appraisal	Treatment	Progression-free		Progressed		CNS-progressed	
		On treatment	Off treatment	On treatment	Off treatment	On treatment	Off treatment
Current appraisal (lorlatinib 1st line)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA670 Brigatinib)	Brigatinib	0.793	0.793	0.624	0.552	-	0.543
	Alectinib	0.793	0.793	0.624	0.550	-	0.539
TA536 (Alectinib)	Alectinib	0.814	0.814	0.725	0.725	0.52	0.52

Use of Roughley et al. multiplier for CNS PD

The EAG considers the use of Roughley *et al*.[23] to estimate the effect of CNS metastases on HRQoL to have a potentially important impact on cost-effectiveness estimates for lorlatinib. Whilst the use of the multiplier derived from this study is consistent with TA536 and TA670, the EAG notes that the appraisal's ERG, technical team, and committee were unsatisfied with the quality, age, and size of the study. The FAD for TA670 of brigatinib notes the committee's concerns that only a small number of

patients with brain metastases were included (n=29), and that co-morbidities, age, and treatment-related adverse events were not reported in these patients. The committee also considered that clinical practice had changed since the publication of this abstract in 2014 – most notably that first- and second-line ALK inhibitors have been recommended, which is likely to have improved the quality of life of people with CNS involvement. The 75.36% multiplier was, however, accepted, due to the small effect of the use of this utility in these appraisals. The claimed benefits of lorlatinib for the treatment and prevention of CNS-metastases mean that the total contribution of this utility to QALY gain is much greater in the present appraisal. At clarification the EAG requested that the company's regression model be re-run with the addition of CNS metastases as a covariate. However, as the company declined to provide a response, it was not possible to produce an analysis using CROWN data to inform the CNS PD health state utility. As discussed in Section 4.2.2, the EAG has concerns about the validity of the CNS PD health state and the accuracy of state occupancy. As the EAG's preference is to remove this health state from the model in its entirety, no further scenarios are presented on the utility associated with CNS PD.

4.2.7.3 Age adjustment of utilities

Utilities were adjusted over time to reflect the effect of aging on health-related quality of life. Adjustment was made according to population norms reported by Ara and Brazier.[24] The EAG is satisfied with the approach taken in the company's economic model.

4.2.7.4 Utility benefit applied to subsequent therapies

In the original model, company applied a one-off utility benefit upon progression to account for QoL benefits associated with subsequent treatment. This benefit was based on the difference between on- and off-treatment utilities in the CNS- and non-CNS progressed patients, and the average duration of subsequent treatment in the CROWN trial.

The EAG considers this approach reasonable given that the model structure cannot fully capture the effect of treatment sequences. Furthermore, the incremental benefits modelled are very small, and are unlikely to have a meaningful impact on the relative cost-effectiveness of lorlatinib.

4.2.7.5 Effect of adverse events on HRQoL

The company did not explicitly apply disutilities relating to adverse events in the original base-case model, assuming instead that the data collected from the CROWN trial will have already captured the effects of any AEs. The company assumed no difference in the impact of the AE burden associated with each of the technologies on HRQoL. In the updated model submitted following clarification, the company explicitly model AEs upon HRQoL, using AE rates derived from each technology's pivotal trials (See Section 4.2.6.6). Adverse events were assumed to last five days, using an annualised disutility of -0.037, which was derived from analysis conducted in TA670. The EAG requested further

details on the duration of AEs reported in CROWN, as a number (in particular lipidaemias, peripheral neuropathy, and cognitive effects) were potentially chronic issues which require long-term management and may have a more lasting impact upon HRQoL. As part of the clarification response the company also provided details on the median duration of adverse events of special interest observed in CROWN.

Table 28 presents a summary of the most relevant data sources for AE duration and disutilities used in the company's base-case model and the alternative sources cited by the company at clarification. The total AE-related QALY decrement in this scenario is [redacted]

Table 28 Comparison of AE related disutilities in model and cited sources

Adverse Event	Utility decrement (annual)	Duration (days) (company)	Duration (days) (TA670/EAG)	Annual rate (lorlatinib)	*Source*
Hypertriglyceridemia	-0.037	[redacted]	[redacted]	0.2207	*TA670 (ALTA-1L)*
Weight increased	-0.037	[redacted]	[redacted]	0.0669	*TA670 (ALTA-1L)*
Increased lipase level	-0.037	[redacted]	28.0	0.0156	*TA670 (ALTA-1L)*
Hypercholesterolemia	-0.037	[redacted]	[redacted]	0.2430	*TA670 (ALTA-1L)*
Aspartate aminotransferase increased	-0.037	[redacted]	28.0	0.0067	*TA670 (ALTA-1L)*
Gamma-glutamyltransferase increased	-0.037	[redacted]	28.0	0.0201	*TA670 (ALTA-1L)*
Hypertension	-0.037	[redacted]	28.0	0.0379	*TA670 (ALTA-1L)*
Anaemia	-0.037	[redacted]	28.0	0.0111	*TA670 (ALTA-1L)*
Amylase increased	-0.037	[redacted]	28.0	0.0000	*TA670 (ALTA-1L)*
Neutropenia	-0.460	[redacted]	28.0	0.0022	*Nafees et al.*
Blood creatine phosphokinase increased	-0.037	[redacted]	28.0	0.0067	*TA670 (ALTA-1L)*
Neutrophil count decreased	-0.037	[redacted]	28.0	0.0000	*TA670 (ALTA-1L)*
Peripheral neuropathy	-0.460	[redacted]	[redacted]	0.0267	*Assumption (equal to neutropenia)*
Cognitive effects	-0.460	[redacted]	[redacted]	0.0847	*Assumption (equal to neutropenia)*
Mood effects	0	[redacted]	[redacted]	0.0580	*EAG Assumption (included in cognitive effects)*

Points for critique

The EAG considers it unlikely that the effects of adverse events experienced on lorlatinib would be appropriately captured by the 'on-treatment' utility due to the statistical segregation of patients who required temporary or permanent withdrawal of treatment to allow the resolution of treatment-related adverse events in the company's regression model.

In the model submitted in their response to clarification, the company applied disutilities sourced from the literature for a number of AEs. However, it was assumed that adverse events persisted for only five days, despite data provided from CROWN which indicated much longer durations (see Table 28).

It was also unclear whether the disutilities were applied correctly. For example, the disutility associated with neutropenia is reported as -0.46 in the UK cohort of the Nafees *et al.* study[25] used by the company. The disutility is the company's analysis is, however, only -0.09.

The EAG also has concerns that the 5-day duration of AEs is a significant underestimate and leads to the per cycle disutility associated with an AEs to be significantly lower compared to those applied in TA670. To address these issues the EAG presents a scenario in Section 6.2 which applies utility decrements in a manner more consistent with TA670. In this scenario, the duration of adverse events is assumed to be 28 days unless data collected in CROWN are available. Furthermore, this scenario updates the disutilities applied to better align with values observed in Nafees *et al*.[25]

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 management of adverse events, monitoring costs, and the cost associated with subsequent treatments, and resource use associated with terminal care of patients with ALK-positive advanced NSCLC.

To identify resource use data, the company carried out an SLR to identify relevant cost and healthcare resource use for therapies in the first line setting for patients with ALK-positive advanced NSCLC. The company also drew heavily on previous appraisals in this indication. The SLR was restricted to English language studies published between 2007 to 2019. The company extracted and synthesised data from 24 unique studies from included 33 publications from the SLR. The cost values for the resources identified were extracted from monthly index of medical specialities (MIMS) online database, NHS reference costs (2019 -2020) and Personal Social Services Research Unit (PSSRU) 2021 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 first-line therapies. The drug cost were calculated based on each drug's unit cost per package, which was derived from the Monthly Index of Medical Specialities (MIMS).[26] Acquisition costs applied for lorlatinib were inclusive of a [redacted] PAS discount on the list price. Alectinib, 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 are 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 Table 29 and were informed by the SmPCs for alectinib and brigatinib[27, 28] and the CROWN trial for lorlatinib.[29]

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 dependent and do not scale on a pro rata basis (see Table 29). 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 90 tablet 25mg pack and the 30 tablet 100mg packs are used to estimate costs, with the former used to model acquisition costs in patients receiving a reduced dose of lorlatinib. Detailed dosing information from CROWN was used to estimate the proportion of patients receiving a lower dose of lorlatinib with 75mg, 50 mg, 25 mg and 0 mg per day permissible in the model. No wastage was assumed for patients receiving a lower dose of lorlatinib.

Detailed dosing information is not available for alectinib and brigatinib acquisition costs were therefore adjusted based on mean relative dose intensity from TA536 for alectinib[30] and from TA670 for brigatinib[1] to account for the dose reductions. To account for wastage, it was assumed that only half of the cost reduction associated with dose reductions would be realised. This aligns with assumptions made in TA 670.[1]

Table 29 Drug unit costs, doses, and dose intensity (adapted from CS, Table 54 - 58, p 102 – 104 and the drug costs worksheet in the model)

Treatment	Cost per pack, £	Pack size	Dose, mg	Dosing schedule	Mean relative dose intensity (%)	Drug cost per month (cycle), £
Lorlatinib	£7,044.00 With PAS discount[redacted]	120	25	100 mg orally once daily	93.2	[redacted]
	5,283.00	90	25			
	With PAS discount:£[redacted]	30	100			
Alectinib	5,032.00	224 capsules	600	600 mg orally twice a day	95.6	5,272.82
Brigatinib	4,900.00	28 tablets	180	180 mg orally once daily	85.5	4,869.64
CS, company submission						

Points for critique

The EAG considers the acquisition costs applied in the model to be largely appropriate. 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, however, notes

several uncertainties especially with regards to wastage and differences in how dose reductions were accounted for.

Wastage and dose reductions

The EAG considers the approach to modelling wastage for alectinib and brigatinib to be broadly appropriate but is concerned about the inconsistent approach used for lorlatinib. The EAG recognises the advantages of using the more detailed information in CROWN to model acquisition costs but has concerns about how the company have implemented this in the model. Specifically, the EAG notes the company assume patients receiving a ≥ 75mg dose of lorlatinib use the 90 tablet 25mg pack. The EAG considers it uncertain whether this pack size will be used in practice and notes that it results in limited cost savings due to the higher per mg costs associated with this pack size. Importantly, these cost savings would increase if patients were to be prescribed the 120 tablet 25mg pack size. Furthermore, the use of detail dosing assumes no wastage. This is inconsistent with the approach for alectinib and brigatinib. The EAG is particularly concerned that wastage could occur if patients transition between different types of pack in the event of a dose reduction. For example, if patients on the full 100mg dose are given the 30 x 100mg pack (as in the company base-case analysis) and require a dose reduction, the remainder of the pack would be wasted to switch to 25mg tablets. This wastage would be avoided if the 120 x 25 mg pack were used in all patients from the outset of treatment.

Given the uncertainties generated by the differential cost per mg across pack sizes and the general inconsistency of using different approaches across technologies, the EAG prefers to use a unified approach across all technologies based on using relative dose intensity (RDI) to model cost savings. This approach is inherently simpler, and has been previously accepted by NICE Committees. The EAG, however, notes that this approach assumes that the 120 x 25 mg tablets will be used in all patients. Clinical advice on the use of lorlatinib in current practice, and plausibility of this assumption, would be useful.

4.2.8.2 Treatment administration 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 £10.80 was applied per pack, sourced from the Personal Social Services Research Unit (PSSRU) 2020 as the cost for 12 minutes of work for a Band 6 community-based scientific and professional staff member (£54 per hour).[31] The estimated 30-day cycle cost in the model for lorlatinib was £10.80 while for alectinib and brigatinib was £11.57. The increased per cycle administration cost in the model for alectinib and brigatinib accounts for the shorter treatment (duration pack lasts) cycle 28 days vs 30 days for lorlatinib.

The EAG has no concerns with the administration costs included in the model. The costs applied are consistent with previous appraisals (TA670 & TA536) and appear to include the all relevant costs incurred from the perspective of the evaluation.

4.2.8.3 Subsequent treatments

The company applied a one-off cost associated with subsequent treatments at the point of disease progression on the patients who had not died, with the average duration of treatment based on reported data from various studies as explained below:

- For patients on lorlatinib, at progression, 100% of the patients received chemotherapy (pemetrexed plus cisplatin), which was based on advice from the company's advisory board.
- For patients on alectinib or brigatinib, at progression, 100% of the patients received lorlatinib as a second-line subsequent treatment. This is inconsistent with the modelled benefits, where lorlatinib PPS is applied to 95% of patients, and chemotherapy PPS is applied to 5%. Third-line treatment was also permitted and assumed 54% received chemotherapy (pemetrexed plus cisplatin).

The mean duration for which patients were on lorlatinib as a second-line treatment was 64.36 weeks as sourced from TA628[32] where lorlatinib was evaluated as a second line treatment for ALK-positive NSCLC. The mean duration over which patients were on chemotherapy as either second-line or third-line treatment was 6.3 weeks as sourced from ASCEND-5 trial.[19] In the scenario analysis conducted by the company, alternative mean duration measurements for subsequent lorlatinib treatment were obtained from TA670 and the CROWN study, while an alternative mean duration measurement for chemotherapy was sourced from CROWN study. The total costs for subsequent treatment for patients on lorlatinib with chemotherapy (pemetrexed and cisplatin) was £3,397.65 while the total costs for subsequent treatments for patients on alectinib or brigatinib with lorlatinib second-line (inclusive of cPAS) was estimated to be [redacted]. Table 30 presents the breakdown of total costs by subsequent treatment received. A month is assumed to be 30.4 days which was calculated as 365.25 divided by 12.

Table 30 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	£1,380.97	£221.35	1.45	£2,322.40	6.30	1.45	£3,364.86
Cisplatin	£15.62	£0.00	1.45	£22.63	6.30	1.45	£32.79
Lorlatinib	[redacted]	£10.80	1.01	[redacted]	64.36	14.80	[redacted]

Points for critique

All patients receive systemic 2nd line treatment

The company's base case assumes that all patients receive second-line treatment following progression of disease. This is inconsistent with evidence from CROWN which indicates that only [redacted] of patients received systemic treatment following progression. Clinical advice received by the EAG supported the figures observed in CROWN suggesting that > 80% of patients would receive further subsequent treatment but not all. The EAG's clinical advisor further elaborated that patients with rapidly progressing disease are often not fit enough to receive further systemic treatment and would receive only palliative care. Aligning with the evidence from CROWN the EAG therefore prefers to assume that only [redacted] of patients would move to second-line treatment following discontinuation of a first line TKI; the EAG considers it reasonable to assume that the proportion of patients receiving 2nd line treatment will be the same regardless of the first-line TKI received.

Inconsistency between clinical parameters and costs

As noted above, the company model assumes that 100% of patients will receive lorlatinib for cost purposes but models health benefits assuming that 95% will receive lorlatinib, with the remainder receiving doublet chemotherapy. The EAG does not consider this inconsistency appropriate and considers that clinical and cost inputs should be consistent wherever possible. Furthermore, the EAG does not consider the use of chemotherapy as a second-line treatment to reflect NHS practice. The EAG notes that this assumption of 95% lorlatinib use was informed by market share data. The EAG considers it likely that this data reflects some historical use of chemotherapy, rather than established practice in 2022. Clinical advice received by the EAG suggested use of lorlatinib in a 2nd line setting is universal, subject to patients' fitness to receive treatment. The EAG presents scenario analysis in Section 6.2, assuming that lorlatinib is the only second-line treatment option following progression on either alectinib or brigatinib.

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). The ASCEND-5 population, therefore, does not match the population modelled as receiving chemotherapy (second or third-line chemotherapy following one or two previous TKIs).

The chemotherapy regimens modelled (doublet treatment) 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 with 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. Sensitivity analysis (not reported) considering alternative durations of chemotherapy demonstrated that the model is not sensitive to this input. The EAG also notes a lack of credible alternative sources of evidence. Notwithstanding the issues raised above, the EAG therefore considers the use of ASCEND-5 acceptable and the uncertainty generated by the noted inconstancies minimal.

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, non-CNS progressed, CNS progressed and death. Resource use and costs for each health state was based on NHS reference costs (2019/20).[33] A micro-costing approach was used with resource use assumed to be equal to that reported in the brigatinib (TA670)[1] and alectinib (TA536)[30] appraisals. In the progression-free, non-CNS progressed, and CNS progressed 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 health state costs were estimated to be £291.61 while in the first cycle it was estimated to be £253.24 as shown in Table 31. The per cycle non-CNS progressed health costs were estimated to be £461.69 as shown in Table 32, while the per cycle CNS progressed health state costs were estimated to be £463.64 which was obtained by adding steroids (dexamethasone) to the estimated non-CNS progressed health state cycle cost. The estimated cycle costs for steroids (dexamethasone) was £1.65 which was sourced from TA670. In addition, a one-off management cost of £8,221.37 was applied to those who progressed into the CNS progressed health state to reflect the resource-intensive nature of this site of progression and the additional resource use. This is presented in Table 32. The proportion of patients to whom CNS progression resource is applied was informed by the brigatinib appraisal (TA670). The specific unit costs and proportion of patients in each health state applied in the model are summarised in Table 31 and Table 32 below. All monitoring costs for NSCLC patients with and without CNS progression were derived from the NHS reference costs (2019/20)[33] and from the PSSRU.[31]

Table 31 Progression-free health state cycle costs (adapted from CS, Table 59, pp 105)

Resource	Unit cost, £	Frequency of use	Cost per cycle, £
Progression-free health state - first cycle			
Healthcare provider visits			
Oncology outpatient (first visit)	£253.20 per visit	100% of patients (1 visit per month)	£249.57
Tests and procedures			
Full blood test	£2.53 per test	100% of patients (1 set of tests per month)	£2.50

Biochemistry	£1.20 per test	100% of patients (1 set of tests per month)	£1.18
Total cost for the first progression-free cycle			***£253.24***
Progression-free health state – second and subsequent cycles			
Healthcare provider visits			
Oncology outpatient (subsequent visit)	£136.36 per visit	100% of patients (0.75 visit per month)	£100.80
GP visit	£39.00 per visit	10% of patients (1 visit per month)	£3.84
Cancer nurse	£99.30 per visit	50% of patients (1 visit per month)	£48.94
Tests and procedures			
Full blood test	£2.53 per test	100% of patients (1 set of tests per month)	£2.50
Biochemistry	£1.20 per test	100% of patients (1 set of tests per month)	£1.18
CT scan	£79.15 per scan	100% of patients (0.5 scans per month)	£39.01
MRI	£211.33 per scan	50% of patients (0.2 scans per month)	£20.83
X-ray	£32.73 per X-ray	50% of patients (0.3 scans per month)	£4.84
ECG	£70.69 per scan	100% of patients (1 scan per month)	£69.67
Total cost per cycle for the second and subsequent progression-free cycles			***£291.61***
CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; MRI: magnetic resonance imaging.			

Table 32 Non-CNS progressed health state cycle costs (adapted from CS, Table 60, pp 105-106)

Resource	Unit cost, £	Frequency of use	Cost per cycle, £
Non-CNS Progressed health state cycle cost			
Healthcare provider visits			
Oncology outpatient (subsequent visit)	£136.36 per visit	100% of patients (1.25 visit per month)	£167.99
GP visit	£39.00 per visit	50% of patients (1 visit per month)	£19.22
Cancer nurse	£99.30 per visit	80% of patients (1.5 visits per month)	£117.45
Tests and procedures			
Full blood test	£2.53 per test	100% of patients (1.5 set of tests per month)	£3.75
Biochemistry	£1.20 per test	100% of patients (1.5 set of tests per month)	£1.77
CT scan	£79.15 per scan	100% of patients (0.75 scans per month)	£58.51

MRI	£211.33 per scan	80% of patients (0.5 scans per month)	£83.32
X-ray	£32.73 per X-ray	60% of patients (0.5 scans per month)	£9.68
Total cost per cycle for the non-CNS progressed health state			***£461.69***
CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; MRI: magnetic resonance imaging.			

Table 33 CNS progressed health state management costs (adapted from CS, Table 61, pp 106)

Resource	**Unit Cost, £**	**Proportion of patients**	**Lifetime exposure limit (dose)**	**Total Cost**
SRS (stereotactic radiotherapy)	£2,399	50%	6	£7,197.15
WBRT (whole brain radiotherapy)	£1,007	5%	6	£302.20
CNS management lump sum				***£8,221.37***
Steroids (dexamethasone)	£16.46	10%	Applied in each CNS progressed health state cycle	£1.65
CNS: central nervous system; SRS: stereotactic radiotherapy; WBRT: whole brain radiotherapy.				

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 progressed-disease health state costs were also reviewed by the EAG's clinical advisor, who considered them reasonable.

The EAG notes previous discussion in TA670 regarding the appropriate CNS management costs to apply with several scenarios explored. The EAG, however, does not explore this uncertainty as in the context of the current model these costs have very little impact on the ICER. Issues raised in Section 4.2.2 regarding the viability of the CNS progressed health state also supersede any issues with the costs applied, as the EAG does not consider it possible to accurately reflect CNS- progression given the currently available evidence.

4.2.8.5 Adverse reaction unit costs and resource use

Costs associated with the management of adverse events were based on Grade 3 or higher events occurring in more than 5% of patients in either the lorlatinib arm of CROWN trial, the alectinib arm of ALEX, or the brigatinib arm of ALTA-1L. Unit costs were derived from NHS Reference Costs 2019/20 and other recent appraisals of brigatinib. The AE costs, resource assumptions, and the sources cited by the company in their submission are summarised in Table 64 of the company submission (Page 108).

Points for critique

The methods used to derive the costs of AEs and implementing them into the model appear reasonable and are broadly comparable to other appraisals of alectinib (TA536) and brigatinib (TA670). The EAG's clinical advisor agreed that the consideration of only Grade 3 or higher adverse events was reasonable. The EAG notes that in the earlier appraisals TA536 and TA670, adverse events were based on Grade 3 or higher events occurring in more than 3% of patients.

At clarification, the EAG requested that the cost associated with treatment with statins for all patients with treatment related dyslipidaemia of any grade, i.e. hypercholesterolaemia, hypertriglyceridemia, hyperlipidaemia, in addition to adding resource use reflecting blood testing and clinician time for Grade 1/2 treatment related dyslipidaemia events. This was corrected and included in the updated version of the company model submitted following clarification.

4.2.8.6 ALK Testing

The company did not include ALK testing in their base-case analysis. The CS states that the base-case analysis assumes that testing for all actionable oncogenic driver mutations is undertaken in all patients with non-squamous NSCLC at diagnosis and, therefore, does not need to be included.[34]

The EAG considers the omission of ALK testing to be appropriate. As stated by the CS, ALK testing would be equally applied to lorlatinib, alectinib, and brigatinib and is thus a cost common to both treatment pathways, and therefore it would not affect the choice between the intervention and comparators.

4.2.8.7 End of life costs

The CS model calculated a one-off cost to account for terminal care sourced from Round *et al*.[35] and uprated to 2019/2020 using the PSSRU.[31] An end-of-life cost of £5,123.24 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.* [35] was assumed to be generalisable to ALK-positive NSCLC in the company model. This method of including the end-of-life costs in the model is line with previous alectinib (TA536)[30] and brigatinib (TA670)[1] appraisals.

Points for critique

The EAG notes that the end of life (EoL) cost applied in the model is sourced from a published study,[35] rather than from a micro-costing of the end of life services provided by the NHS to ALK-positive NSCLC patients. Therefore, the resource use for EoL cannot be varied in the company model. The EAG has some minor concerns regarding the source and composition of the EoL cost. The EAG, however, notes that the EoL cost used in this model is higher than what was used in the brigatinib appraisal (TA670; EoL cost estimate: £1,772) or the alectinib appraisal (TA536; EoL cost

estimate: £3,679.37). The EAG notes that the model results are not sensitive to this parameter, therefore, any uncertainty around this parameter is not explored further.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's updated base case analysis as presented in the clarification response. The results presented in the following sections are inclusive only of the PAS discounts for lorlatinib unless otherwise stated. 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 4.2.4. The incremental cost effectiveness ratio is the ratio of expected additional total cost to those of expected additional QALYs compared with alternative technologies. In addition, the company presents the expected net health benefit (NHB) at a willingness-to pay threshold of £30,000 per QALY gained.

The results of the company's cost-effectiveness analysis after application of the lorlatinib PAS discount are summarised in Table 34 and Table 35. Including only the lorlatinib PAS discount, in the company base-case, [redacted]

Table 34 Company base-case results: fully incremental deterministic analysis (lorlatinib PAS only)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lorlatinib	[redacted]	[redacted]			
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years					

Table 35 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)	NHB
Lorlatinib vs brigatinib								
Brigatinib	[redacted]	[redacted]	[redacted]					
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib vs alectinib								
Alectinib	[redacted]	[redacted]	[redacted]					
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit

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 certainty in the results. The mean probabilistic ICER for lorlatinib compared to each of the comparators are presented in Table 36 and

Table 37. With the 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 and [redacted] probability at a willingness-to-pay threshold of £30,000 per QALY (Figure 8). 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 (Figure 8).

Table 36 Company base-case results: incremental probabilistic analysis (lorlatinib PAS only)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lorlatinib	[redacted]	[redacted]			
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Table 37 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)	NHB
Lorlatinib vs brigatinib								

Brigatinib	[redacted]	[redacted]	[redacted]					
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib vs alectinib								
Alectinib	[redacted]	[redacted]	[redacted]					
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit								

Figure 8 Cost-effectiveness acceptability curve for the fully incremental probabilistic analysis (generated from company's model)

[redacted]

5.2 Company's additional analyses

At the clarification stage, the EAG requested that the company present a number of scenarios which explored alternative assumptions and parameter inputs. These scenarios were presented in pairwise fashion against alectinib and brigatinib separately. The results of these pairwise analysis are presented in Table 38 and Table 39. The scenarios explored were as follows:

i. Treatment waning effect applied for lorlatinib for 10 and 20 years;
ii. Time horizon of the model set to 20 years or 40 years;
iii. Using mean relative dose intensity from CROWN study from instead of detailed dosing for lorlatinib;
iv. The incorporation of ALESIA trial in the NMA analysis network for the PFS curve estimate;
v. Fitting a conservative Weibull parametric distribution to the PFS curve estimate;
vi. Fitting an optimistic Gompertz parametric distribution to the PFS curve;
vii. Discounting of cost and QALY outcomes at 6% or 0%;

viii. Fitting an optimistic log-normal distribution and most conservative Gompertz distribution to the mean PPS for second-line lorlatinib after alectinib or brigatinib first-line.

ix. Chemotherapy treatment as second line treatment (2L) after alectinib or brigatinib for 10% and 20% of the patients respectively.

Table 38 Company's additional scenario analysis (deterministic): lorlatinib vs alectinib (inclusive of lorlatinib PAS)

Parameter varied	Incremental costs	Incremental LYGs	Incremental QALYs	ICER	NHB
Lorlatinib vs Alectinib					
Discounting set to 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounting set to 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon set to 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon set to 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Used RDI instead of detailed lorlatinib dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning at 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning at 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean PPS after alectinib based on log-normal distribution for second-line lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean PPS after alectinib based on Gompertz distribution for second-line lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS - Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA analysis network including ALESIA study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% of alectinib patients receiving 2L chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% of alectinib patients receiving 2L chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit					

Table 39 Company's additional scenario analysis (deterministic): lorlatinib vs brigatinib (inclusive of lorlatinib PAS)

Parameter varied	Incremental costs	Incremental LYGs	Incremental QALYs	ICER	NHB
Lorlatinib vs Brigatinib					
Discounting set to 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounting set to 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon set to 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon set to 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Used RDI instead of detailed lorlatinib dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning at 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning at 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean PPS after brigatinib based on log-normal distribution for second-line lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean PPS after brigatinib based on Gompertz distribution for second-line lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS - Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA analysis network including ALESIA study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% of alectinib patients receiving 2L chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% of alectinib patients receiving 2L chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit					

5.3 Model validation and face validity check

5.3.1 Validation undertaken by the company

The CS stated that the outcomes of the model were clinically validated to ensure the face validity of predictions. This was undertaken by comparing PFS and OS data from the model to data from CROWN trial[4] for lorlatinib, ALEX study [11, 36] for alectinib and ALTA-1L study [37] for brigatinib and was further supported by internal health economist working on the model and validation by an independent external health economist.

5.3.2 Internal validation undertaken by 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.

One significant error was identified in the updated model provided in the company's clarification response. The EAG found that contrary to the model structure described by the company, patients could not transition from the PFS health state to death. This means that the model overestimated the proportion of patients remaining alive and transitioning to the progressed disease health state, and thus

total costs and QALYs were overestimated. The proportion of PFS events as death used to adjust costs following progression was [redacted], based on the overall proportion of PFS events that were death in the CROWN study. As this transition between PFS and death was depicted in the model schematic and described in the company submission, this omission was assumed to be in error. The EAG therefore corrected its implementation using the [redacted] rate applied elsewhere in the model. Revised results correcting for this omission are reported in Section 6.

Another health state transition described in the company submission was also found not to be populated in the economic model. Patients conceptually should be able to move from the non-CNS PD state to the CNS PD state, a transition described in the submission and depicted in the model schematics. However, the EAG could not identify appropriate data was not available to inform this transition. Scenarios in which this health state is removed are presented in Section 6.2.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the cost-effectiveness analysis presented by the company, which are discussed in detail in Section 4.

The following section presents a number of alternative scenarios in areas the EAG considered alternative approaches and assumptions to be plausible, with particular emphasis on those with a potentially significant impact upon cost-effectiveness estimates. Given the high level of uncertainty associated with available trial evidence for lorlatinib, particular consideration has been given to the exploration of the impact of uncertainty upon the estimates of cost-effectiveness.

Descriptions of the EAG's exploratory analyses are provided in Section 6.1, and the degree of change on the ICERs and other cost effectiveness outcomes compared to the company's base-case is explored in Section 6.2. The company implemented a range of changes and additional scenarios in their response to the EAG's clarification questions. These changes went some way to addressing the key concerns raised at the clarification stage, and with the exception of the correction implemented by the EAG, results in a plausible representation of the very limited data available if the distribution of probabilistic results is fully appreciated.

The analyses presented throughout the following sections are inclusive of the correction made by the EAG to the representation of PFS events described in Section 4.2.2 and 5.3.2.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The scenarios presented by the EAG represent plausible alternative interpretations of the available data with varying degrees of optimism and complexity. It may be inappropriate for the EAG to take a

position on a number of the remaining issues. In these areas, alternative scenarios are presented but no preference is expressed in the form of inclusion in the EAG's base-case.

The EAG also presents a preferred base-case in Section 6.3, which represents a simplified scenario making fewer assumptions, given the uncertainties and other issues within the available data.

1. Results of 'Global NMA' applied in the model (including ALESIA study)

As discussed in Sections 3.4 and 4.2.3, the EAG considered the NMA for the PFS outcome which included the ALESIA study (alectinib) most appropriate for decision-making. As previously described, the ALEX and ALESIA pivotal trials separated non-Asian and Asian centres (respectively), whereas all corresponding centres were included in CROWN and contribute to efficacy estimates for lorlatinib. The EAG therefore considers it appropriate to include both ALESIA and ALEX to maintain consistency between the trial populations.

2. Direct application of CROWN PFS KM for lorlatinib up to 30 months

In Section 4.2.6 the EAG highlighted the poor fit of the exponential model to CROWN PFS data for lorlatinib over the period for which we have KM data available. Over the first two years of the model, PFS is estimated at around 8% higher than the corresponding observed data for lorlatinib patients. This scenario presents a simple exploration of the effect of this poor fit, setting PFS equal to the Kaplan-Meier data until approximately Month 30, at which point the curves intersect and the exponential curve is used. This scenario is methodologically inconsistent with the model as a whole, but simply aims to illustrate the effect of the poor fit of the only clinically plausible PFS extrapolation. As the crizotinib PFS data were far more complete, this approach is unnecessary for the comparators.

3. Waning of the treatment effect over 7 to 15 years

As discussed in Section 4.2, there are two primary reasons for considering treatment effect waning in this appraisal. Firstly, while the exponential curve for PFS on lorlatinib is the most pessimistic of those fitted by the company, long-term estimates generated were considered highly optimistic by the clinical adviser to the EAG. The EAG therefore uses treatment waning as a means of exploring alternative long-term assumptions regarding the maintenance of the treatment effect in light of current clinical understanding of this indication. Secondly, treatment waning has been used to inform the decisions made in TA670 for brigatinib where of treatment effect was assumed at 7, 10, or 20 years and in TA536 for alectinib where treatment waning was assumed at 3, 5, 7, or 10 years.

4. Arm-specific death as a proportion of PFS

Further to the correction described in Section 5.3.2, the EAG disagreed with the company's interpretation of the observed data in CROWN (see Section 4.2.2). Rather than calculating deaths as a proportion of PFS events across both arms, the disparity between the arms ([redacted] vs [redacted] for crizotinib and lorlatinib respectively) suggested this approach misrepresents the trial data. That is, under the company's preferred assumption, the additional [redacted] of patients who died in the trial whilst progression free were assumed in the model to remain alive and continue to accrue QALYs. This analysis applies treatment arm-specific values instead, as the crizotinib arm value more closely resembles that of brigatinib (5.1%) in ALTA-1L.

5. Removal of the CNS Progressed Disease health state

As discussed throughout Section 4, the EAG considered the inclusion of this health state to be inappropriate and potentially misleading, and moreover, that the description of the health state in the company submission and model schematic is not representative of the approach taken within the model. There is a mismatch between the data applied in the model from CROWN and what the model purports to represent. Patients cannot enter the model with CNS metastases, and much of the treatment benefit in these patients cannot be captured. Patients with progressed disease cannot subsequently develop CNS-metastases. The magnitude of benefit of lorlatinib compared to alectinib and brigatinib has not been statistically or clinically substantiated. The sources of PPS data applied in the model are unlikely to adequately represent the prognosis of a population comprising patients with CNS metastases. The above issues cannot be resolved using an alternative modelling approach given the limitations in the underlying data. The EAG considers the treatment benefits to be better represented in the three-state model if a more appropriate utility set is applied (see Scenario 6).

6. Utilities from TA670

In Section 4.2.7 the EAG identified that the utilities derived from the CROWN study and applied in the present model were considerably higher than those accepted in the brigatinib appraisal TA670 (see Section 4.2.7. The utilities applied in the company submission implied little to no benefit of preventing disease progression, and a similar utility set was rejected by the Committee in TA670. The EAG therefore presents a scenario in which the utility values for the health states is derived from the preferred values applied in TA670, the most recent appraisal for treatments for ALK-positive advanced NSCLC. This applies a utility of 0.793 to the progression-free health state, 0.623 for progressed disease, and 0.470 for CNS progression.

7. Adverse event disutility correction and use of CROWN durations

The EAG considered the company's implementation of the AE-related disutilities from TA670 inconsistent with the approach described in that appraisal. The EAG therefore presents a scenario in

which AEs are assumed to last for one model cycle, except in cases where durations have been reported from CROWN for AEs of special interest. The EAG also implements a preferred interpretation of the neutropenia disutility from Nafees *et al*.,[25] as referenced by the company in their clarification response.

8. Treatment beyond progression allowed (5.7 months)

As discussed in Section 4.2.6 and 4.2.8 in response to clinical advice, 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 considers only the additional acquisition cost associated with treatment beyond progression, exploring the assumption that the duration of treatment with lorlatinib is equal to median PFS plus 5.7 months.[20]

9. RDI method used consistently for all treatments

As discussed in Section 4.2.8, the EAG prefers to use a unified approach to calculating dose intensity across all technologies, given uncertainties generated by the use of pack sizes with different costs per mg. This scenario uses relative dose intensity (RDI) to model cost savings from dose reductions. This approach is inherently simpler, and is consistent with that accepted by the Committee in the previous appraisals in this indication. The EAG notes that this approach assumes that the 120 x 25mg packs for lorlatinib are used in all patients. The use of this pack type in all patients is a point to be resolved in the Technical Engagement step.

10. Proportion of comparator patients progressing onto chemotherapy consistent with CROWN

As discussed in Section 4.2.6 and 4.2.8, the EAG's clinical adviser considered the assumption that 5% of patients would not be expected to receive lorlatinib following progression on alectinib and brigatinib an overestimate. The EAG therefore present a scenario in which the proportion of comparator patients going on to second-line lorlatinib is equal to the proportion of patients who received a subsequent anti-cancer therapy in CROWN after progression on lorlatinib. This equated to [redacted] it was assumed this population represented those fit enough to receive further active anti-cancer treatment (i.e. a subsequent TKI), with the remainder assumed to receive best supportive care (BSC). Patients assumed to receive BSC were assumed to receive second-line chemotherapy PPS outcomes.

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 are presented in Table 40. These results include the PAS discount for lorlatinib only. Incremental net health benefit (INHB) is presented at a

willingness to pay threshold of £30,000. The exploratory scenarios presented in Table 40 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 40 EAG Exploratory incremental scenario Analyses (Including lorlatinib PAS only)

Scenario	Technology	Total		Incremental		ICER	INHB
		Costs	QALYs	Costs	QALYs		
EAG-corrected company base-case	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Global NMA HRs (including ALESIA)	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Direct application of lorlatinib PFS KM up to 30 months	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3a. Treatment effect waning: 7 years	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3b. Treatment effect waning: 10 years	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3c. Treatment effect waning: 15 years	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Arm-specific deaths as proportion of PFS events	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Removal of CNS-PFS health state	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. TA670 utilities	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. AE disutility correction & CROWN duration data	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Treatment beyond progression allowed (5.7 months)	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. RDI costing method used consistently for all treatments	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10. Comparator patients progressing onto chemo vs lorlatinib based on CROWN	[redacted]	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years							

6.3 EAG's preferred assumptions

The cumulative impact of the EAG's preferred assumptions are presented in Table 41 below. As the company implemented a number of changes to the model in response to concerns raised by the EAG, the EAG's preferred base-case is primarily driven by the removal of the CNS PD health state, and the use of an alternative utility set from TA670. 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.

A further set of analyses is also presented below, which reflects a less optimistic outcome of the use of lorlatinib, including a limit on the duration of the treatment effect to reflect uncertainty around PFS, the assumption that lorlatinib will continue to be used beyond the point of progression, and the inclusion of the EAG's interpretation of AE disutilities, reflecting clinical concerns regarding the toxicity of lorlatinib. Note that all results are inclusive only of the PAS discount available for lorlatinib. Results inclusive of all available commercial arrangements are presented in the confidential appendix to this report.

The EAG base-case adopts the following scenarios described in Section 6.1:

Scenario 1: Global NMA PFS HRs (including ALESIA)
Scenario 5: Removal of CNS PD health state
Scenario 6: TA670 utilities
Scenario 9: RDI costing method used consistently for all treatments
Scenario 10: Comparator patients progressing onto chemo vs lorlatinib based on CROWN

Table 41 EAG's preferred model assumptions (Deterministic)

Preferred assumption	Section in EAG report	Cumulative ICER
Scenario 1: Global NMA HRs (including ALESIA)	3.4, 4.2	[redacted]
Scenario 5: Removal of CNS PD health state	3.3, 4.2.1, 4.2.6	[redacted]
Scenario 6: TA670 utilities	4.2.7	[redacted]

Scenario 9: RDI costing method used consistently for all treatments	4.2.8	[redacted]
Scenario 10: Comparator patients progressing onto chemo vs lorlatinib based on CROWN	4.2.6, 4.2.8	[redacted]

Probabilistic results for the EAG's alternative base-case are presented in Table 42. The model was set to the EAG's preferred assumptions and run with 2,000 iterations. [redacted]

Table 42 EAG's alternative base-case analysis results (probabilistic)

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

The EAG also considers this less optimistic set of assumptions a potentially plausible alternative scenario, more closely reflecting a number of clinical concerns described in the report is presented in Table 43. This analysis adopts the following scenarios described in Section 6.1:

Scenario 1: Global NMA HRs (including ALESIA)
Scenario 3b: Treatment effect waning: 10 years
Scenario 4: Arm-specific deaths as proportion of PFS events
Scenario 5: Removal of CNS PD health state
Scenario 6: TA670 utilities
Scenario 7: AE disutility correction & CROWN duration data
Scenario 8: Treatment beyond progression
Scenario 9: RDI costing method used consistently for all treatments
Scenario 10: Comparator patients progressing onto chemo vs lorlatinib based on CROWN

The incremental impact of these assumptions on the ICER vs brigatinib [redacted] are presented in Table 43. The deterministic ICER for lorlatinib versus brigatinib is [redacted] The probabilistic results of this analysis (2000 iterations) are presented in Table 44. Again, these results include only the lorlatinib PAS discount. The EAG notes that the inclusion of all commercial arrangements for the comparators and chemotherapy has a

substantial effect on the apparent cost-effectiveness of lorlatinib. Equivalent results including all available commercial arrangements are provided in the confidential appendix to this report.

Table 43 EAG's conservative alternative model assumptions (Deterministic)

Preferred assumption	Section in EAG report	Cumulative ICER (vs brigatinib)
Scenario 1: Global NMA HRs (including ALESIA)	3.4, 4.2	[redacted]
Scenario 3b: Treatment effect waning: 10 years	4.2.6	[redacted]
Scenario 4: Arm-specific deaths as proportion of PFS events	4.2.2	[redacted]
Scenario 5: Removal of CNS PD health state	3.3, 4.2.1, 4.2.6	[redacted]
Scenario 6: TA670 utilities	4.2.7	[redacted]
Scenario 7: AE disutility correction & CROWN duration data	4.2.7	[redacted]
Scenario 8: Treatment beyond progression	4.2.8	[redacted]
Scenario 9: RDI costing method used consistently for all treatments	4.2.8	[redacted]
Scenario 10: Comparator patients progressing onto chemo vs lorlatinib based on CROWN	4.2.6, 4.2.8	[redacted]

The probabilistic ICER of lorlatinib in this scenario was [redacted]. The difference in the probabilistic and deterministic ICERs is driven by higher total costs for brigatinib, but the reason for this disparity is unclear. [redacted].

Table 44 EAG's conservative alternative base-case analysis results (probabilistic)

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

Figure 9 EAG conservative alternative base-case cost-effectiveness plane (pairwise lorlatinib vs brigatinib)

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 non-small-cell lung cancer. The company's model comprised four health states (progression free, non-CNS progressed disease, CNS progressed disease) in the form of a hybrid partitioned survival model/state transition 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 a net health benefit 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, and a [redacted] probability at a willingness-to-pay threshold of £30,000 per QALY gained. Note that these results are based on the net price of lorlatinib inclusive of a patient access scheme, but are exclusive of available confidential discounts for alectinib and brigatinib.

6.4.1 Conclusions of the EAG's critique

The EAG considers the submitted evidence to broadly reflect the decision problem defined in the final scope, and that the submitted analyses meet the requirements of the NICE reference case. The EAG's review of the company submission identified several areas of significant uncertainty, and a number of

key methodological issues which the EAG has sought to characterise and address where possible in the revised base case and scenario analyses.

The primary area of uncertainty relates to the immaturity of PFS data available for lorlatinib. Due to the design of the CROWN trial, PFS is the sole outcome which is sufficiently generalisable to the NHS setting and treatment pathway to meaningfully inform a decision between lorlatinib and its comparators. Differences in PFS are also the principal driver of cost-effectiveness. The EAG's primary concern relates to the lack of plausible alternative extrapolations available due to the extreme immaturity of PFS data for lorlatinib, resulting in all alternative parametric curves fitted by the company producing clinically implausible long-term predictions of PFS. This means that even the most pessimistic extrapolation of PFS results in 10-year PFS predictions considered extremely optimistic by the EAG's clinical adviser. Improved maturity of this outcome will serve to reduce much of the resolvable uncertainty associated with the duration of the treatment effect and the comparative effectiveness. In the absence of alternative clinically plausible PFS extrapolations, and the limitations of the exponential function in capturing changing hazards over time, the EAG explored the use of effect waning to examine the effect of reducing the expected treatment effect on cost-effectiveness.

The EAG also has substantive concerns regarding the company's implementation of the model structure described in their submission and clarification response. The EAG highlighted further concerns that given the limitations in the data collected in CROWN, a four-state model as proposed by the company cannot be meaningfully informed. Firstly, the model did not allow patients to die from the progression-free health state, which meant the model misrepresented the trial outcome and observed data, leading to a significant overestimate of the number of patients alive in the model. This was corrected by the EAG, with an alternative interpretation suggested as a scenario analysis.

Secondly, patients who have experienced a disease progression event were described as being able to further develop intracranial metastases. The link between these two health states was not built into the model, further, due to the censoring of patients in CROWN who received a subsequent anticancer therapy from the CNS progression endpoint, it is unlikely that this transition can be populated with relevant data from CROWN. Furthermore, no comparable data exists for alectinib or brigatinib. This represents one of the several fundamental flaws with the four-state model as proposed in this appraisal. Further, the company assumed the survival of patients with CNS PD would be equivalent to the mixed populations in Study 1001 and PROFILE 1001/1005. This is likely to result in an overestimate of post-progression survival in this population. Inconsistent outcome assessment across studies means any treatment benefit in terms of delaying or preventing CNS progression events would be challenging to implement in a model, even with more mature data. Given the limitations in the available data to inform transitions, the EAG considers it more appropriate to remove the CNS PD

health state, and thus only capturing improvements in control of CNS metastases in the context of whole-population PFS and PPS data.

The EAG also has concerns regarding the company's approach to capturing the HRQoL of patients in the model. The collection of post-progression EQ-5D-5L data in CROWN at or near the point of clinical progression resulted in only a negligible difference between the pre-progression and progressed disease utilities. These values were inconsistent with technology appraisals, and meant a treatment more effective at preventing progression would not necessarily generate more QALYs from doing so. The regression methods used by the company to derive utilities from the data collected in CROWN may also mean that the effects of adverse events associated with lorlatinib were not captured in the model, as utility data from patients who had treatment withdrawn to allow the resolution of TRAEs were not included in the utility applied to the progression-free population. As a result, the company's base-case model may overestimate the QALYs generated by lorlatinib.

The ERG identified several additional resource use issues, which have a smaller impact on the results. This includes a preference for a unified RDI approach to modelling treatment wastage and acquisition costs across treatments, the potential cost implications of treatment with lorlatinib beyond the point of progression, and issues with the assumption that 95% of patients will receive second-line lorlatinib after progressing on alectinib and brigatinib. These issues were explored in scenario analysis presented by the EAG and were demonstrated to have a modest impact on the cost-effectiveness of lorlatinib.

The impact of these uncertainties was considered in a series of exploratory analyses. The assumptions with the largest impact upon the cost-effectiveness of lorlatinib included capping the duration of the treatment effect (i.e. effect waning), removal of the CNS-PD health state, implementing the EAG's alternative interpretation of AE data for lorlatinib, and reflecting the cost of treatment beyond progression. The EAG's alternative base-case produced a deterministic ICER of [redacted] A more conservative set of plausible assumptions generated a deterministic ICER of [redacted]. The EAG notes that the inclusion of available commercial arrangements for alectinib, brigatinib, and chemotherapy drugs has a substantial effect on estimates of the cost-effectiveness of lorlatinib.

7 SEVERITY MODIFIER

The company has not made a case for a severity modifier. The EAG agrees that the severity modifier would not apply for this population.

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Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

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 1 August 2022** 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 separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Removal of CNS-progressed health state

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3896 Lorlatinib EAG report 25072022KM [ACIC] Page 16 The EAG has suggested the CNS-PD health state be removed from the model.	Pfizer requests that the CNS-PD health state should be maintained in the model for committee consideration, whilst acknowledging the limitations.	We acknowledge the limitations of the evidence base for the CNS-progressed health state because we do not have data on patients transitioning from the non-CNS progression to the CNS-PD health state. However, lorlatinib was specifically designed to penetrate into the CNS and has demonstrated a [redacted] reduction in the risk of intracranial progression versus crizotinib. Therefore, we believe it would lead to greater modelling inaccuracy to remove the CNS-PD health state vs maintaining it. Furthermore, there is precedent for including this health state (for alectinib and brigatinib) despite data limitations, we believe this approach is likely conservative (underestimating the true incremental value of preventing patients from entering the CNS-PD	Not a factual error. The ERG acknowledges the specific CNS-related benefits of lorlatinib but does not feel that there is an appropriate way to capture this given the current evidence base. The ERG is open to creative solutions and would encourage the company to submit further evidence at technical engagement.

		health state relative to comparators), and we maintain that the clinical value of including the CNS-PD health state outweighs the limitations of the evidence base.	

Issue 2 Current and anticipated NHS practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ID3896 Lorlatinib EAG report 25072022KM [ACIC] Page 33 Current and anticipated NHS practice would be to use: • Alectinib or brigatinib as first-line treatment, followed by lorlatinib at second-line (which is current practice), or • Lorlatinib as first-line treatment, with some patients continuing on lorlatinib	Current and anticipated NHS practice would be to use: • Alectinib or brigatinib as first-line treatment, followed by lorlatinib at second-line **and chemotherapy at third-line** (which is current practice). **Some patients may continue on lorlatinib after progression.** • Lorlatinib as first-line treatment, followed by chemotherapy at second-line. **Some patients may continue on lorlatinib after progression.**	It is not clear how many patients may continue on lorlatinib after progression. It is anticipated this number would be similar if lorlatinib was used in first or second line.	This has been revised to reflect the company's comments.

after progression (and some receiving chemotherapy)			

Issue 3 Inaccuracy in the proportion of progression events as death for crizotinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ID3896 Lorlatinib EAG report 25072022KM [ACIC] Page 59 *"The proportions differed markedly between treatment arms in CROWN, with [redacted] ([redacted]%) of events in the **lorlatinib arm** being death, compared to only [redacted] ([redacted]%) on **lorlatinib.**"*	*"The proportions differed markedly between treatment arms in CROWN, with [redacted] ([redacted]%) of events in the **lorlatinib arm** being death, compared to only [redacted] ([redacted]%) on **crizotinib.**"*	Error in the EAG's report.	This has been amended as suggested.

Issue 4 Factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3896 Lorlatinib EAG report 25072022KM [ACIC] Page 88 *"Although the **per mg** 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."*	*"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."*	The per mg cost is not the same for the 90 x 25 mg and 30 x 100 mg packs. However, the acquisition cost is the same for each pack.	This has been revised as suggested.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Technical engagement response form

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **9 September 2022**. 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.

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Pfizer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. The anaplastic lymphoma kinase (ALK) inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE.	No	CROWN is a Phase III study directly comparing lorlatinib monotherapy to crizotinib monotherapy for the first-line treatment of patients with ALK-positive NSCLC. The trial was designed to assess the head-to-head safety and efficacy of lorlatinib versus crizotinib, given crizotinib was the relevant comparator at the time of trial design. Since then, two second generation ALK TKIs have obtained regulatory approval and been recommended by NICE for the treatment of ALK-positive NSCLC: alectinib (TA536) and brigatinib (TA670). Given that the treatment used in the comparator arm of CROWN crizotinib has limited use in NHS practice, and in the absence of alternative trials directly comparing lorlatinib to alectinib and brigatinib, indirect treatment comparisons were conducted to assess the relative efficacy and safety of lorlatinib compared to alectinib and brigatinib.
2. Nearly all patients in the CROWN trial had an Eastern Cooperative Oncology Group	No	Data from the National Lung Cancer Audit published in 2022, for the audit period 2019 England, Wales and Guernsey and 2020 England provides information on performance status (PS).

Performance Status (ECOG PS) score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS.		In the 2019, 33,091 patients diagnosed with lung cancer were available for analysis, while in 2020 there were 31,371 cases registered. Comparison of the 2019 and 2020 audits shows that PS distribution has been adversely affected in 2020 with 38% of patients presenting with PS >2 in 2019 compared with 40% in 2020. In addition, clinical feedback was sought from n=3 clinicians, who advised that 25-30% of patients have PS2 or higher, however that true PS is often difficult to measure in ALK+ patients who tend to be younger and without co-morbidities. Additional data collection in the CDF will help validate the generalisability of baseline characteristics observed in the CROWN trial to clinical practice.
3. Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	No	At the September 2021 CROWN data cut, median duration of follow-up for PFS was [redacted] and [redacted] in the lorlatinib and crizotinib treatment arms, respectively. Median PFS for lorlatinib was [redacted]. There remains substantial uncertainty in OS estimates for lorlatinib, and the relationship between PFS and OS. We cannot provide any additional evidence at this time to address this uncertainty. Data maturity will help address this issue, with the next data cuts planned for [redacted].
4. Grade 3 or 4 adverse events occur more frequently with lorlatinib than with alectinib.	Yes	We agree that the side effect profile is different for lorlatinib versus alectinib/brigatinib. From a clinical perspective it is important for patients and physicians to be able to choose their preferred first-line treatment from a number of available options, as having more options available to them may help them find a treatment which provides the right balance between efficacy, toxicity and QoL for the specific medical situation. From a recent survey conducted by ALK+UK, and presented at World Conference on Lung Cancer 2022, it was found that when considering only

		the side effects, 63% of respondents reported that lorlatinib was the preferable ALK inhibitor drug. This survey was based on responses from 93 patients diagnosed with ALK+ NSCLC in the UK and is included with this response. During the clarification question stage, the EAG requested an NMA on results of any grade AEs for peripheral neuropathy, cognitive and mood effects (which were judged to be key AEs by the EAG's clinical advisor). However, we were unable to conduct this NMA owing to an absence of comparator data on peripheral neuropathy, cognitive and mood effects for brigatinib and alectinib reported in ALTA-1L and ALEX trials. As reported in the published NMAs, Chuang et al. found that lorlatinib was associated with an increased risk of experiencing ≥ Grade 3 adverse events when compared with alectinib (relative risk [RR] 1.62, 95% credible interval [CrI] 1.24 to 2.12). There were limited differences between lorlatinib and brigatinib (RR 1.07, 95% CrI 0.84 to 1.37). Ando et al. drew similar conclusions that lorlatinib was associated with greater risk compared with alectinib (RR 1.92, 95% CrI, 1.49 to 2.48) and similar risk compared with brigatinib (RR 1.18, 95% CrI 0.90 to 1.55) of experiencing ≥ Grade 3 adverse events. However, a limitation of these NMAs is that they only capture grade 3-5 AEs by proportion, and do not capture the heterogeneity in the side effect profile of the ALK TKIs. Treatment discontinuation rates observed in clinical trials also indicate that lorlatinib is tolerable to patients. There was a low treatment discontinuation rate due to AEs for lorlatinib [redacted] versus crizotinib [redacted] treatment discontinuation) in the CROWN study. This is slightly lower than 11% for alectinib and 12.5% for brigatinib in ALEX and ALTA-1L, respectively.

		Cognitive adverse events associated are expected to be managed with dose modifications. In the phase I/II safety study (NCT01970865), 39.7% of patients experienced CNS effects, and baseline CNS metastases were present in 71.8% of patients with CNS effects. However, cognitive effects associated with lorlatinib were generally mild in severity and intermittent and improved or resolved upon dose modifications.[1]
5. Baseline central nervous system (CNS) metastases as a potential treatment effect modifier.	No	The proportion of patients with baseline brain metastases across clinical trials are: • ALEX (alectinib 42%, crizotinib 38%) • ALTA-1L (brigatinib 29%, crizotinib 30%) • CROWN (lorlatinib 26%, crizotinib 27%). We received clinical advice from n=3 clinicians, who advised that approximately one third of patients present with baseline brain metastases, compared to 26% receiving lorlatinib and 27% receiving crizotinib in CROWN. However, there was no evidence that CNS metastases at baseline impacted PFS estimates comparing lorlatinib with alectinib. This is supported by the evidence from published NMAs (Wang et al; Chuang et al) who found similar PFS estimates for those with and without CNS metastases. In contrast, PFS differences between lorlatinib and brigatinib were potentially impacted by the presence of CNS metastases at baseline. Lorlatinib was more effective than brigatinib in patients without CNS metastases. Additional data collection in the CDF will help validate the generalisability of the baseline characteristics observed in CROWN to clinical practice.

6. The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate.	No	We appreciate the EAG's concerns around the exclusion of ALESIA in the NMA and presented a scenario analysis for the inclusion of ALESIA in our clarification question response. In TA670, ALESIA was excluded from the ITC as only east Asian patients were enrolled in the trial. We believe this remains a decision for the clinical experts and committee to determine the generalisability of the ALESIA population to UK clinical practice.
7. Immaturity of PFS outcome leading to lack of alternative extrapolations.	Yes	In acknowledgement of the uncertainty around this assumption, we selected the most conservative survival extrapolation for lorlatinib (exponential) which estimates that less than 5% of patients alive after 20 years and less than 1% of patients alive after 30 years. This extrapolation was clinically validated – with clinical advice that the exponential, Weibull or gamma extrapolations could be clinically plausible. Scenario analyses exploring the uncertainty in PFS extrapolations were provided in our response to the clarification questions. Additional data maturity will assess some of this uncertainty, with the next data cut in [redacted]. To characterise this uncertainty, additional piecewise survival analyses will be provided as an addendum to this response.
8. Death was not modelled as a PFS event.	No	We accept the EAG's update to this modelling error.
9. There are insufficient data available to model CNS progressed disease (PD) health state appropriately.	Yes	In our model, the progressed health state is divided into non-CNS progressed disease and CNS-progressed disease, which is relevant as CNS progression can have a substantial impact on a patient's quality of life.[2] A medical advisory board was conducted by Pfizer in April 2022. When comparing CROWN BICR-assessed PFS data with ALTA-1L at 36 months, confidence intervals do not overlap and the median PFS for lorlatinib is not met. Clinical advisors agreed that these data boosted their confidence in the brain penetration of lorlatinib.

		A limitation of the model is that it does not move patients from the non-CNS-PD to the CND-PD health state as data is not available from CROWN due to the censoring of patients who first experience a non-progression event. The question here should be with what frequency patients' transit between these two states, it should not be whether the two states should mutually exist. In clinical practice, patients progress with CNS and without CNS. Twice the NICE appraisal committee accepted that a model using a separate state for each was relevant for ALK-inhibitors in 1L NSCLC (TA536 and TA670). These two groups of patients have differing treatment outcomes (a [redacted] reduction in intracranial progression with lorlatinib versus crizotinib, data well received by physicians at a recent Advisory Board) and different utilities once progressed, as a CNS multiplier from Roughley et al. is applied in line with previous appraisals. It is both relevant and accurate that a CNS-PD and a non-CNS state health state should be mutually modelled. Uncertainty around the transition probability between the two progressed states should not be grounds for excluding the state and departing from the model structures previously accepted by NICE. Instead, we propose exploring this uncertainty's impact on the ICER: a range of transition probabilities (25-75%) will be included in an addendum to this response, with an increased PAS. Utilities, costs and survival (using data from trials) are all already modelled for the two states.
10. Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation)	Yes	MHRA marketing authorisation states that patients may continue to receive treatment *"as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity".* The EAG have utilised second-line data (Ou et al.) indicating that 75.6% patients in the first-line are treated beyond progression for 5.7 months.

but benefits cannot be captured.		We have sought clinical advice on this issue from n=3 clinicians, who confirmed that for ALK TKIs generally, clinicians may treat beyond progression in the case of oligoprogression. Advice received by the company from clinicians is that approximately half of patients are treated beyond progression, for an average of 3 months. Furthermore, clinical advice confirms that it is likely that the same approach would be taken in first and second-line. Therefore, we have explored a range of scenarios, in which the proportion of patients treated beyond progression ranges from 50-90%, and the length of treatment beyond progression ranges from 3-5.7 months in the first- and second-line settings. These scenario analyses will be presented as an addendum to this response with a revised PAS.
11. Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities.	No	In our clarification question response we presented a scenario analysis for TA670 as the utility source.
12. Dosing calculations and proportion of patients receiving subsequent treatment.	Yes	Market research data conducted by Pfizer included with this response indicates that [redacted] of patients had their dose reduced from the second cycle, although this research is limited to second- and third-line usage. This aligns with clinical advice we have received, that patients will start on 100 mg tablets. Blood tests will be taken prior to the second cycle and the prescription will be amended to the 25 mg strength if necessary. Therefore, as patients will complete the first cycle, minimal wastage of the 100 mg tablets is expected to be incurred.

References

1. Bauer TM, Felip E, Solomon BJ, et al. Clinical management of adverse events associated with lorlatinib. The Oncologist. 2019;24(8):1103-1110
2. 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

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1. About you

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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Pfizer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2. Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 7. Immaturity of PFS outcome leading to lack of alternative extrapolations.	**Yes**	Flexible parametric survival models were used to model the progression-free survival (blinded independent central review), PFS (BICR), from the CROWN study. The methods used fall under two main categories: two-piece models and cubic spline models, as suggested by the EAG. **Two-piece models** When using two-piece models, survival estimates were taken directly from the trial for an initial period and are modelled by standard parametric methods thereafter. In CROWN, tumour assessments were performed at screening and then every 8 weeks (±1 week) starting from randomisation until independently assessed RECIST-defined disease progression. The two-piece models used the Kaplan–Meier estimates for survival up to a selected time point from which parametric survival models are fitted. For the models, the rebased times (Week 17 [or 3.91 months] and Week 25 [or 5.75 months]) were selected by consideration of the tumour assessment timings.

		The Kaplan–Meier plot in Figure 1 exhibits recognisable steps every 8 weeks (±1 week) which coincide with the protocoled tumour assessment. In Figure 2, the initial 21 months are displayed, the pronounced drops every 8 weeks can be clearly identified. On the x-axis time breaks are set to 1.84 months (8 weeks) and horizontal lines for these are provided to demonstrate the times at which these drops are expected to occur (the expected time of a tumour assessment visit). It is clear from the crizotinib arm that these drops coincide with the time breaks as is expected from the study protocol defined in Shaw 2020. The drops are less pronounced in the lorlatinib treatment arm. Using PSMs for data with such steep steps may result in unreliable estimates. This is because the large drops at each assessment are artifacts of the study protocol. In actuality, one would expect true progression events (if measured continuously) to be well dispersed over each interval of 8 weeks. **Figure 1. Kaplan-Meier plot of PFS (BICR) in CROWN** 

		Figure 2. First 21 months of PFS (BICR)  From the **Error! Reference source not found.**, we see that the most pronounced drop for PFS occurs at the second tumour assessment (3.68 months). This is also the time at which the treatment curves for PFS begin to separate. The rebase time should be 1 week after this assessment to align with the tumour assessment definition of every 8 weeks (±1 week). Thereby a rebasing time of 3.91 months which is approximately 17 weeks after randomisation was used. Figure 3 shows the fitted curves for rebasing from Week 17. Visually these curves show better fit than the original standard parametric survival models . All curves modelling the lorlatinib arm (red) show much closer fit than the previously selected exponential model.

		The crizotinib curves also appear to have visibly better fit over the period of 6 to 25 months compared to the standard parametric survival models . **Figure 3. PSMs with rebasing from 3.91 months extrapolated up to 54**  For lorlatinib the extrapolated portion of the curve (beyond 52 months) is slightly less varied between models with respect to survival estimates compared to the standard parametric survival models . However, the extrapolations are still variable with survival estimates at 10 years ranging between [redacted] with the exponential distribution and [redacted] with the Gompertz distribution. **<u>One knot spline</u>** In addition to the two-piece models, cubic spline models with both one-knot and two-knots were fitted. Three spline models (normal, proportional hazards and proportional odds) were fitted for one and two knots respectively, resulting in six models in total.

		Whether a one-knot or two-knot model is used, the three spline models provided very similar model fits. Figure 4 shows great visual fit to the lorlatinib data over the 52-month trial period. This fit is visually much better than standard PSMs used previously and has a far better fit than the chosen exponential model. **Figure 4. One-knot spline model for lorlatinib extrapolated up to 54 months** 

		At 200 months, the survival estimates predicted by the spline models are similar to those predicted by the Gompertz and generalized gamma standard parametric survival models . As the one-knot spline survival estimates are more optimistic than the five other standard PSM models (including the base case model), it is expected that the survival estimates produced by the spline models will be considered too optimistic to be clinically plausible. For crizotinib, at 60 months and 200 months the survival estimates predicted by the spline models are similar to those predicted by the standard parametric survival models (including the base case model). **Two-knot splines** The fit of the two-knot spline model for lorlatinib is very similar to the one-knot spline model in Figure 4. At 200 months, the survival estimates predicted for the spline models are similar to the estimates from the one-knot spline models, but the two-knot models have slightly more pessimistic survival estimates at this timepoint. Similarly, for crizotinib, at 60 months and 200 months the survival estimates predicted by the spline models are similar to the standard parametric survival models (including the base case model). **Conclusion** The EAG's preference was for more flexible survival analysis techniques to be explored, which could have examined the fit and projections of spline models or two-piece models, as we have presented here. This may have allowed a greater range of clinically plausible PFS projections to be explored. Details of the extrapolated progression-free survival probabilities for lorlatinib and crizotinib are provided in Table 2a and Table 2b respectively. In particular, at Year 10 for lorlatinib, the previous exponential model suggests a progression-free survival probability of [redacted], whereas the survival probability for each of the investigated flexible models ranges from [redacted]. The two-piece models give estimates around [redacted], and most of

the spline models give estimates closer to [redacted]. These values are much higher than the clinical advice received by the EAG. Therefore, the flexible survival models fitted do not provide extrapolated survival estimates that would be considered clinically plausible. For crizotinib, the investigated models also provide 10-year survival estimates greater than or equal to the previous exponential model.

Table 2a. Comparison of survival estimates for standard parametric models (exponential), two-piece models and spline models for lorlatinib in CROWN

Time		1 year	5 years	10 years	20 years
Standard parametric survival model	**Exponential**	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece model with rebased time at Week 17	**Exponential**	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]
One-knot Spline	**Normal**	[redacted]	[redacted]	[redacted]	[redacted]
	Proportional hazards	[redacted]	[redacted]	[redacted]	[redacted]

	Proportional odds	[redacted]	[redacted]	[redacted]	[redacted]
Two-knot Spline	**Normal**	[redacted]	[redacted]	[redacted]	[redacted]
	Proportional hazards	[redacted]	[redacted]	[redacted]	[redacted]
	Proportional odds	[redacted]	[redacted]	[redacted]	[redacted]

Table 2b. Comparison of survival estimates for standard parametric models (exponential), two-piece models and spline models for crizotinib in CROWN

Time		**1 year**	**5 years**	**10 years**	**20 years**
Standard parametric survival model	**Exponential**	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece model with rebased time at Week 17	**Exponential**	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
	Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]
One-knot Spline	**Normal**	[redacted]	[redacted]	[redacted]	[redacted]

		<table><tr><td rowspan="2"></td><td>**Proportional hazards**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>**Proportional odds**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td rowspan="3">**Two-knot Spline**</td><td>**Normal**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>**Proportional hazards**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>**Proportional odds**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>
Issue 9. There are insufficient data available to model CNS progressed disease (PD) health state appropriately.	**Yes**	In our model, the progressed health state is divided into non-CNS progressed disease and CNS-progressed disease, which is relevant as CNS progression can have a substantial impact on a patient's quality of life.[2] A medical advisory board was conducted by Pfizer in April 2022. When comparing CROWN BICR-assessed PFS data with ALTA-1L at 36 months, confidence intervals do not overlap and the median PFS for lorlatinib is not met. Clinical advisors agreed that these data boosted their confidence in the brain penetration of lorlatinib. A limitation of the model is that it does not move patients from the non-CNS-PD to the CND-PD health state as data is not available from CROWN due to the censoring of patients who first experience a non-progression event. The question here should be with what frequency patients' transit between these two states, it should not be whether the two states should mutually exist. In clinical practice, patients progress with CNS and without CNS. For comparator treatments, the NICE appraisal committee accepted that a model using a separate state for each was relevant for ALK-inhibitors in 1L NSCLC (TA536 and TA670). These two groups of patients have differing treatment outcomes (a [redacted] reduction

		in intracranial progression with lorlatinib versus crizotinib, data well received by physicians at a recent Advisory Board) and different utilities once progressed, as a CNS multiplier from Roughley et al. is applied in line with previous appraisals. It is both relevant and accurate that a CNS-PD and a non-CNS state health state should be mutually modelled. Uncertainty around the transition probability between the two progressed states should not be grounds for excluding the state and departing from the model structures previously accepted by NICE. The impact of the uncertainty on the ICER is explored in a scenario analysis presented in Table 3 and Table 4. The analysis demonstrates that varying the proportion of patients progressing per cycle [redacted]. Therefore, despite the limitations, the inclusion of the CNS-progressed health state is important to model disease progression for ALK-positive NSCLC patients.
Issue 10. Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	**Yes**	MHRA marketing authorisation states that patients may continue to receive treatment *"as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity"*. The EAG have utilised second-line data (Ou et al.) indicating that 75.6% patients in the first-line are treated beyond progression for 5.7 months. We have sought clinical advice on this issue from n=3 clinicians, who confirmed that for ALK TKIs generally, clinicians may treat beyond progression in the case of oligoprogression. Advice received by the company from clinicians is that approximately half of patients are treated beyond progression, for an average of 3 months. Furthermore, clinical advice confirms that it is likely that the same approach would be taken in first and second-line. Therefore, we have explored a range of scenarios, in which the length of treatment beyond progression ranges from 1.5-5.7 months in the first- and second-line settings. These scenario analyses are presented in Table 5 and Table 6.

Sensitivity analyses around revised base case
Results are presented below with a [redacted] PAS for lorlatinib.

Table 3. CNS-PFS health state sensitivity analysis (versus brigatinib)

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	Base-case	[redacted]	[redacted]	[redacted]
1	Non-CNS PD to CNS PD progression per cycle: 10% lorlatinib, 10% brigatinib	[redacted]	[redacted]	[redacted]
2	Non-CNS PD to CNS PD progression per cycle: 30% lorlatinib, 30% brigatinib	[redacted]	[redacted]	[redacted]
3	Non-CNS PD to CNS PD progression per cycle: 50% lorlatinib, 50% brigatinib	[redacted]	[redacted]	[redacted]
4	Non-CNS PD to CNS PD progression per cycle: 70% lorlatinib, 70% brigatinib	[redacted]	[redacted]	[redacted]
5	Non-CNS PD to CNS PD progression per cycle: 90% lorlatinib, 90% brigatinib	[redacted]	[redacted]	[redacted]

Table 4. CNS-PFS health state sensitivity analysis (versus alectinib)

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	Base-case	[redacted]	[redacted]	[redacted]
1	Non-CNS PD to CNS PD progression per cycle: 10% lorlatinib, 10% alectinib	[redacted]	[redacted]	[redacted]
2	Non-CNS PD to CNS PD progression per cycle: 30% lorlatinib, 30% alectinib	[redacted]	[redacted]	[redacted]
3	Non-CNS PD to CNS PD progression per cycle: 50% lorlatinib, 50% alectinib	[redacted]	[redacted]	[redacted]
4	Non-CNS PD to CNS PD progression per cycle: 70% lorlatinib, 70% alectinib	[redacted]	[redacted]	[redacted]
5	Non-CNS PD to CNS PD progression per cycle: 90% lorlatinib, 90% alectinib	[redacted]	[redacted]	[redacted]

Table 5. Treatment beyond progression (versus brigatinib)

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	Base-case	[redacted]	[redacted]	[redacted]
1	Treatment beyond progression (1.5 months in 1L and 3 months 2L)	[redacted]	[redacted]	[redacted]
2	Treatment beyond progression (3 months in 1L and 2L)	[redacted]	[redacted]	[redacted]
3	Treatment beyond progression (3 months in 1L and 5.7 months in 2L)	[redacted]	[redacted]	[redacted]
4	Treatment beyond progression (5.7 months in 1L and in 2L)	[redacted]	[redacted]	[redacted]

Table 6. Treatment beyond progression (versus alectinib)

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	Base-case	[redacted]	[redacted]	[redacted]
1	Treatment beyond progression (1.5 months in 1L and 3 months 2L)	[redacted]	[redacted]	[redacted]
2	Treatment beyond progression (3 months in 1L and 2L)	[redacted]	[redacted]	[redacted]
3	Treatment beyond progression (3 months in 1L and 5.7 months in 2L)	[redacted]	[redacted]	[redacted]
4	Treatment beyond progression (5.7 months in 1L and in 2L)	[redacted]	[redacted]	[redacted]

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 7. Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 8. Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with untreated ALK-positive advanced non-small-cell lung cancer (NSCLC) or caring for a patient with untreated ALK-positive advanced NSCLC. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR section 1.1.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 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.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **9 September 2022.** 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 during engagement, 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 during engagement 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.

NICE National Institute for Health and Care Excellence

Part 1: Living with or caring for a patient with untreated ALK-positive advanced non-small-cell lung cancer (NSCLC)

Table 1 About you, untreated ALK-positive advanced NSCLC, current treatments and equality

1. Your name	Ai Choo Bennett
2. Are you (please tick all that apply)	☐ A patient with untreated ALK-positive advanced NSCLC? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with untreated ALK-positive advanced NSCLC? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): I am answering these questions on the basis of what I felt, before treatment started
3. Name of your nominating organisation	ALK positive UK Ltd
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 untreated ALK-positive advanced NSCLC? **If you are a carer (for someone with untreated ALK-positive advanced NSCLC) please share your experience of caring for them**	I was suffering from severe plueral effusion. Within a short time of having been drained (a few days as I recall), I felt faint several times and fainted once. My legs were weak and I was unable to support myself and tripped once. As it went on over a few days, I became unable to walk more than 10 feet, needing to rest. Getting dressed was an effort- I didn't have any energy.
7a. What do you think of the current treatments and care available for untreated ALK-positive advanced NSCLC on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a. I am currently a private patient, but I was NHS before. At that time, 7 years ago, NHS did not provide targeted treatment, but I understand it does now.** **7b. I believe that everyone who is on Lorlatinib with NHS is very grateful, but there seems to be a lack of staff and CT results are not prompt, nor carried out 3 monthly, in some cases.**
8. If there are disadvantages for patients of current NHS treatments for untreated ALK-positive advanced NSCLC (for example, how they are given or taken, side effects of treatment, and any others) please describe these	# Delays in receiving the tablets # Lack of communication from overworked nurses and doctors # Side effects of the tablets: and lack of advice on how to manage the side effects.
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?**	**9a. I am retired, but with Lorlatinib, I am able to live a basically normal life, with some side effects which are being managed.** **I exercise at least 30 minutes a day, often more. During the ski season, I went out skiing all day every day. I travel, I work as a volunteer, I cycle, I walk. I'm currently training to become a Citizens Advice volunteer.** **9b. My continuing independence.**

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	**9c. No. Lorlatinib causes the side effects, eg bowel incontinence, high cholesterol**
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	The side effects are manageable. I'm learning to cope with them through medication. Lorlatinib's advantages far outweigh the disadvantages.
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	Not that I know of.
12. Are there any potential equality issues that should be taken into account when considering untreated ALK-positive advanced NSCLC and lorlatinib? 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.	
13. Are there any other issues that you would like the committee to consider?	No.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

The anaplastic lymphoma kinase (ALK) inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE.	

Patient expert statement

In your opinion, do the treatment sequences of the CROWN trial apply to an NHS setting? *If first-line lorlatinib were to be recommended by NICE, what percentage of first line lorlatinib patients would you expect to continue to receive lorlatinib after progression, rather than a different ALK-inhibitor in NHS practice?*	
Nearly all patients in the CROWN trial had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS. *In the CROWN trial, more than 95% of the recruited cohort had an ECOG PS score of 0 or*	

1, although participants with an ECOG PS score of 2 were eligible for inclusion. *Is the population of the CROWN trial generalisable to clinical practice in NHS England? Does ECOG PS score impact the prognosis of progression free survival (PFS) and overall survival (OS) in people with ALK-positive advanced NSCLC?*	
Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	
Grade 3 or 4 adverse events occur more frequently with	

lorlatinib than with alectinib. *How does lorlatinib's safety profile compare with those of alectinib and brigatinib in clinical practice?* *How well are side effects tolerated in lorlatinib 2nd line treatment for ALK-positive patients in current practice?* *Would you expect side effects to be similar to 2nd line treatment if lorlatinib was used in first-line treatment?*	
Baseline central nervous system (CNS) metastases as a potential treatment effect modifier. *Is the presence of CNS metastases at baseline a modifier of the PFS treatment effect? If yes, please provide details.*	
The exclusion of the ALESIA study from	

the PFS network meta-analysis (NMA) is inappropriate. *The ALESIA study of alectinib was excluded from the company's NMA on the basis that it was conducted in Asian centres and was therefore not applicable to the UK population. Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* *Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* *Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details.*	
Immaturity of PFS outcome leading to lack of alternative extrapolations.	

Death was not modelled as a PFS event.	
There are insufficient data available to model CNS progressed disease (PD) health state appropriately.	
Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	
Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities. *The company estimated health state utilities from CROWN quality of life data, stratified by health state, treatment status and treatment arm. The EAG's preference is to use the*	

utility set from TA670 (brigatinib). *What is the most appropriate utility set for HRQoL associated with progressed disease?*	
Dosing calculations and proportion of patients receiving subsequent treatment. *The company used detailed dosing data from the CROWN study to estimate the proportion of patients receiving a lower dose of lorlatinib. The EAG preferred to use relative dose intensity (RDI) to model acquisition costs for all treatments.* *Is the use of detailed dosing data from CROWN to estimate the proportion of patients receiving a lower dose of lorlatinib appropriate?*	

Patient expert statement

What proportion of patients would receive a second line systemic treatment after a first-line TKI?	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR section 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Do not include medical information about yourself or another person that could identify you or the other person.

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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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **9 September 2022.** 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 during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

NICE National Institute for Health and Care Excellence

Comments received during engagement 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.

Part 1: Treating untreated ALK-positive advanced non-small-cell lung cancer (NSCLC) 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 upon Tyne Hospitals NHS Trust
3. Job title or position	Senior Lecturer and Honorary Consultant in Medical 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 untreated ALK-positive advanced NSCLC? ☒ A specialist in the clinical evidence base for untreated ALK-positive advanced NSCLC? 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 untreated ALK-positive advanced NSCLC? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptoms. Prevent or delay Central Nervous System 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)	An improvement in survival by 3 months. An improvement in PFS of 4 months . A significant improvement in health related quality of life maintained for over two months. A delay in CNS disease by 6 months, or 5% reduction in CNS disease incidence.
10. In your view, is there an unmet need for patients and healthcare professionals in untreated ALK-positive advanced NSCLC?	Whilst high response rates and long progression free survival can be seen with the present available ALK inhibitors, progression invariably occurs. Relapse in the brain is a frequent complication and leads to high degrees of disability. Given the young age at which this cancer commonly presents it continues to have a major impact on life expectancy and quality of life
11. How is untreated ALK-positive advanced NSCLC 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?	Care is driven by previous nice single technology appraisals with both alectinib and brigatinib used in the 1st line setting. On progression subsequent treatment options include a switch to lorlatinib, carboplatin or pemetrexed based chemotherapy, or the combination of chemotherapy and immunotherapy of carboplatin, paclitaxel, atezolizumab and bevacizumab. I think this has been well defined in past STA. We know there may be variability in practice and this has been well captured in patient surveys by the UK ALK group. In general I expect most patients will be switched to lorlatinib with some patients then moving on to the chemotherapy options. If available and used this would mean patience would get lorlatinib up front, with the subsequent chemotherapy options available on progression.

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) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This would be used in tertiary care oncology centres and units. Lorlatinib is already used in the 2nd line setting and there would be no need for extra training or facilities.
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?	I think this is uncertain. The data suggests that this would reduce the impact of CNS disease which is a clinically meaningful outcome in this setting. The impact on survival is uncertain.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
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?	Lorlatinib is already used in the 2nd line setting. There are minimal practical implications. This will require frequent lipid checking on the bloods and many patients will end up on treatment with a statin (pravastatin or rosuvastatin due to interactions with the other medications)

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No. Patients would be followed as in the first line setting with CT scans looking for evidence of tumour response and subsequent progression. This will be evaluated in conjunction with clinical symptomatology, subsequent treatment options and tolerance to evaluate the length of treatment
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?	I do not regard this as a step change however as described above the control of central nervous system disease is an important unmet medical need in this population
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?	The most common side-effect is elevated cholesterol. This has no clinical impact or effect on patient's quality of life. However other side-effects commonly seen including weight gain, mood disturbance and neuropathy. These can have significant effects on patient's quality of life and require dose reductions and rarely therapy discontinuation.

	I would expect this all to be captured in the clinical trial data and associated quality of life
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?	This does not affect reflect the present management in the UK as the comparator arm was crizotinib which is not now are used as the standard first line treatment option in these patients. We would normally use either alectinib or brigatinib. In addition many of the subsequent treatments used would not be available in the NHS as discussed below. The trial data can be used as in the company submission to perform a network meta-analysis and subsequent treatments can be modelled based on UK clinical expert opinion and NHS England rules. the appropriate endpoints of response, progression free survival, overall survival and control of central nervous system disease were captured appropriately. There have been no additional adverse events come to light subsequently.
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 treatment(s) since the publication of NICE technology appraisal guidance Alectinib [TA536], and Brigatinib [TA670]?	no
23. How do data on real-world experience compare with the trial data?	In general real world data does match clinical trial data. However UK outcomes do tend to be poorer then in some other countries, possibly due to variability in management.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any	None forseen

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.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

The anaplastic lymphoma kinase (ALK) inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE. *In your opinion, do the treatment sequences of the CROWN trial apply to an NHS setting?* *If first-line lorlatinib were to be recommended by NICE, what*	**as discussed in the company submission many of those patients who did progress on Lorlatinib, received subsequent treatment with ALK inhibitors. I agree with their experts that this approach would not be allowed within HS England rules and would not be used in the UK with subsequent treatments being based around chemotherapy with or without immunotherapy.** **As with all oral targeted therapies it is likely that patients will be treated beyond radiological progression, as they may derive ongoing benefit. It is possible that this maybe like more likely with lorlatinib where the only treatment option to change to would be chemotherapy based compared to alectinib and brigatinib where there would be the potential switch to lorlatinib as another non chemotherapy based option.** **in previous appraisals we have suggested that it is likely that patients would on average receive 3 months of targeted therapy beyond progression. I think this may still be a reasonable estimate in this setting.**

percentage of first line lorlatinib patients would you expect to continue to receive lorlatinib after progression, rather than a different ALK-inhibitor in NHS practice?	
Nearly all patients in the CROWN trial had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS. *In the CROWN trial, more than 95% of the recruited cohort had an ECOG PS score of 0 or 1, although participants with an ECOG PS score of 2 were eligible for inclusion.* *Is the population of the CROWN trial generalisable to clinical practice in NHS England? Does ECOG PS score impact the prognosis of progression free survival (PFS) and overall survival (OS) in people with ALK-positive advanced NSCLC?*	There are a significant number of patients in NHS who will present with a performance status of greater than one. although in general in lung cancer performance status is extremely prognostic this may not be as clear cut in patients with ALK lung cancer where they are younger and perform status may be driven by tumour related symptoms with rapid improvements on onset of therapy. There is limited trial data but a study looking at alectinib in patients with poor performance status showed similar outcomes to those with a better performance status. Given the likely restriction to patients with performance status 0-2 if funded within the NHS I would not expect the inclusion of this population (PS2) to have a dramatic effect on efficacy compared to the clinical trial population.

Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	I am not sure what the question is. This seems like a statement. Given the life expectancy of ALK patients it is not surprising that survival data is immature at present. I note the plans for future data cuts.
Grade 3 or 4 adverse events occur more frequently with lorlatinib than with alectinib. *How does lorlatinib's safety profile compare with those of alectinib and brigatinib in clinical practice?* *How well are side effects tolerated in lorlatinib 2nd line treatment for ALK-positive patients in current practice?* *Would you expect side effects to be similar to 2nd line treatment if lorlatinib was used in first-line treatment?*	As described above many of the grade 3-4 events are due to disturbances in lipid profile or cholesterol with no clinical impact on patients. However there are significant side effects associated with lorlatinib with those observed in clinical practice similar to those seen in clinical trials. there is no reason to suspect that the adverse event profile of lorlatinib will be different between patients receiving it in the first line setting or the second line setting.
Baseline central nervous system (CNS) metastases as a potential treatment effect modifier. *Is the presence of CNS metastases at baseline a modifier of the PFS treatment*	Yes. Central nervous system disease is associated with a poorer outcome and in general a shorter time on therapy.

effect? If yes, please provide details.	
The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate. *The ALESIA study of alectinib was excluded from the company's NMA on the basis that it was conducted in Asian centres and was therefore not applicable to the UK population. Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* *Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* *Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details.*	As per previous appraisals, the ALESIA study was excluded. Alectinib was initially licenced in a different dose in the Asian population then the non Asian population. Have a much of this effect may be due to differences in body weight and pharmacokinetics. There is not a difference in the licenced dose for lorlatinib. Much of the difference is in outcomes in the Asian population are thought to be at least partially due to differences in the healthcare systems. For example Japan has significantly more MRI scanners and better CNS surveillance algorithms then presently in place in the UK. I do not think there would be any major modifier on a treatment effect of an Asian patient treated within the UK health system
Immaturity of PFS outcome leading to lack of alternative extrapolations.	I am not sure what the question is. This seems like a statement
Death was not modelled as a PFS event.	I am not sure what the question is. This seems like a statement
There are insufficient data available to model CNS	I am not sure what the question is. This seems like a statement

progressed disease (PD) health state appropriately.	
Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	I am not sure what the question is. This seems like a statement
Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities. *The company estimated health state utilities from CROWN quality of life data, stratified by health state, treatment status and treatment arm. The EAG's preference is to use the utility set from TA670 (brigatinib).* *What is the most appropriate utility set for HRQoL associated with progressed disease?*	I think it would be very reasonable in this situation to use the appropriate quality of life as captured within the clinical trial given there was reasonable numbers and completion of data.
Dosing calculations and proportion of patients receiving subsequent treatment. *The company used detailed dosing data from the CROWN*	I think it is reasonable to use the dosing data generated from the CROWN To estimate the number of patients who receive lower doses of lorlatinib. It may also be possible to look at the UK environment and the number of likely does reductions through SACT data in the second line setting.

study to estimate the proportion of patients receiving a lower dose of lorlatinib. The EAG preferred to use relative dose intensity (RDI) to model acquisition costs for all treatments. *Is the use of detailed dosing data from CROWN to estimate the proportion of patients receiving a lower dose of lorlatinib appropriate?* *What proportion of patients would receive a second line systemic treatment after a first-line TKI?*	
Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There continues to be unmet need in patients with ALK Lung Cancer
Control of central nervous system disease remains a key outcome for clinicians and patients
Some of the adverse events seen with lorlatinib have minimal clinical impact such as elevated cholesterol combat but others can have a major impact on quality of life including neuropathy and mood disturbance.
Click or tap here to enter text.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with untreated ALK-positive advanced non-small-cell lung cancer (NSCLC) or caring for a patient with untreated ALK-positive advanced NSCLC. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR section 1.1.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 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.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **9 September 2022.** 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 during engagement, 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 during engagement 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.

Part 1: Living with or caring for a patient with untreated ALK-positive advanced non-small-cell lung cancer (NSCLC)

Table 1 About you, untreated ALK-positive advanced NSCLC, current treatments and equality

1. Your name	Debra Montague
2. Are you (please tick all that apply)	☐ A patient with untreated ALK-positive advanced NSCLC? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with untreated ALK-positive advanced NSCLC? ☒ 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 untreated ALK-positive advanced NSCLC? **If you are a carer (for someone with untreated ALK-positive advanced NSCLC) please share your experience of caring for them**	Patients don't usually have to wait more than a week or two untreated once diagnosed as ALK-positive to be Rxed a targeted treatment. The time from first appt with a secondary care consultant (usually Respiratory or Oncology) to an ALK+ Dx can be up to 10 or 11 weeks as it can now take 5 weeks (or more) in some hospitals to get scan results back. This is obviously a very stressful time for patients and many patients' symptoms escalate exponentially during this time resulting in many being very unwell by the time they are confirmed as ALK+
7a. What do you think of the current treatments and care available for untreated ALK-positive advanced NSCLC on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Current treatment options are very good as they have excellent data confirming their efficacy and are generally well tolerated. 1st line Rxed options are currently Alectinib or Brigatinib although because Alectinib has been available for longer many Oncologists are still Rxing Alectinib 1st line so there are fewer Brigatinib initiations. Our real world data collected from 100 ALK+ patients showed that Brigatinib is better tolerated than Alectinib. Alectinib causes significant fatigue, which is often not appreciated or taken seriously by Oncologists. Patients can be reluctant to report side effects as they are scared they will be taken off their meds and switched to the next treatment. As there are only 2 currently this could result in a very short time on TKI's which they know are so much easier to take than chemo which would follow the TKIs.
8. If there are disadvantages for patients of current NHS treatments for untreated ALK-positive advanced NSCLC (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The number of Alectinib tablets to be taken (4 morning and night) could be a small issue for some patients particularly if they are being Rxed other medications, however the mind set tends to be 'I will put up with anything to stay alive' for most patients.

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**	A. Lorlatinib would seem to have several advantages over current treatments – Better brain coverage which means better brain mets control in patients with brain mets or potentially a longer time before brain mets develop. It is accepted by Oncologists patients without brain mets tend to live longer than those with. B. Fewer side effects - our real world data reports this. Patients don't report sin-burning which occurs with Alectinib. This burning isn't like sunburn, it feels like boiling water being poured on to the skin and can occur in the winter sun which means patients need to avoid the sun at all times. Patients don't report fatigue as a side effect on Lorlatinib in the charities experience. Patients generally report feeling better than they have felt in a long time and many report feeling 'like their old selves'.
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	Lorlatinib can cause some neurological side effects, such as feeling more agitated/feeling 'hyper'/experiencing hallucinations or having feelings of pins & needles in their legs. These aren't life threatening and many patients don't report them for fear of being taken off their TKI. I wouldn't call any of the above risks and most are managed by a dose reduction to 75mg if necessary.
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	The once daily dose could benefit some patients – those taking many other medications or those with dexterity issues (only needing to remove 1 tablet from a pack). Patients identified with brain mets at the time of their diagnosis may benefit from having a TKI that crosses the blood brain barrier extremely well could potentially remain stable for longer?
12. Are there any potential equality issues that should be taken into account when considering untreated ALK-positive advanced NSCLC and lorlatinib? Please explain if you think any groups of people with this condition are particularly disadvantaged	There aren't any equality issues.

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.	
13. Are there any other issues that you would like the committee to consider?	Patients vary considerably in how they tolerate TKI's and the more options available the more likely it is to find one they can tolerate asnd hopefully stay on for many years. These patients are NEVER-smokers, many were very fit and healthy (regular gym goers/running marathons/Personal Trainers) with healthy diets. They did nothing to bring this cancer upon themselves. Many are young with families, still working and contributing to society. I say this so you can picture these patients correctly when assessing this submission. Anyone with lungs can get lung cancer, any one of us.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

The anaplastic lymphoma kinase (ALK) inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE.	At the time of the trial commencing Crizotinib was the 1st line choice, however once Alectinib was approved by NICE prescribing habits changed almost over night. Currently our experience suggests a greater proportion of newly diagnosed patients are being prescribed Alectinib even though Brigatinib has been available for many months. We are seeing Brigatinib routinely prescribed at the centres of excellence – The Chrisities, Royal Marsden, Newcastle, Liverpool but smaller hospitals are slower to follow. Currently, Lorlatinib is the only 2nd line TKI for ALK-positive lung cancer in the UK although in this setting we are aware of many patients still taking it 12mths even 5yrs.

Patient expert statement

In your opinion, do the treatment sequences of the CROWN trial apply to an NHS setting? *If first-line lorlatinib were to be recommended by NICE, what percentage of first line lorlatinib patients would you expect to continue to receive lorlatinib after progression, rather than a different ALK-inhibitor in NHS practice?*	We would support the evidence of the Crown study as Crizotinib was the comparator for both Alectinib and Brigatinib and whilst direct comparisons between the 3 TKIs can not be made (due to potential differences in patient pool etc) the results can be compared and a broad overview appreciated. *If first-line lorlatinib were to be recommended by NICE, what percentage of first line lorlatinib patients would you expect to continue to receive lorlatinib after progression, rather than a different ALK- inhibitor in NHS practice? –* We as a charity and myself personally, as a patient aren't qualified to answer this question.
Nearly all patients in the CROWN trial had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS. *In the CROWN trial, more than 95% of the recruited cohort had an ECOG PS score of 0 or*	We as a charity and myself personally as a patient aren't qualified to answer this question.

1, although participants with an ECOG PS score of 2 were eligible for inclusion. *Is the population of the CROWN trial generalisable to clinical practice in NHS England? Does ECOG PS score impact the prognosis of progression free survival (PFS) and overall survival (OS) in people with ALK-positive advanced NSCLC?*	
Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	From a non-statistician's perspective, increased progression-free survival must surely lead to increased overall-survival. We understand the pattern of progression of this disease and we have seen that increased PFS with other TKI's has lead to increased OS, therefore we would suggest that there is nothing in the Lorlatinib data that would suggest this wouldn't be the case here.
Grade 3 or 4 adverse events occur more frequently with	The adverse effects that occurred with Crizotinib would have a significant effect on the patients QoL far greater than the adverse effects reported with Lorlatinib.

lorlatinib than with alectinib. *How does lorlatinib's safety profile compare with those of alectinib and brigatinib in clinical practice?* *How well are side effects tolerated in lorlatinib 2nd line treatment for ALK-positive patients in current practice?* *Would you expect side effects to be similar to 2nd line treatment if lorlatinib was used in first-line treatment?*	All patients prescribed Lorlatinib are also prescribed statins to manage the raised lipids experienced. This hasn't been an issue for patients in our experience. To date our experience has been that very few patients have stopped Lorlatinib due to adverse events. Many patients have stopped treatment on Alectinib due to liver toxicity whereas we haven't seen anywhere as many stopping treatment with Lorlatinib. We would accept the argument that we have fewer patients on Lorlatinib, however they are all in the 2nd line setting so would potentially not e as healthy as the Alectinib stoppers.
Baseline central nervous system (CNS) metastases as a potential treatment effect modifier. *Is the presence of CNS metastases at baseline a modifier of the PFS treatment effect? If yes, please provide details.*	We as a charity and myself personally as a patient aren't qualified to answer this question.

The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate. *The ALESIA study of alectinib was excluded from the company's NMA on the basis that it was conducted in Asian centres and was therefore not applicable to the UK population. Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* *Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* *Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details.*	We are aware that the Dose of Alectinib used for Asian patients was half that now prescribed in the UK. A lower dose would certainly give rise to a lower potential for side effects and therefore withdrawals.
Immaturity of PFS outcome leading to	We see the immaturity of the PRS data as a good sign.

lack of alternative extrapolations.	
Death was not modelled as a PFS event.	
There are insufficient data available to model CNS progressed disease (PD) health state appropriately.	We as a charity and myself personally as a patient aren't qualified to answer this question.
Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	All patients receive treatment beyond progression however the site of progression significantly affects the prognosis at that point. For example, progression extracranially wouldn't be treated with radiotherapy as this isn't NICE approved. Chemo is the only treatment available after Lorlatinib currently which is only effective in 20% of ALK-positive patients to our knowledge. If the progression was intracranially than radiotherapy would be an option, again depending on the site and previous exposure. This can lead to many more years of life.
Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities. *The company estimated health state utilities from CROWN quality of life data, stratified by health state, treatment status and treatment*	Adverse events that were more common with crizotinib than with lorlatinib included diarrhea (occurring in 52% of the patients vs. 21%), nausea (in 52% vs. 15%), vision disorder (39% vs. 18%), vomiting (39% vs. 13%), increased alanine aminotransferase level (34% vs. 17%), fatigue (32% vs. 19%), constipation (30% vs. 17%), increased aspartate aminotransferase level (27% vs. 14%), decreased appetite (25% vs. 3%), dysgeusia (16% vs. 5%), and bradycardia (12% vs. 1%) (**Table 3**). We would suggest that many of these adverse effects have a significant effect on QoL – Diarrhoea can result in patients not being able to leave the house

Patient expert statement

arm. The EAG's preference is to use the utility set from TA670 (brigatinib). *What is the most appropriate utility set for HRQoL associated with progressed disease?*	Nausea can affect a person's ability to carry out daily activities and interact with family & friends Vision disturbance is dangerous esp. at night Decreased appetite often results in weight loss which can affect a persons ability to recover from a serious illness Fatigue can affect a person's ability to carry out daily activities and interact with family & friends
Dosing calculations and proportion of patients receiving subsequent treatment. *The company used detailed dosing data from the CROWN study to estimate the proportion of patients receiving a lower dose of lorlatinib. The EAG preferred to use relative dose intensity (RDI) to model acquisition costs for all treatments.* *Is the use of detailed dosing data from CROWN to estimate the proportion of patients receiving a*	We as a charity and myself personally as a patient aren't qualified to answer this question.

lower dose of lorlatinib appropriate? *What proportion of patients would receive a second line systemic treatment after a first-line TKI?*	
Are there any important issues that have been missed in EAR?	We are not aware of any.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Lorlatinib is very well tolerated in the second line setting and we believe this would be no different in the first line setting
- A significant proportion of patients have brain mets at the time of diagnosed
- Lorlatinib has fewer QoL side effects than current TKIs
- Effective management of brain mets is vital for a good QoL for patients and the chance to be stable for as long as possible
- These patients are young, with families and led healthy lives before their diagnosis. Many are still contributing to the economy and society.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR section 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **9 September 2022.** 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 during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

NICE National Institute for Health and Care Excellence

Comments received during engagement 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating untreated ALK-positive advanced non-small-cell lung cancer (NSCLC) 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 untreated ALK-positive advanced NSCLC? ☒ A specialist in the clinical evidence base for untreated ALK-positive advanced NSCLC? 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 untreated ALK-positive advanced NSCLC? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Prolonging survival and maintaining quality of life Due to the high incidence of brain metastases – any treatment that treats or prevent brain metastases is highly desirable
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 of 3 years or more ORR of greater that 60% CNS activity
10. In your view, is there an unmet need for patients and healthcare professionals in untreated ALK-positive advanced NSCLC?	Yes
11. How is untreated ALK-positive advanced NSCLC 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?	Currently there is a choice of 4 targeted drugs first line. A targeted approach should be the primary approach (as opposed to chemotherapy) The choice of drugs first line are Crizotinib, Ceritinib, Alectinib or Brigatinib Based on trial data and efficacy the choice of first line agent should be between Alectinib or Brigatinib only The pathway is well defined. There is variation in choice (but this should be between Alectinib and Brigatinib only) The technology would provide another first line treatment option, which potentially demonstrates greater clinical activity
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be implemented into first line treatment of ALK positive NSCLC patient. This is an established pathway in secondary care / cancer centres. No extra investment would be required

• 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) • 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?	Yes I expect the technology to provide improved clinical outcomes than current care I expect it to maintain health-related quality of life compared with current care
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)	No

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No – would be the same as is already standard of care for this population
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	n/a
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 – this is potentially a treatment than can improve clinical outcomes compared with current standard of care
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?	The technology has a different side effect profile to current standard of care. However most clinicians have experience of the drug and managing adverse events (as the drug is already approved in the second line setting). The adverse events are manageable with appropriate modifications
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?	They reflected UK clinical practice at the time the trial was set up. The comparator in the CROWN trial was Crizotinib, which was the standard of care at that point in time. Crizotinib is not the standard of care now, but this purely reflects the evolution of the treatment landscape in ALK positive NSCLC

• 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?	
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 treatment(s) since the publication of NICE technology appraisal guidance Alectinib [TA536], and Brigatinib [TA670]?	No
23. How do data on real-world experience compare with the trial data?	Unable to comment for first line Lorlatinib as I am unaware of any real-world experience For Alectinib and Brigatinib it is comparable
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	n/a

• 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.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

The anaplastic lymphoma kinase (ALK) inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE. *In your opinion, do the treatment sequences of the CROWN trial apply to an NHS setting?* *If first-line lorlatinib were to be recommended by NICE, what*	**Treatment beyond progression is a recognised treatment modality – particularly patients on targeted drugs for driver mutated NSCLC. This can be either continuing treatment based on slow / low volume progression or treating oligo-progression with a local therapy and continuing the drug treatment.** **There is no guidance or protocols on treating beyond progression and this is predominately driven by the Oncologist's subjective assessment of the disease process.** **It is difficult to quantify the number of patients that would be treated beyond progression if Lorlatinib were approved. A very rough estimate would put it at 20% of patients.**

percentage of first line lorlatinib patients would you expect to continue to receive lorlatinib after progression, rather than a different ALK-inhibitor in NHS practice?	
Nearly all patients in the CROWN trial had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS. *In the CROWN trial, more than 95% of the recruited cohort had an ECOG PS score of 0 or 1, although participants with an ECOG PS score of 2 were eligible for inclusion.* *Is the population of the CROWN trial generalisable to clinical practice in NHS England? Does ECOG PS score impact the prognosis of progression free survival (PFS) and overall survival (OS) in people with ALK-positive advanced NSCLC?*	The CROWN population (as with any clinical trial) is likely to have a greater proportion of fitter (better performance status) patients than real life. It is not uncommon for NHS ALK positive NSCLC to present with a PS of 2 (which for the vast majority will be driven by symptoms related to their volume of disease). These patient s have the same chance of responding and benefiting from Lorlatinib as PS 0 / 1 patients (and will tolerate the treatment just as well). The vast majority will also respond very quickly to the treatment resulting in the performance status improving to 0 /1. Hence the inclusion of PS 2 patients is highly welcomed by the Oncology population as well as by patients

Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	This is the case now with many of our new NSCLC treatments. Marketing authorisation and re-imbursement is being sought on PFS. This is a very pragmatic approach as clearly (especially in the case of the CROWN study) it will take a long time still for OS data to mature. It would not be appropriate to wait for OS data to assess the appraisal. A pragmatic approach should be used with the available data – to ensure access to patients as soon as possible
Grade 3 or 4 adverse events occur more frequently with lorlatinib than with alectinib. *How does lorlatinib's safety profile compare with those of alectinib and brigatinib in clinical practice?* *How well are side effects tolerated in lorlatinib 2nd line treatment for ALK-positive patients in current practice?* *Would you expect side effects to be similar to 2nd line treatment if lorlatinib was used in first-line treatment?*	Lorlatinib has a very different toxicity profile to Alectinib and Brigatinib. With the caveat of cross trial comparison – although there were more grade 4 and 4 toxicities, discontinuation rates are actually lower in the CROWN trial compared with Alectinib and Brigatinib. This suggests that with appropriate modifications and supportive measures, the AE's are manageable In the 2nd line setting in my experience side effects are manageable. We are now getting more familiar with the toxicity profile and with this experience our ability to manage them effectively improves I would expect a similar toxicity profile regardless of whether Lorlaitnib was used first or second line. However in the first line exposure to the drug (and hence to toxicities) is likely to be more prolonged
Baseline central nervous system (CNS) metastases as a potential treatment effect modifier. *Is the presence of CNS metastases at baseline a modifier of the PFS treatment*	PFS was pronounced for the Lorlatinib arm regardless of the presence or not of CNS disease at baseline

effect? If yes, please provide details.	
The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate. *The ALESIA study of alectinib was excluded from the company's NMA on the basis that it was conducted in Asian centres and was therefore not applicable to the UK population. Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* *Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* *Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details.*	I do not believe that race as such impacts on prognosis or is a treatment effect modifier in the ALK landscape. There are differences in clinical practice and the treatment landscape, which can impact on how AE's are managed and subsequent therapies – which could have an impact on clinical outcomes. However in my opinion the trials that have been submitted (in particular the inclusion of the ALEX trial) are more then adequate
Immaturity of PFS outcome leading to lack of alternative extrapolations.	The immaturity of PFS outcome is driven by the low number of events, which ultimately confirms the high clinical efficacy of the drug.
Death was not modelled as a PFS event.	
There are insufficient data available to model CNS	I have discussed treatment beyond progression above

progressed disease (PD) health state appropriately.	
Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	
Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities. *The company estimated health state utilities from CROWN quality of life data, stratified by health state, treatment status and treatment arm. The EAG's preference is to use the utility set from TA670 (brigatinib).* *What is the most appropriate utility set for HRQoL associated with progressed disease?*	
Dosing calculations and proportion of patients receiving subsequent treatment. *The company used detailed dosing data from the CROWN*	In my opinion detailed dosing is an appropriate methodology to assess dosing calculations and is more reflective of real world

study to estimate the proportion of patients receiving a lower dose of lorlatinib. The EAG preferred to use relative dose intensity (RDI) to model acquisition costs for all treatments. *Is the use of detailed dosing data from CROWN to estimate the proportion of patients receiving a lower dose of lorlatinib appropriate?* *What proportion of patients would receive a second line systemic treatment after a first-line TKI?*	The number of patients moving onto a subsequent therapy is likely to be around 60%
Are there any important issues that have been missed in EAR?	n/a

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.
Click or tap here to enter text.
Click or tap here to enter text.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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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 [ID3896]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **9 September 2022**. 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 during engagement, 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 during engagement 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.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Takeda UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The anaplastic lymphoma kinase (ALK) inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE.	~~Yes~~/**No**	We agree with the issues raised by the EAG on limited applicability of the ALK inhibitor treatment sequences in the CROWN trial, which leads to concerns on generalisability of the trial to NHS clinical practice. In addition, the CROWN trial did not permit prior treatment with chemotherapy. The absence of data for lorlatinib treatment following chemotherapy raises generalisability challenges. As noted by the EAG (EAR, Page 23), "*a small number of squamous cell carcinoma patients may at first receive chemotherapy before ALK-positive NSCLC is identified (after which an ALK inhibitor can be started).*" This trial design is also not aligned with the marketing authorisation for lorlatinib, which permits treatment in any patients who have not been previously treated with an ALK inhibitor (i.e. treatment following chemotherapy would be permitted), meaning the NICE submission presents data narrower than the marketing authorisation. It is also notable that the CROWN trial did not allow for crossover and we regard this as another factor that limits its relevance to real-world clinical practice. These factors should be considered in NICE's decision-making.

Nearly all patients in the CROWN trial had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS.	~~Yes~~/**No**	N/A
Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	~~Yes~~/**No**	N/A
Grade 3 or 4 adverse events occur more frequently with lorlatinib than with alectinib.	~~Yes~~/**No**	N/A
Baseline central nervous system (CNS) metastases as a potential treatment effect modifier.	~~Yes~~/**No**	N/A
The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate.	~~Yes~~/**No**	N/A
Immaturity of PFS outcome leading to lack of alternative extrapolations.	~~Yes~~/**No**	N/A
Death was not modelled as a PFS event.	~~Yes~~/**No**	N/A

There are insufficient data available to model CNS progressed disease (PD) health state appropriately.	~~Yes~~/**No**	N/A
Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	~~Yes~~/**No**	**Modelling of ToT > PFS** Time on treatment (ToT) for lorlatinib and comparators should be modelled as greater than, rather than equal to, progression-free survival (PFS) to ensure costs of all technologies are estimated accurately. The CROWN trial did not permit treatment beyond progression, meaning ToT could not exceed PFS within the trial. However, as noted in the EAR (Pages 64–65), "*treatment [with lorlatinib] beyond progression… is likely to occur in practice given the licence phraseology*": • Lorlatinib Summary of Product Characteristics: *"Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity."* We would encourage the EAG's scenarios for modelling ToT > PFS to be reconsidered for the base case. This would more accurately reflect the treatment duration on lorlatinib expected in clinical practice, and clinical advice sought by the EAG: • EAR, Page 65: *"Clinical advice received by the EAG stated an expectation that many patients would be treated beyond the point of clinical progression, and noted that this was consistent with historical practice for other TKIs used in the treatment of ALK-positive NSCLC."* **Consistency with prior NICE appraisals in ALK+ NSCLC** During the NICE appraisal for lorlatinib for previously treated ALK+ advanced NSCLC (TA628, May 2020), an assumption of 3.5 months of lorlatinib treatment beyond progression was adopted based on expert clinical opinion, which the NICE technical team deemed appropriate for decision-making.

		Similarly to lorlatinib, the comparator brigatinib has a statement in the marketing authorisation to permit treatment beyond progression: *"Treatment [with brigatinib] should continue as long as clinical benefit is observed."* In order to align with this, the previous NICE appraisals for brigatinib modelled ToT based on time to treatment discontinuation (TTD) rather than PFS: • Brigatinib (TA670, January 2021) for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor • Brigatinib (TA571, March 2019) for treating ALK-positive advanced non-small-cell lung cancer after crizotinib This was highlighted by the EAG in response to the current lorlatinib NICE appraisal: • EAR, Page 65: *"The EAG also notes that in the previous TAs for crizotinib, alectinib, and brigatinib treatment beyond progression was assumed to occur."* Consistency with prior appraisals in the same disease area (i.e. ALK+ NSCLC) is key in order for NICE to reach an informed decision, and lorlatinib treatment should therefore be modelled beyond progression.
Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities.	~~Yes~~/**No**	N/A
Dosing calculations and proportion of patients receiving subsequent treatment.	~~Yes~~/**No**	N/A

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Factual inaccuracies in ALTA-1L data	Company submission, Section B.2.9.2, Table 21, Page 53	~~Yes~~/No	Baseline characteristics for the ALTA-1L trial of brigatinib vs crizotinib are reported inaccurately. Please see below for corrections in red.
Additional issue 2: Most recent trial data from ALTA-1L not used	Company submission, Section B.2.9	Yes/No	Data from the ALTA-1L trial is presented from the first interim analysis (Camidge et al. 2018; median follow-up 11.0 months in the brigatinib arm, 9.3 months in the crizotinib arm). However, the final analysis from the ALTA-1L trial is now publicly available and should be used preferentially throughout to reflect the greater follow-up and data maturity (Camidge et al. 2021; median follow-up 40.4 months in the brigatinib arm and 15.2 months in the crizotinib arm).

References:

- Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2027-2039. doi: 10.1056/NEJMoa1810171. Epub 2018 Sep 25. PMID: 30280657.
- Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib Versus Crizotinib in ALK Inhibitor-Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. J Thorac Oncol. 2021 Dec;16(12):2091-2108. doi: 10.1016/j.jtho.2021.07.035. Epub 2021 Sep 16. PMID: 34537440.

Correction to Company Submission, Table 21

Trial name	Treatment / comparator	N	Age Median (range)	Gender Male (%)	Brain metastasis Proportion with brain metastasis (%)	Race Asian (%)	Smoking Never / current or former (%)	ECOG PS 0 or 1 (%)	Prior treatment Prior chemotherapy (%)
ALTA-1L	Brigatinib	137	58 (27, 86)	50	29	43	61/38	94	26
	Crizotinib	138	60 (29, 89)	41	30	36	54/46	95	27

Reference: Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib Versus Crizotinib in ALK Inhibitor-Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. J Thorac Oncol. 2021 Dec;16(12):2091-2108. doi: 10.1016/j.jtho.2021.07.035. Epub 2021 Sep 16. PMID: 34537440.

Single Technology Appraisal (STA)

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

EAG addendum: review of company's response to technical engagement

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None.

Rider on responsibility for report

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

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the EAG in its report, which were discussed at technical engagement.

The technical engagement covered 12 key issues for consideration. The company's response to technical engagement indicated that they accepted the EAG's correction to the modelling error as applied in the EAG base-case (Issue 8), in which patients in the PFS health-state could not die in line with rates observed in the CROWN trial.

The results of scenarios presented by the company in response to Issue 9 and Issue 10 are replicated inclusive of all cPAS discounts in a confidential appendix to this document. As no new base-case analyses were presented by the company, [redacted], the EAG has not updated the confidential appendix to the EAR.

Table 1: Summary of the key issues

Issue		Resolved?
1	The ALK inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE	No
2	Nearly all patients in the CROWN trial had an ECOG PS score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS	No*
3	Overall survival data from the CROWN trial are immature. There is currently no evidence that increased progression free survival (PFS) from lorlatinib leads to increased overall survival (OS).	No*
4	Grade 3 or 4 adverse events occur more frequently with lorlatinib than with alectinib.	Partially resolved
5	Baseline central nervous system (CNS) metastases as a potential treatment effect modifier.	No
6	The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate.	No
7	Immaturity of PFS outcome leading to lack of alternative extrapolations.	Partially resolved
8	Death was not modelled as a PFS event.	Yes
9	There are insufficient data available to model CNS progressed disease (PD) health state appropriately.	No
10	Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured.	Partially resolved
11	Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities.	No
12	Dosing calculations and proportion of patients receiving subsequent treatment.	Partially resolved

* May be partly resolved by data collection in CDF

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Issue 1: The ALK inhibitor treatment sequences used in both arms of the CROWN trial have very limited applicability to both current NHS practice and to what would happen if first-line lorlatinib were to be recommended by NICE

The company stated that crizotinib has limited use in NHS practice and that in the absence of alternative trials directly comparing lorlatinib to alectinib and brigatinib, indirect treatment comparisons were conducted.

The EAG's response

The company acknowledged that crizotinib is now an obsolete comparator, even though it was a relevant comparator when the CROWN trial was undertaken. Nevertheless, both alectinib and brigatinib were used as subsequent treatments in CROWN and the second-line use of alectinib after lorlatinib falls outside of alectinib's marketing authorisation. The issue of unrepresentative comparators and treatment sequences in the evidence-base can only be resolved by a future trial.

2.2 Issue 2: Nearly all patients in the CROWN trial had an ECOG PS score of 0 or 1 but lorlatinib's marketing authorisation is not restricted by ECOG PS

The company presented data suggesting that, in practice, a significant proportion of patients may present with an ECOG PS score of ≥2. It is possible that the proportions presented for ECOG PS score >2 (which were quite high) actually related to ≥2.

The EAG's response

There is a lack of trial efficacy data for patients with ECOG PS scores ≥2 and it is plausible that lorlatinib is less effective (and less likely to be used) in this subgroup of patients. Clinical advice may provide further insight into the size and relevance of the ECOG PS scores ≥2 population. Data collection via the CDF may also help confirm whether patients with an ECOG PS score of ≥2 are given lorlatinib in NHS practice (and so help to clarify the uncertainty about efficacy in this subgroup).

2.3 Issue 3: OS data from the CROWN trial are immature. There is currently no evidence that increased PFS from lorlatinib leads to increased OS

The company stated that there remains substantial uncertainty in OS estimates for lorlatinib and the relationship between PFS and OS, adding that data maturity will help address this issue, with the next data cuts planned for [redacted] and [redacted].

The EAG's response

The EAG concurs with the company's view, though notes that the longer-term data will be limited because patients in the CROWN trial received treatment sequences which are not used in the NHS (e.g. second-line alectinib after first-line lorlatinib).

2.4 Issue 4: Grade 3 or 4 adverse events occur more frequently with lorlatinib than with alectinib

The company accepted that lorlatinib is associated with an increased risk of experiencing adverse events ≥ Grade 3, when compared with alectinib. This information was missing from the original submission and was not addressed when raised in clarification question A12(a), in which the EAG requested that the company perform an NMA on the risk of Grade 3 or higher AEs.

The EAG's response

Given the lack of a company NMA on this outcome, the EAR summarised key results from published NMAs which compared the incidence of grade ≥ 3 AEs across ALK inhibitors. In light of lorlatinib's [redacted] improvement in PFS compared to other ALK inhibitors, the EAG considered it important to ensure that analyses comparing the relative safety of the ALK inhibitors was also presented. The company did not disagree with the EAG's interpretation of the published evidence on Grade 3 or higher adverse events.

2.5 Issue 5: Baseline central nervous system (CNS) metastases as a potential treatment effect modifier

The company summarised the uncertainty surrounding the PFS results for this subgroup of patients, although no new data were presented.

The EAG's response

Given the continued uncertainty about whether the presence of CNS metastases (when treatment commences) affects PFS across the different ALK-TKIs, it is unclear how additional data collection via the CDF could help to resolve this issue. However longer follow-up data from the CROWN trial may help reduce uncertainty.

2.6 Issue 6: The exclusion of the ALESIA study from the PFS network meta-analysis (NMA) is inappropriate

The company presented no new information on this issue.

The EAG's response

The EAG reiterates that its preferred approach is to use the 'Global NMA' results, which includes the ALESIA study.

2.7 Issue 7: Immaturity of PFS outcome leading to lack of alternative extrapolations

In response to the EAG's request that alternative survival analysis techniques be used to identify and explore the effect of using other clinically plausible extrapolations of PFS, the company presented a number of flexible parametric survival models to BICR PFS data from CROWN. These models comprised a selection of two-piece models and cubic spline models. For the two-piece models, the company determined a rebasing point of 17 weeks on the basis of a visual assessment of the Kaplan-Meier curves and the timing of tumour assessments in the CROWN study. The company stated that these curves showed a much improved visual and statistical fit to both treatment arms (see Figure 1). Fit statistics were not presented in the company's Technical Engagement response.

Figure 1 Two-piece extrapolations of BICR PFS with rebasing at 3.91 months (17 Weeks)

The predictions of PFS at key long-term time points remained variable, this ranged from [redacted] using the exponential (vs [redacted] in the company's original base-case), to [redacted] using the Gompertz distribution at 10 years. The company did not state which of these models had the best statistical fit to each arm.

The company also explored one- and two-knot cubic spline models, with three models (normal, proportional hazards, and proportional odds) fitted for each. The company stated that the statistical fits remained similar for each model and were 'far better' than the exponential model used in the original submission. The graphical representations of model fits provided in the response were incomplete, and are thus not replicated here. The company noted that the survival estimates produced by the spline models would be too optimistic to be clinically plausible.

The EAG's response

The EAG agrees that the better fit provided by the two-piece and spline models may not mean they present clinically plausible alternatives. While some of these curves better represent the underlying data statistically, they cannot resolve the issues associated with its immaturity. As all curves are significantly more optimistic than the exponential applied in the original submission, they are unlikely to present more realistic predictions about long-term survival than the simple parametric models already considered.

The EAG is satisfied that the company have explored the full range of realistic approaches to survival analysis using the data available, insofar as other methods are unlikely to yield realistic alternative extrapolations. Further, it may be beyond the capacity of the information available to generate alternative clinically plausible extrapolations without manipulation in the executable model itself (i.e. through imposition of effect waning). The EAG considers this issue resolved in the context of current data limitations, but notes that future data cuts will contribute to reducing the uncertainty associated with this issue.

2.8 Issue 8: Death was not modelled as a PFS event

The company accepted the EAG's correction to the modelling error as applied in the EAG base-case. The EAG assumed that patients in the PFS health state would experience death events at the rate observed in the CROWN trial.

The EAG's response

The EAG considers this issue resolved.

2.9 Issue 9: There are insufficient data available to model CNS progressed disease (PD) health state appropriately

The company stated that while no data existed to inform transitions between the non-CNS-PD and CNS-PD health states, it is 'both relevant and accurate' that the CNS-PD health state should be modelled, reiterating that a four-state model was previously accepted in TA536 and TA670. The company state that uncertainty around transition probabilities between the non-CNS-PD and CNS-PD health states should not be grounds for the exclusion of the health state altogether.

The company present a number of analyses which purport to explore the impact of modelling a per cycle transition rate between the non-CNS-PD and CNS-PD health states, ranging from 10% per cycle to 90% per cycle. These rates were applied to lorlatinib and the comparator treatments equally in each scenario. However, it was not clear how this was implemented. These scenarios did not pass simple validation tests in the economic model, where increasing the per cycle rate of CNS progression events only affects the progression rate between the PFS and non-CNS-PD health states (see details below).

The EAG's response

The EAG reiterates the arguments in favour of a three-state model structure described in the EAR. The EAG again recognises the precedent of a four-state model in TA536 and TA670, but does note the circumstances in these cases differed from the present appraisal, both in terms of the evidence availability and the decision context the structure was used to inform. In the ALEX trial used in TA536, CNS-PFS events secondary to systemic progression were captured, meaning this data source was better able to inform the model transitions necessary to include the CNS-PD health state. The EAG also notes that use of the CNS-PD health state in TA670 was in the context of an argument for non-inferiority versus alectinib, with some statistical demonstration of non-inferiority. However, the company's base-case in the present appraisal assumed significant benefits versus alectinib and brigatinib, with little statistical support and poor comparability of outcome assessment.

The EAG acknowledges the clinical rationale for a benefit relating to prevention of CNS progression but does not feel there is an appropriate way to capture this given the available evidence. The model structure adopted must be evidence driven, and in the absence of sufficient evidence to inform the parameters necessary to extend the PSM framework to include CNS events, the EAG prefers the simplified model used in the EAG base case. The EAG does not disagree in principle with exploring the use of assumptions to populate model transitions, but no new data have been provided by the company to inform these transitions. The EAG contends that the benefits as modelled by the company are not a meaningful representation of real clinical data and outcomes, and are instead an attempt to translate a qualitative prediction into a quantitative analysis – akin to an arbitrary addition of QALYs to the lorlatinib treatment arm. The EAG also notes the lack of presented evidence which would be required to inform outcomes in a population comprising only patients with CNS-metastases (i.e. the CNS-PD group).

In the context of CDF candidacy, it is important that the currently available data is used in the most transparent way possible, with uncertainties defined clearly and explicitly. The EAG therefore prefers a simplified model with a caveat of potential uncaptured benefits, instead of attempting to incorporate potential but undefined benefits into the modelling results, and in doing so introducing unnecessary uncertainty.

The EAG noted that the structural link between the non-CNS-PD and CNS-PD seemed to be implemented incorrectly by the company. The EAG performed simple black box tests on the new model functionality included by the company, and examined changes to the formulae used to determine health state membership. The expected result of adjusting the transition rate between the non-CNS-PD and CNS-PD health states to 100% per cycle would be that all patients in the non-CNS-PD health state in a given cycle should move to the CNS-PD health state in the following cycle. However, doing this actually had the effect of increasing the rate of progression from PFS to non-

CNS-PD, i.e. the rate of non-CNS progression events was increased. This also had the effect of reducing the overall rate of CNS progression events, which was against the stated intention of this structural addition. The company have appeared to applied these changes to the wrong progression event, and have not added the missing structural link between the non-CNS-PD and CNS-PD health states. For the above reasons and those described in the EAR, the EAG maintains that the three-state model is most appropriate in this decision-making context.

2.10 Issue 10: Treatment beyond progression on lorlatinib is likely (and not restricted by the marketing authorisation) but benefits cannot be captured

The company consulted a panel of three clinicians who confirmed that for ALK TKIs more generally, clinicians will continue treatment beyond the point of progression in approximately half of patients, for an average of three months. These clinicians confirmed that this approach is likely to be taken in both first and second line. The company present scenarios in which treatment beyond progression ranges from 1.5 to 5.7 months in both first- and second-line settings.

The EAG's response

The EAG consider the elicitation-based parameters used to explore the possibility of treatment beyond progression plausible and informative for committee discussion. Further and more granular discussion with clinicians present at the committee meeting may also be informative, as these assumptions have a moderate impact upon incremental costs.

The EAG note that the company's approach to modelling treatment beyond progression differs to that previously implemented by the EAG. The company's approach is inclusive of the assumption that treatment has an effect upon HRQoL independent of progression status using CROWN EQ-5D data (see also Issue 11). These scenarios therefore reduce incremental QALY gain for lorlatinib, as the post-progression utilities on the comparator therapies are increased during patients' time on treatment.

2.11 Issue 11: Health-related quality of life (HRQoL) data from CROWN is not reflective of real-world utilities

In their response, the company referred to a scenario presented in their clarification response in which TA670 utilities were applied. The company did not comment on the EAG's suggested approach to modelling AE disutilities.

The EAG's response

The company's position on the EAG's preferred utility value set is unclear. The EAG maintains that the utility value set applied in the EAG's updated base-case is the most appropriate.

2.12 Issue 12: Dosing calculations and proportion of patients receiving subsequent treatment

The company summarised market research data on second- and third-line use of lorlatinib, which indicated that only [redacted] of patients had their dose reduced from the second cycle. This suggests that there would be minimal wastage of 100mg tablets, as dose reductions would be made following completion of a treatment cycle, at which point a prescription would be amended to the 25mg tablet strength if necessary.

The EAG's response

The EAG considers the company's explanation sufficient to support the assumption that there will be no additional wastage of 100mg tablets due to dose reductions.

The EAG notes that no further argument has been made against the EAG's preference for consistency with the use of RDI to calculate acquisition costs across comparators, which was highlighted as a part of this key issue. The EAG therefore maintains the position set out in the EAR and EAG preferred base-case analyses.