Medicinrådet

Bilag til Medicinrådets vurdering af lorlatinib (Lorviqua) til behandling af ALK-positiv uhelbredelig ikke-småcellet lungekræft i 1. linje

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. lorlatinib
2. Forhandlingsnotat fra Amgros vedr. lorlatinib
3. Ansøgers endelige ansøgning vedr. lorlatinib

Høringssvar fra Pfizer Aps til Medicinrådet vedrørende revurderingen af lorlatinib til behandling af ALK-positiv NSCLC-patienter

Kære Medicinrådet,

Pfizer takker for det fremsendte udkast til Medicinrådets vurderingsrapport vedrørende revurderingen af Lorviqua (lorlatinib). Pfizer er enig i Medicinrådets konklusioner vedrørende den kliniske effekt.

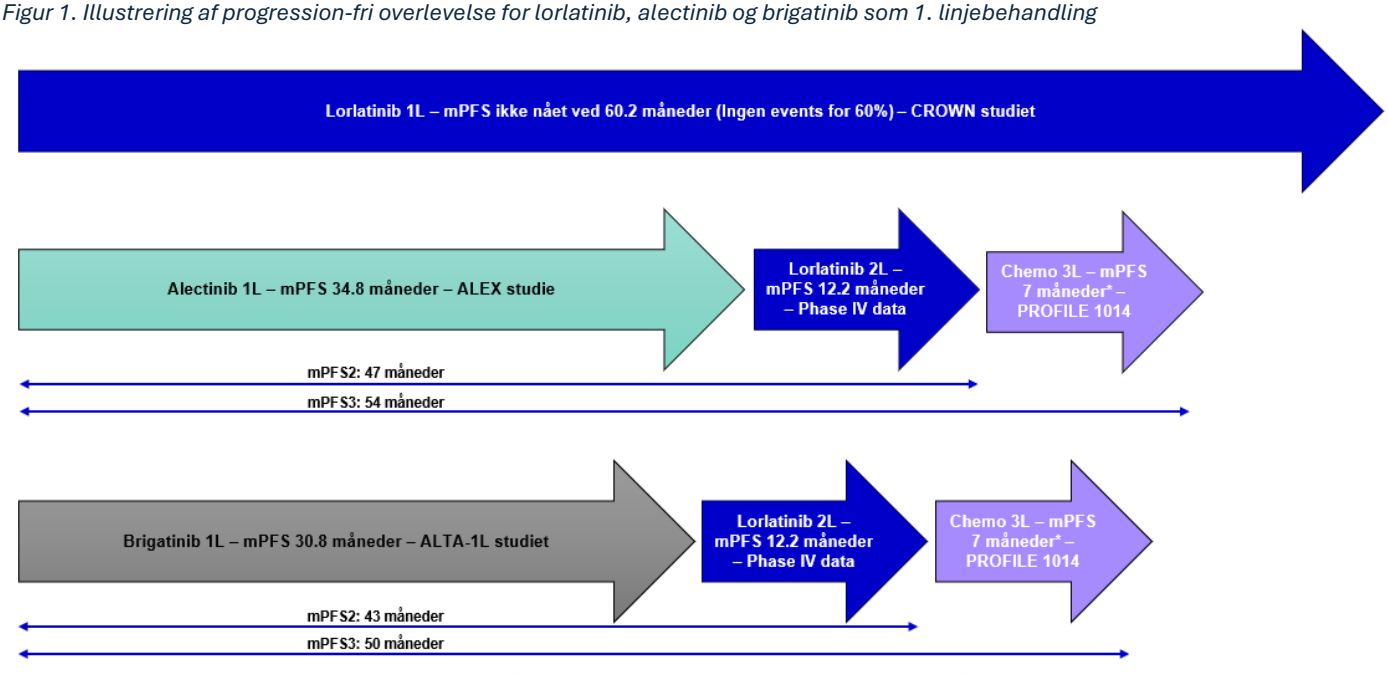
Lorviqua (lorlatinib) er en selektiv tyrosin kinase hæmmer af ALK og ROS1, der er godkendt til behandling af patienter med fremskreden ALK-positiv ikke-småcellet lungekræft (NSCLC), som ikke tidligere er behandlet samt efter behandling med anden ALK-rettet behandling. Lorlatinib er designet til at forhindre kræften i at sprede sig, samt til at gå over blodhjernebarrieren, så man ligeledes opnår god effekt i hjernen. Medicinrådet estimerer cirka 35 patienter med fremskreden ALK-positiv NSCLC i Danmark er relevant til lorlatinib 1.linjebehandling om året.

Effekten af lorlatinib:

Bedre progressionsfri overlevelse (PFS): Efter 5 års opfølgning (60,2 måneder) er median PFS (mPFS) med lorlatinib endnu ikke nået i CROWN studiet. Efter 60,2 måneders opfølgning lever 60% af lorlatinib patienterne stadig uden sygdomsprogression. Fra 3. til 5. behandlingsår er der blot 6 PFS-events.(1) Til sammenligning viste alectinib og brigatinib en mPFS på henholdsvis 34,8 og 30,8 måneder i 1. linje.(2, 3) Lorlatinibs progressionsfri overlevelse overstiger således klart den nuværende 1. linje behandling i Danmark.

Som det er illustreret i Figur 1, så overstiger lorlatinibs PFS alene, tre på hinanden følgende linjer af behandling svarende til nuværende klinisk praksis. Altså alectinib eller brigatinib i 1. linje med mPFS på henholdsvis 34,8 og 30,8 måneder efterfulgt af lorlatinib 2. linje med mPFS på 12,2 måneder (4) og kemoterapi i 3. linje med mPFS på 7 måneder.(5) Dette er endda optimistiske på vegne af kemoterapi, da mPFS stammer fra et studie med 1. linje patienter. Ydermere forventes det at en signifikant del af patienterne ikke når 3. linjebehandling.(6)

Figur 1. Illustrering af progression-fri overlevelse for lorlatinib, alectinib og brigatinib som 1. linjebehandling



*Estimatet for kemoterapi PFS i 3. behandlingslinjer er baseret på data fra 1.linje patienter. Derfor er det sandsynligt at 7 måneders PFS er overestimeret.

Bedre effekt for patienter med biomarkører: CROWN data viser, at patienter med forventet dårlig prognose opnår en forbedret effekt på lorlatinib. Patienter med EML4-ALK variant 3 opnår en mPFS med lorlatinib på 60,0 måneder og patienter, der er TP53 mutations-positive en mPFS på 51,6 måneder. Tilsvarende data med alectinib for EML4-ALK variant 3 viste mPFS på 17,7 måneder og med brigatinib mPFS på 16,0 måneder for EML4-ALK variant 3 og 18,0 måneder for TP53 muterede. Lorlatinibs effekt på patienter med EML4-ALK variant 3 og TP53 er også fremhævet i danske kliniske retningslinjer udarbejdet af danske speciallæger.(7)

Bedre effekt på hjernemetastaser: 26-40% af patienter med fremskreden ALK+ NSCLC diagnosticeres med hjernemetastaser fra starten og omkring 20% udvikler hjernemetastaser gennem behandlingen.(8) Udvikling af

hjernemetastaser har stor indvirkning på prognosen og patientens livskvalitet. Lorlatinib forlænger tiden til hjernemetastaser da 92% af alle patienterne stadig er uden nye hjernemetastaser efter 60 måneder (mPFS endnu ikke nået). Lorlatinib har profylaktisk virkning imod hjernemetastaser, i det 96% af patienterne uden hjernemetastaser ved start, stadig var uden hjernemetastaser efter 60 måneder på lorlatinib (mPFS endnu ikke nået). Desuden stabiliserer lorlatinib sygdommen i hjerne, i det 83% af patienterne med hjernemetastaser ved start ikke havde yderligere sygdom i hjernen efter 60 måneder på lorlatinib (mPFS endnu ikke nået).(1)

Bedre forventet øget overlevelsen (OS): Der er endnu ikke præsenteret modne OS-data med en median for hverken alectinib, brigatinib eller lorlatinib. I ALEX studiet ses det, at alectinib har 5-års OS-rate på 62,5%, imens brigatinib har en 4-års OS-rate på 66% i ALTA-1L studiet. (2, 3) Med en 5-års PFS-rate på 60% for lorlatinib er OS antageligt bedre end ved både alectinib og brigatinib. (1) I samtale med danske lungeonkologer der behandler ALK-patienter, har Pfizer fået bekræftet, at disse kliniske eksperter også forventer at lorlatinib 1. linjebehandling vil forøge OS sammenlignet med alectinib og brigatinib. Det samme vurderer Medicinrådet i deres vurderingsrapport, i det de skriver at "det er sandsynligt, at den betydelige forbedring af PFS samt den længere tid til CNS-progression vil føre til en forskel i OS på længere sigt".

Hvem bør behandles med lorlatinib?

Patienter med ALK-positiv NSCLC forventes at have en gennemsnitsalder for debut på 62 år. Heraf er halvdelen ikke-rygere og 70% af patienterne debuterer med stadie IIIb–IVb sygdom.(6)

Pfizer mener at danske ALK-patienter bør behandles med det bedste produkt i 1. linje. Dette skal ses i lyset af at 28% af patienterne ikke når til 2. linje, og disse patienter vil således ikke få gavn af lorlatinib. Som nævnt tidligere, så viser seneste fase IV data for lorlatinib i 2. linje blot en mPFS på 12,2 måneder,(4) hvilket må siges at være en moderat effekt sammenlignet med resultaterne i 1. linje. Dette understreger vigtigheden af at bruge det bedste produkt i 1. linje.

Lorlatinib har siden 26. oktober 2022 været godkendt til brug i 1. linje. Dette har dog været i klinisk ligestilling med alectinib og brigatinib, hvilket betyder, at ikke at alle relevante patienter har fået tilbudt lorlatinib.

Økonomiske konsekvenser ved at indføre lorlatinib som 1L. behandlings af ALK+ NSCLC-patienter:

Pfizer har valgt at sænke den af Medicinrådet tidligere godkendte pris på lorlatinib i forbindelse med revurderingen – dette er gjort for at sende et klart signal om, at vi mener, at alle relevante danske patienter skal kunne få tilbudt lorlatinib i 1. linje.

I Medicinrådets vurderingsrapport, som er beregnet på listepriser, ses det, at lorlatinib er omkostningsbesparende i de fem år, som medtages i budgetanalysen. Dette sker fordi der ved indførsel af lorlatinib vil være færre omkostninger relateret til fx behandling af hjernemetastaser. Ved indførelse af lorlatinib i 1.linje ses således en besparelse for Danske Regioner på knap 6 millioner kroner over de fem år.

Baseret på ovennævnte argumenter, sætter vi vores lid til, at Medicinrådet anbefaler lorlatinib som den foretrukne 1. linjebehandling til danske patienter med fremskreden ALK-positiv NSCLC.

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22.05.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.06.2025
Leverandør	Pfizer
Lægemiddel	Lorviqua (lorlatinib)
Ansøgt indikation	Behandling af voksne patienter med anaplastisk lymfomkinase-positiv (ALK-positiv), fremskreden ikke-småcellet lungecancer (NSCLC), der ikke tidligere er behandlet med en ALK-hæmmer.
Nyt lægemiddel / indikationsudvidelse	Revurdering

Prisinformation

Amgros har forhandlet følgende pris på Lorviqua (lorlatinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Lorviqua	100 mg (30 stk.)	35.970,68	[redacted]	[redacted]	[redacted]	[redacted]
Lorviqua	25 mg (90 stk.)	35.970,68	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Lorviqua, indkøbes Lorviqua til den nuværende SAIP.

Aftaleforhold

[redacted]

Konkurrencesituationen

[redacted]

*Tabel 2: Sammenligning af lægemiddeludgifter pr. patient**

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Lorviqua (lorlatinib)	100 mg (30 stk.)	100 mg 1 gang dagligt, oral	[redacted]	[redacted]
Alecensa (alectinib)	150 mg (224 stk.)	600 mg 2 gange dagligt, oral	[redacted]	[redacted]
Alunbrig (brigatinib)	90 mg + 180 mg (7 + 21 stk.) og 180 mg (28 stk.)	90 mg i 7 dage derefter 180 mg dagligt, oral	[redacted]	[redacted]

*Opstartsår. [redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Ikke anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of lorlatinib for first-line treatment of ALK-positive advanced non-small-cell lung cancer

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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Abbreviations

Abbreviation	Full Name
AE	Adverse Event
AIC	Akaike Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
AIP	Pharmaceutical purchasing price
AJCC	American Joint Committee on Cancer
AKT	Protein kinase B
ALK	Anaplastic Lymphoma Kinase

ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATMP	Advanced Therapy Medicinal Products
BEP	Biomarker-Evaluable Population
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
CHF	Congestive Heart Failure
CI	Confidence Interval
CM	Carcinomatous Meningitis
CNS	Central Nervous System
CR	Complete Response
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DCIS	Ductal Carcinoma In Situ
DLCG	Danish Lung Cancer Group
DMC	Danish Medicines Council
DOR	Duration of Response
DRG	Diagnosis-Related Group
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EORTC	European Organisation for Research and Treatment of Cancer
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
FFPE	Formalin Fixed, Paraffin Embedded
FISH	Fluorescence In Situ Hybridization
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life

HSUV	Health State Utility Value
ICER	Incremental Cost-Effectiveness Ratio
IC-OR	Intracranial Objective Response
IC-TTP	Intracranial Time to Progression
IC-TTR	Intracranial Time to Tumor Response
IFU	Instructions For Use
IHC	Immunohistochemistry
INV	Investigator assessed
IQR	Interquartile Range
IRT	Interactive Response Technology
ITT	Intention-To-Treat
IV	Intravenous
IxRS	Interactive Voice or Web-based Response Systems
KM	Kaplan-Meier
LCIS	Lobular Carcinoma In Situ
LMD	Leptomeningeal Disease
LVEF	Left Ventricular Ejection Fraction
MAIC	Matching-Adjusted Indirect Comparison
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
msec	Milliseconds
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next Generation Sequencing
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PI3K	Phosphoinositide 3-kinase
PR	Partial Response
PRO	Patient-Reported Outcome
PSA	Probabilistic Sensitivity Analysis
PSM	Partitioned Survival Model

QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QTcF	QT Interval Corrected Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
RDI	Relative Dose Intensity
RET	Rearranged During Transfection
RNA	Ribonucleic Acid
ROS1	c-ros Oncogene 1
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Standard Deviation
SE	Standard Error
SHBG	Sex Hormone-Binding Globulin
SLR	Systematic Literature Review
SMD	Standardized Mean Difference
SOC	System Organ Class
SRS	Stereotactic Radiosurgery
STAT 3	Signal Transducer and Activator of Transcription 3
TA	Technical appraisal
TEAEs	Treatment Emergent Adverse Events
TKI	Tyrosine Kinase Inhibitor
TNM	Tumor-Node-Metastasis
ToT	Time on Treatment
TRAEs	Treatment Related Adverse Events
TTD	Time to Deterioration
TTR	Time to Tumor Response
UICC	Union for International Cancer Control
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Lorviqua
Generic name	lorlatinib
Therapeutic indication as defined by EMA	Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.
Marketing authorization holder in Denmark	Pfizer Europe MA EEIG. Boulevard de la Plaine 17, 1050 Bruxelles Belgium
ATC code	L01ED05
Combination therapy and/or co-medication	NA
Date of EC approval	16th of December 2021 for this indication. Initial marketing authorisation on 6th of May 2019. (1)
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	NA
Other therapeutic indications approved by EMA	Lorviqua as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after: • alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or • crizotinib and at least one other ALK TKI.
Other indications that have been evaluated by the DMC (yes/no)	Yes
Joint Nordic assessment (JNHB)	The product is not suitable for a joint Nordic assessment, as this is a reassessment of lorlatinib.
Dispensing group	BEGR

Packaging – types, sizes/number of units and concentrations	Lorviqua 25 mg film-coated tablets: Each pack contains 90 film-coated tablets in 9 blisters. Lorviqua 100 mg film-coated tablets: Each pack contains 30 film-coated tablets in 3 blisters.

2. Summary table

Summary	
Indication relevant for the assessment	Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.
Dosage regiment and administration	The recommended dose is 100 mg lorlatinib taken orally once daily as a filmcoated tablet. Treatment with lorlatinib should be continued until disease progression or unacceptable toxicity.
Choice of comparator	Alecensa (alectinib) and Alunbrig (brigatinib)
Prognosis with current treatment (comparator)	As listed in the DMC recommendation, an ALK positive patient will today be treated with an ALK TKI, brigatinib, alectinib or lorlatinib. International real-world studies have found that treatment with multiple lines of ALK-TKIs can lead to overall survival from 28 month to more than 80 months in selected advanced-stage patients after receiving several lines of ALK-TKI-based (incl. lorlatinib) or chemotherapy treatments (2-4).
Type of evidence for the clinical evaluation	Indirect treatment comparison using fixed effects network meta-analysis (NMA).
Most important efficacy endpoints (Difference/gain compared to comparator)	In the new updated analysis from the CROWN trial, a phase III randomised study in ALK-positive advanced non-small-cell cancer treated with lorlatinib or crizotinib, with a median follow-up period of 60 months shows a continued superior efficacy for the lorlatinib-arm over the crizotinib-arm. The long-term efficacy of lorlatinib surpassed that of other currently approved ALK TKIs as alectinib and brigatinib and median progression free survival (PFS) is still not reached. PFS: In CROWN, with a median follow-up of 60.2 months, median PFS by investigator assessment (INV) is not reached at 60 months and 5-years PFS was 60 %. In ALEX, with a median follow-up of 37.8 months, median PFS by INV is 34.8 months for alectinib. In ALTA-1L with a median follow-up of 40.4 months, median PFS by INV of brigatinib is 30.8 months. In the NMA, lorlatinib was statistically significantly superior in PFS-INV compared to both alectinib and brigatinib with HRs (lorlatinib versus comparator) of 0.44 (95% CI: 0.28 to 0.71) and 0.44 (95% CI: 0.27 to 0.72), respectively. Overall survival (OS): Median OS in CROWN is still not mature after median 60.2 months follow-up and further analysis will be done in the future. For alectinib the ALEX trial showed a 5-year OS rate of 62,5 %

	and median OS is not expected to be analysed as hierarchical testing exclude significance. Brigatinib in the ALTA-1L trial showed a 4-years OS rate of 66 %. No significant difference was identified for OS in NMA. IC-TTP: For intracranial time to progression, in the NMA, lorlatinib was statistically significantly superior to both alectinib and brigatinib with hazard ratios (HRs) (lorlatinib versus comparator) of 0.38 (95% CI: 0.16 to 0.89) and 0.20 (95% CI: 0.08 to 0.53), respectively. Drug discontinuation rate: In the CROWN study with 60.2 months follow-up, drug discontinuation rate is 11 % and is in line with drug discontinuation rates of alectinib (14.5 %) and brigatinib (13%). No statistically significant difference was identified between comparators for drug discontinuation in the NMA.
Most important serious adverse events for the intervention and comparator	The most frequent reported serious adverse events for the three ALK TKIs were pneumonia/pneumonitis, dyspnoea and pyrexia. For lorlatinib the frequence was 8.1%, 2.7% and 2.0%; for alectinib the numbers were 3%, 1% and 1% and for brigatinib 4.4%, 2.2% and 2.9%.
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L was captured in the CROWN study. Health economic model: Based on the health economic model, lorlatinib provides a gain in health-related quality of life.
Type of economic analysis that is submitted	A cost-utility analysis based on a three-state model. In the base case, lorlatinib is estimated using a partitioned survival model, while alectinib and brigatinib is modelled using a pseudo transition model.
Data sources used to model the clinical effects	CROWN clinical data and result from the NMA. Alectinib and brigatinib post-progression survival is modelled using Solomon et al., 2018. (5)
Data sources used to model the health-related quality of life	CROWN data along with utility data from ALTA-1L identified in NICE Technical appraisal (TA) 670. (6)
Life years gained	1.65 years versus alectinib and 1.74 years versus brigatinib
QALYs gained	[redacted] years versus alectinib and [redacted] years versus brigatinib
Incremental costs	DKK [redacted] versus alectinib and DKK [redacted] versus brigatinib
ICER (DKK/QALY)	DKK 355,645/QALY versus alectinib and DKK 339,689/QALY versus brigatinib
Uncertainty associated with the ICER estimate	Efficacy estimates in terms of parametric curve parameters and efficacy hazard rations are the biggest drivers in the model.
Number of eligible patients in Denmark	Incidence: 35 patients per year (7) Prevalence: 200 patients (2022) (8)
Budget impact (in year 5)	DKK 3,426,044

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 ALK-positive non-small cell lung cancer

Lung cancer is the second most common cancer in Denmark and most lung cancer patients will die of their disease (9). In 2022, 5,200 patients were diagnosed with lung cancer, and more women than men were diagnosed with lung cancer in 2022 (9).

There are two main types of lung cancer, non-small cell (NSCLC, 85% of cases) and small cell (SCLC, 15% of cases). NSCLC can again be divided into squamous cell carcinoma and non-squamous carcinoma, mostly adenocarcinoma. Specific subtyping of non-small lung cancer is necessary for therapeutic decision making and will be determined based on biopsies (10). Recommended molecular tests for specific tumour biomarkers in NSCLC includes EGFR, ALK, KRAS, NTRK, ROS1, BRAF V600 and MET mutations and translocations (11).

NSCLC will be staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM (tumour –node- metastasis) 8th edition staging manual and be grouped into the staging categories I-IV (12). One third of patients will be diagnosed in the early stages (Stage I-IIIA) of disease and will potentially be curable, but most often lung cancer is diagnosed at advanced inoperable stages (stage IIIB-IV) (9).

One of the reasons behind the late diagnosis is the uncharacteristic symptoms such as coughing, shortness of breath or symptoms from metastases in bones, liver, or brain. Some patients will have other illnesses such as chronic obstructive pulmonary disease or asthma with similar symptoms. For 85% of patients, lung cancer will be a random secondary finding at scanning (9).

ALK-positive NSCLC is characterized by ALK translocations in the tumour tissue, which activate several signalling cascades involved in tumour formation. The most common ALK fusion partner is EML4. More than 15 EML4:ALK fusion variants have been identified, the most common being variants 1 (v1, 37% of the cases), 2 (v2, 12% of the cases), and 3a/b (v3, 42% of the cases) (13). ALK-positive lung cancer represents 3-5% of adenocarcinomas (12).

Patients with ALK-positive advanced NSCLC experience higher symptom burden and poorer survival compared with ALK-wildtype advanced NSCLC patients. Patients with ALK-positive advanced NSCLC are younger and often non-smokers compared with other lung cancers (11). NSCLC with ALK translocation often metastasizes to the central

nervous system (CNS). For patients, this leads to significant morbidity and reduced quality of life. The effect on the development of brain metastases is important for ALK targeted treatment (14). Patients with brain metastasis experience more morbidity, reduced quality of life and a shorter median survival (15).

Treatments for lung cancer are surgery, radiotherapy, chemotherapy, and other types of medical treatments, such as immunotherapy and targeted treatment related to identified biomarker. The treatment choice depends on the histological subtype of lung cancer, the extent of the disease and the patient's performance status at the time of treatment initiation (11).

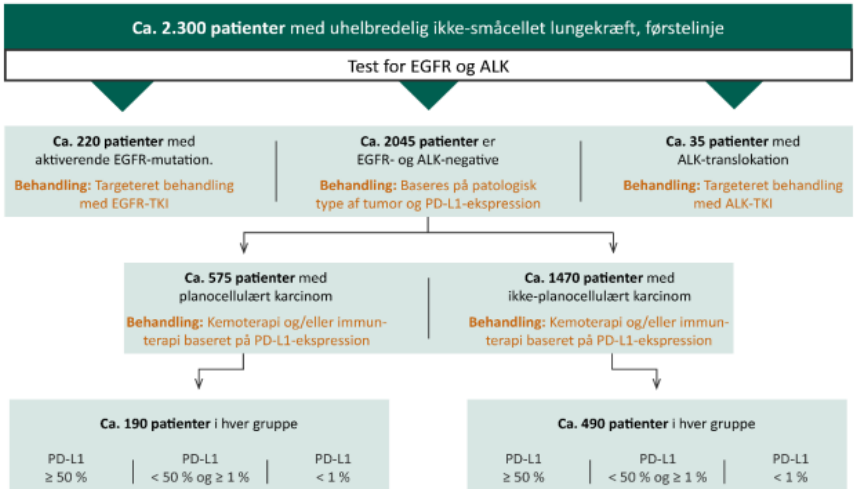
For metastatic ALK+ NSCLC the standard of care treatment (SoC) in first-line is anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) (7). In Denmark the following ALK-TKIs are approved for use: 1. generation ALK-TKI crizotinib, 2. generation ALK-TKIs alectinib, ceritinib, and brigatinib, and finally 3. generation ALK-TKI lorlatinib (7). Introduction of targeted treatment together with increased reflex testing has changed the prognosis for ALK+ NSCLC patients the last decade. Availability of more efficacious ALK TKIs from 1. generation to later generations has also improved the prognosis, and clinical trials have shown that PFS in treated ALK+ NSCLC patients is improved since the introduction of targeted treatment to more than 35 months (16) and now up to at least 60 months with lorlatinib (17). In studies of first-line use of 2. generation ALK-TKIs, a proportion of patients do not receive second-line treatment at disease progression, mainly due to clinical deterioration, thus the time to progression outcome of first-line ALK-TKI becomes important (16, 18, 19).

Real-World studies have reported survival outcomes with different results, depending on the availability of 2. and 3. generation ALK TKIs. A Danish real-world study reports an immature median OS of 42.5 months for unselected patients with advanced disease receiving ALK-TKIs as first treatment (2). As the patients were diagnosed between 2011-2018, many were treated with a 1st generation ALK TKI crizotinib first-line, which is not the preferred choice today. Other international real-would studies have found that treatment with multiple lines of ALK-TKIs can lead to overall survival ranging from 28 month to more than 80 months in selected advanced-stage patients receiving several lines of ALK-TKI-based treatments (2-4).

3.2 Patient population

The estimated number of patients is based on the Danish Lung Cancer Group's (DLCG) 2022 annual report (12) and the Danish Medicine Councils (DMCs) treatment recommendation (7). Around 2,700 patients were diagnosed with advanced lung cancer, of which about 85% of the patients have NSCLC (about 2,300 patients). Of these, about 75% of patients have adenocarcinoma (non-squamous) incurable NSCLC (about 1,725 patients), and about 25% have squamous incurable NSCLC (about 575 patients). ALK translocations occur primarily in patients with non-squamous NSCLC and account for approximately 2% in the annual report, resulting in an incidence rate of approximately 35 adult patients per year (2% of 1,725 patients) (Figure 1) (12).

Figure 1 Overview populations of incurable NSCLC patients in Denmark (20)



In a nationwide retrospective study of patients with ALK+ NSCLC in Denmark diagnosed between 2012 and 2018 (8), the investigators showed that during the study period the yearly incidence of detected ALK+ NSCLC patients increased threefold from 15 patients/year to 46 patients/year (8). Correspondingly, the prevalence increased almost eightfold from 2.7/million to 21.0/million during the same period (8). This partly reflects the significant increase in ALK rearrangements testing ("ALK positivity") during the studied period, which transitioned from being performed at single institutions to becoming standard of care at all Danish cancer centers. It is not possible to find newer data for prevalence in Denmark than 2018, so the prevalence is estimated until 2022 by Danish clinical expert in lung cancer.

Table 1 Incidence and prevalence in the past 5 years in Denmark

Year	2018	2019	2020	2021	2022
Incidence in Denmark	44	30	29	42	36
Prevalence in Denmark	120	140*	160*	180*	200*
Global prevalence	NA	NA	NA	NA	NA

* Estimated by Danish expert in lung cancer.

Based on feedback from a Danish clinical expert, prevalent patients are not expected to switch treatment even if lorlatinib is recommended as standard treatment. Therefore, the expected number of eligible patients is approximately 35 per year, calculated based on the incidence from previous years (Table 1) and the DMC's guideline for first-line treatment of incurable lung cancer (7), Table 2.

Table 2 Estimated number of patients eligible for treatment.

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	35	35	35	35	35

3.3 Current treatment options

The goal of treating incurable ALK+ NSCLC is life prolongation and symptom relief. Current Danish clinical practice recommends ALK-targeted treatment as the first choice for most patients. According to Danish Lung Cancer Group's treatment guidelines for palliative treatment of oncogene-driven non-small-cell lung cancer patients with ALK+ NSCLC and performance status 0-2, ALK-TKIs should be offered first-line (21).

The DMC equalized alectinib, brigatinib and lorlatinib in the treatment guidelines for first-line treatment of ALK+ metastatic NSCLC until progression or intolerable adverse reactions, based on a clinical comparative analysis, published 26.10.2022 by DMC. The DMC analysis was based on the CROWN 36-months follow-up, while 60-months follow-up data is now available. Crizotinib is listed as a treatment that may be considered, while ceritinib is not recommended for routinely use (20).

The ranking of the three equivalent ALK-TKIs, as shown in Table 3, is based on drug prices over a period of 2 years, as the costs of administration, monitoring, side effects and subsequent treatment were assessed equally for the three equivalent drugs. (7)

Table 3 DMC Recommendation for ALK positive NSCLC treatment (7)

Recommendation	Drug inclusive administration and dose	Treatment length
Use for minimum 95% of population	Alunbrig (brigatinib), oral, 90 mg x 1 daily in 7 days and hereafter 180 mg x 1 daily	Until progression or intolerable adverse events
2. choice	Alecensa (alectinib), oral, 600 mg x 2 daily	Until progression or intolerable adverse events
3. choice	Lorviqua (lorlatinib), oral, 100 mg x 1 daily	Until progression or intolerable adverse events
4. choice (consider)	Xalkori (crizotinib), oral, 250 mg x 2 daily	Until progression or intolerable adverse events
5. choice (do not use routinely)	Zykadia (ceritinib), oral, 450 mg x 1 daily	Until progression or intolerable adverse events

According to the Danish Lung Cancer Groups guideline for Palliative oncology treatment of oncogene-driven NSCLC, will patients, after progression on a first-line ALK-TKI, be evaluated for further treatment. Patients with ALK translocation, performance status 0-2 and systemic progression, may after re-biopsy, be offered second- or third-line treatment with lorlatinib or chemotherapy (21). Lorlatinib is approved by the Danish Medicine Council (DMC) to be used in second- and third-line according to the indication and brigatinib has approval by DMC for second-line treatment after crizotinib.

3.4 The intervention

Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases. In non-clinical studies, lorlatinib inhibited catalytic activities of non-mutated ALK and clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays (1). Lorlatinib demonstrated marked

antitumour activity in mice bearing tumour xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T. Two of these ALK mutants, G1202R and I1171T, are known to confer resistance to alectinib, brigatinib, ceritinib, and crizotinib. Lorlatinib is also capable of penetrating the blood-brain barrier. Lorlatinib demonstrated activity in mice bearing orthotopic EML4-ALK or EML4-ALKL1196M brain tumour implants (1).

Overview of intervention	
Indication relevant for the assessment	Lorviqua (lorlatinib) as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor (1)
ATMP	NA
Method of administration	Oral
Dosing	The recommended dose is 100 mg lorlatinib taken orally once daily (1)
Dosing in the health economic model (including relative dose intensity)	100 mg lorlatinib taken orally once daily. RDI of 92.3% is applied in the model (22)
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment with lorlatinib should be continued until disease progression or unacceptable toxicity (1)
Necessary monitoring, both during administration and during the treatment period	Serum cholesterol and triglycerides must be monitored prior to initiation of lorlatinib and 2-, 4- and 8-weeks post-initiation and regularly thereafter. Blood pressure must be measured before initiation of lorlatinib, and 2-weeks post-initiation and at least monthly thereafter. Electrocardiogram (ECG) should be monitored prior to initiation of lorlatinib and monthly thereafter, especially in patients predisposed to clinically significant cardiac events. Cardiac monitoring, including left ventricular ejection fraction (LVEF) assessment, at baseline and during treatment should be considered in patients at risk of cardiac disease and patients with diseases that may affect LVEF. Patients should be monitored for elevated lipase and amylase prior to initiation of lorlatinib and regulary thereafter. Body weight must be recorded before and during treatment.

Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Detection of ALK-positivity, standard part of reflex test done routinely at the diagnosis of NSCLC or with Next Generation Sequencing (NGS) testing. (1) Costs related to diagnosing is not included in the model, as these are expected to be the same for all comparators.
Package size(s)	Lorviqua 25 mg film-coated tablets: Each pack contains 90 film-coated tablets in 9 blisters. Lorviqua 100 mg film-coated tablets: Each pack contains 30 film-coated tablets in 3 blisters (1).

3.4.1 The intervention in relation to Danish clinical practice

Current Danish clinical practice recommends ALK-targeted treatment as the first choice for most ALK+ advanced NSCLC patients. According to DLCG treatment guidelines for palliative treatment of oncogene-driven NSCLC patients with ALK+ disease, with performance status 0-2, ALK-TKI's should be offered first-line (21). According to the DMC recommendation brigatinib is the first-, alectinib second- and lorlatinib third-choice based on prices from latest tender, Table 3 (7). Following the updated assessment of lorlatinib, it is expected to be recommended as 1st choice for Danish ALK+ advanced NSCLC patients based on superior efficacy.

Current standard, after progression on a first-line ALK-TKI, patients will be evaluated for further treatment, ideally after a re-biopsy. Patients with ALK translocation and performance status 0-2 may be offered second-line treatment with lorlatinib or platinum-based chemotherapy (21). Patients treated with lorlatinib first-line is expected to be treated with chemotherapy, another ALK TKI or included in a clinical trial, as second-line options (21).

3.5 Choice of comparator(s)

Alectinib and brigatinib are chosen as comparators to lorlatinib, as alectinib, brigatinib and lorlatinib represent three equal options for first-line treatment of ALK+ advanced NSCLC according to DMC recommendation (7). The ALEX study, investigated the efficacy of alectinib versus crizotinib, is broadly comparable to the CROWN study in terms of design and patient population, and thus provides the best opportunities to make a statistically valid comparison (23). The ALTA study examining the effect of brigatinib versus crizotinib, included patients that had received one systemic anticancer therapy for advanced disease and allowed crizotinib treated patients to crossover for brigatinib after progression (19).

Overview of comparator	
Generic name	Alectinib
ATC code	L01ED03

Mechanism of action	Alectinib is a highly selective and potent ALK and rearranged during transfection (RET) tyrosine kinase inhibitor. In pre-clinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including signal transducer and activator of transcription 3 (STAT 3) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and induction of tumour cell death (apoptosis). (24)
Method of administration	Oral
Dosing	The recommended dose of Alecensa is 600 mg (four 150 mg capsules) taken twice daily with food (total daily dose of 1200 mg) (24)
Dosing in the health economic model (including relative dose intensity)	600 mg twice daily with an RDI of 95.6%.
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Treatment with Alecensa should be continued until disease progression or unacceptable toxicity. (24)
Need for diagnostics or other tests (i.e. companion diagnostics)	A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. ALK-positive NSCLC status should be established prior to initiation of Alecensa therapy. (24)
Package size(s)	Alecensa hard capsules 150 mg, 224 pieces (4x56) blisters (24)

Overview of comparator	
Generic name	Brigatinib
ATC code	L01ED04
Mechanism of action	Brigatinib is a tyrosine kinase inhibitor that targets ALK, c-ros oncogene 1 (ROS1), and insulin-like growth factor 1 receptor (IGF-1R). Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling protein STAT3 in in vitro and in vivo assays. (25)
Method of administration	Oral
Dosing	The recommended starting dose of Alunbrig is 90 mg once daily for the first 7 days, then 180 mg once daily. (25)

Dosing in the health economic model (including relative dose intensity)	90 mg once daily for the first 7 days, then 180 mg once daily with an RDI of 85.5%.
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Treatment should continue as long as clinical benefit is observed. (25)
Need for diagnostics or other tests (i.e. companion diagnostics)	ALK-positive NSCLC status should be known prior to initiation of Alunbrig therapy. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients (25)
Package size(s)	Alunbrig 30 mg film-coated tablets, 28 pieces (blister) Alunbrig 90 mg film-coated tabl., 28 pieces (blister) Alunbrig 180 mg film-coated tabl., 28 pieces (blister) (25)

3.6 Cost-effectiveness of the comparator(s)

Lorlatinib, alectinib and brigatinib are currently deemed clinically equivalent for 1st line treatment of adult ALK-positive NSCLC patients by the DMC. According to the latest DMC 1st line ALK-positive NSCLC recommendation, brigatinib is the current 1st choice due to a lower estimated treatment cost (7). As such, both alectinib and brigatinib should be considered relevant comparators in terms of clinical efficacy and cost-effectiveness.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application.

Table 4 Efficacy outcome measures relevant for the application (26-28)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS)	18.3 months follow-up	OS is defined as the time from date of randomization to date of death due to any cause.	Time measured from randomization until death from any cause. Patients last known to be alive will be censored at date of last contact.
Progression free survival (PFS), by Blinded independent Review committee (BIRC) or	BIRC:18.3 months, 36.7 month, and INV: 60.2 month	PFS is defined as the time from randomization to the date of the first documentation of objective progression of disease or death due to any cause, whichever occurred first, according	Tumour assessment done at screening as CT and/or MRI scans and done at every 8 weeks +/- 1 week while on treatment or post-treatment follow-up (until progressed disease (PD)) and responses will be confirmed ≥4 weeks later until documented progression of disease by RECIST by BIRC or INV.

Investigator assessment (INV) or independent review committee (IRC).		to RECIST-defined disease progression. ALTA-1L: included local radiotherapy for Central Nervous System (CNS) lesions as progression.	Tumour assessment were repeated at the EOT visit, if more than 8 weeks have passed since the last evaluation. Patients who discontinue treatment without PD was followed radiologically until PD was confirmed by BICR regardless of subsequent anti-cancer treatments. Assessment of response made using RECIST v.1.1. ALEX: Assessment done by investigator for primary endpoint
Intracranial time to progression (IC-TTP)	60.2 months	CROWN and ALEX: IC-time to progression (IC-TTP) based on BICR or INV assessment is defined as the time from date of randomization to the date of the first documentation of progression of intracranial disease, based on either new brain metastases or progression of existing brain metastases. ALTA-1L: Protocol do not mention IC-TTP definition, but Intracranial PFS is defined as the time interval from the date of randomization until the first date at which CNS disease progression is objectively documented, or death due to any cause, whichever occurs first. Intracranial PFS will be assessed in patients with and without intracranial CNS metastases at baseline. It will be censored at the last disease assessment for patients without documented CNS disease progression.	Brain MRI (Gadolinium contrast enhanced) were used for assessment of CNS lesions (even if brain metastases were not suspected), scans were done at every 8 weeks +/- 1 week while on treatment or post-treatment follow-up (until PD) and responses confirmed ≥4 weeks later until documented progression of disease. Assessment of response of measurable intracranial disease made using a modified version of RECIST v.1.1 by BIRC. If only extracranial progression was documented, intracranial assessments were performed until IC progression by RECIST 1.1.
Discontinuation due to Adverse Events (AE)	60.2 months	Numbers of patients discontinuing due to AE from first dose until 30 days after last dose.	Reason for and date of discontinuation of study drug are noted on disposition CRF pages. ALTA-1L: Sign and symptoms associated with progression of the

			underlying disease are considered as an AE.
Grade 3-4 AE	60.2 months	Adverse events (AEs) (graded by NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 as provided by the investigator	AEs were classified using MedDRA classification. Severity of toxicities were graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 as provided by the investigator on the AE CRF page. ALTA-1L: Sign and symptoms associated with progression of the underlying disease are considered as an AE.
Quality of Life: Time to Deterioration (TTD)	36.7 months	Time to Deterioration (TTD) in pain, in chest, dyspnoea, or cough individually from the EORTC QLQ-LC13 and as a composite endpoint will be defined as the time from randomization to the first time the patient's score shows a 10 point or greater increase after baseline in any of the 3 symptoms.	TTD were assessed by EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L questionnaires on day 1 of each cycle and at end of treatment, and at post treatment follow-up.

Validity of outcomes

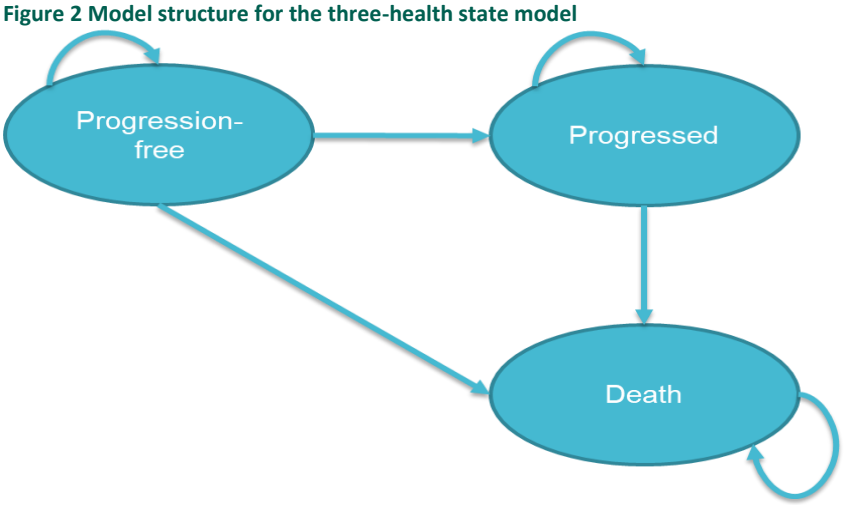
PFS and OS are considered the gold standard measures of efficacy in clinical trials in oncology and are required by regulatory authorities for the approval of new cancer treatments. PFS and OS as endpoints are routine in clinical trials and precisely measured based on objective and quantitative assessment. Together with discontinuation rates due to AEs, grade 3-4 AEs and Quality of Life (QoL), PFS and OS are included in the DMC list of important efficacy outcomes for NSCLC. For targeted treatments for NSCLC the DMC also list time to CNS-progression as an important outcome (29).

4. Health economic analysis

4.1 Model structure

To capture differences in cost and effects, a cost-utility analysis was conducted. The cost-utility analysis was based on a three-health state model, developed to assess the cost-effectiveness of lorlatinib versus relevant comparators in untreated ALK-positive NSCLC patients. In the model, the alive health states (progression-free and progressed) are further divided into on and off treatment periods, to capture treatment acquisition and administration costs more accurately. The model structure is presented in Figure 2.

Figure 2 Model structure for the three-health state model



The model can allow patients to discontinue treatment before progression (i.e. progression-free off treatment), while some patients may receive treatment beyond progression (i.e. progressed on treatment). All patients enter the model in the progression-free state, receiving lorlatinib or comparator treatment. Patients may remain progression-free, their disease may progress, or they may die. Patients whose disease has progressed can remain alive with progressed disease or die. Death is an absorbing state.

In the model, health state membership for lorlatinib is determined using a standard partitioned survival model (PSM). However, the PSM approach was not found appropriate for the modelling of alectinib and brigatinib given the mismatch between subsequent treatments in the comparator trials, ALEX and ALTA-1L and lorlatinib second-line use in Danish clinical practice. In short, fewer patients received lorlatinib as second-line treatment in ALEX and ALTA-1L than what is expected in Danish clinical practice, as lorlatinib is currently recommended as standard treatment in second-line. (30) Moreover, issues with the overall survival trial data from ALEX and ALTA-1, described in section 6.1.5 and 6.2.6, further underlined the necessity of an alternative modelling approach for alectinib and brigatinib. Therefore, the health state membership of alectinib and brigatinib is determined using a pseudo state transition approach. The pseudo state transition approach applies a parametric curve to model PFS, while post-progression survival is modelled separately, which enables a more plausible estimation of long-term survival of alectinib and brigatinib patients.

The pseudo state transition approach was also considered for lorlatinib, however, as a Danish clinical expert found the distribution of subsequent treatments in the lorlatinib arm of the CROWN trial to be appropriate for an expected Danish clinical practice, the standard PSM was applied for lorlatinib in the base case.

4.2 Model features

The main model features are described in Table 5.

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with untreated ALK-positive advanced NSCLC	Equal to the population presented in section 3.2
Perspective	Restricted societal perspective	According to DMC guidelines (31)
Time horizon	30 years	Life time horizon.
Cycle length	30 days	Aligning with the 30-day pack size for lorlatinib.
Half-cycle correction	Included	To account for events and transitions occurring at any point within a cycle.
Discount rate	3.5%	DMC applies a discount rate of 3.5%
Intervention	Lorlatinib 100 mg once daily	Intervention of interest.
Comparator(s)	Alectinib 600 mg twice daily Brigatinib 180 mg once daily	Alectinib, brigatinib and lorlatinib are currently deemed to be clinically equal by the DMC (7)
Health state modelling	Lorlatinib is modelled by standard partitioned survival modelling, while alectinib and brigatinib are modelled using a pseudo state transition approach.	The pseudo state transition option was added to capture post-progression survival given the mismatch between subsequent treatments in the comparator trials and lorlatinib second-line use in real-world practice.
	If the OS and PFS curves overlap, the PFS curve is capped by the OS curve.	To maintain plausibility in cases where the OS and PFS curves are overlapping, the PFS curve is capped by the OS curve. The feature also remains in the pseudo transition model, meaning that PFS can be capped by the parametric OS curve, despite death is modelled separately using post- and pre-progression survival.
Comparator modelling	Alectinib and brigatinib are modelled based on crizotinib by applying the relevant HR.	While the proportional hazards assumption was violated in CROWN, the proportional hazards assumption could be reasonable in the ALEX and ALTA-1L trials (Table 71). Given the underlying assumption of proportional hazards when applying HRs, alectinib and brigatinib was modelled by applying a HR to the parametric survival curves of the crizotinib arm of CROWN.
Outcomes for model input	OS, PFS, ToT and IC-TTP	Outcomes of interest

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment was based on the systematic literature research (SLR) presented in Appendix H. The relevant literature is presented in Table 6.

Table 6 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number) *	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Shaw, A. T., Bauer, T.M.. de Marinis, F., Felip, E., Goto, Y. Liu, G. et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. N Engl J Med 2020, Vol 383(21): 2018-2029. (32)	CROWN	NCT03052608	Start: 27/04/17, expected completion: 31/12/28, data cut-off 20/03/20	Lorlatinib and crizotinib in ITT population for OS
Solomon, J.S., Bauer, T.M., Mok, T.S.K., Liu, G, Mazieres, J. de Marinis,F. et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. Lancet Respir Med 2022, 11(4):354-366. (33)	CROWN	NCT03052608	Start: 27/04/17, expected completion: 31/12/28, data cut-off 20/09/21	Lorlatinib and crizotinib in ITT population HRQoL
Solomon, J.S., Liu, G., Felip, E., Mok, T.S.K., Soo, R.A., Mazieres, J. et al. Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. J Clin Oncol 2024,42:3400-3409. (17)	CROWN	NCT03052608	Start: 27/04/17, expected completion: 31/12/28, data cut-off 30/10/23	Lorlatinib and crizotinib in ITT population for PFS(BIRC), PFS(INV), IC-TTP, Grade 3-4 AE, Discontinuation rate due to AEs,
Solomon, B.J., Bauer, T.M., Ou, SH.I., Liu, G., Hayashi, H., Bearz, A. et al. Post Hoc Analysis of Lorlatinib Intracranial Efficacy and Safety in Patients With *ALK*-Positive Advanced Non-Small-Cell Lung Cancer From the Phase III CROWN Study. J Clin Oncol,2022,40:3593-3602. (34)	CROWN	NCT03052608	Start: 27/04/17, expected completion: 31/12/28, data cut-off: 20/03/20	Lorlatinib and crizotinib in ITT population
CROWN Clinical Study Report, October 2023, data on file (35).	CROWN	NCT03052608	Data cut-off 30/10/2023	Lorlatinib and crizotinib, for Subsequent therapy, SAE
Peters, S., Camidge, D.R., Shaw, A.T., Gadgeel, S. Ahn, J.S., Kim, D.-W. et al. Alectinib versus Crizotinib in Untreated *ALK*-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2017; 377:829-38. (27)	ALEX	NCT02075840	Start:19/08/14, expected completion: 29/09/26, data cut-off: 09/02/17	Alectinib and crizotinib in ITT population of PFS-IRC, time to CNS progression.

Camidge, D.R., Dziadziuszko, R., Peters, S., Mok, T., Noe, J., Nowicka, M. et al. Updated Efficacy and Safety Data and Impact of the *EML4-ALK* Fusion Variant on the Efficacy of Alectinib in Untreated *ALK*-Positive Advanced Non-Small Cell Lung Cancer in the Global Phase III ALEX Study.J Thor Oncol. 2019;14: 1233-1243. (36)	ALEX	NCT02075840	Start:19/08/14, expected completion: 29/09/26, data cut-off: 01/12/17	Alectinib and crizotinib in efficacy by EML4-ALK fusions variant and DOR in ITT population.
Mok, T., Camidge, D.R., Gadgeel, S.M., Rosell, R., Dziadziuszko, R., Kim, D.-W. et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced *ALK*-positive non-small-cell lung cancer in ALEX study. Ann Oncol 2020; 31 (8): 1056-1064. (23)	ALEX	NCT02075840	Start: 19/08/14, expected completion: 29/09/26 Data cut-off: 29/11/19	Alectinib and crizotinib in ITT population of OS, PFS(INV), Grade 3-4 AES and discontinuation rate due to AEs.
Pérol, M., Pavlakis, N., Levchenko, E., Platania, M.,Oliveira, J., Novello, S. et al. Patient-reported outcomes from the randomized phase III ALEX study of alectinib versus crizotinib in patients with *ALK*-positive non-small-cell lung cancer. Lung Cancer 2019; 138:79-87. (37)	ALEX	NCT02075840	Start: 19/08/14, expected completion: 29/09/26, data cut-off: 09/02/17	Alectinib and crizotinib in ITT population of HRQOL
Alecensa-H-C-4164-II-0001: EPAR- Assessment report, 2018 European Medicines Agency, Ref. No.: EMA/CHMP/833519/2017	ALEX	NCT02075840	Start:19/08/14, data cut-off: 01/12/17	Alectinib and crizotinib for SAE
Camidge, D.R., Kim, H.R., Ahn, M.-J., Yang, J.C.-H., Han, J.-Y., Lee, J.-S., et al. Brigatinib versus Crizotinib in *ALK*-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2018; 379:2027-2039. (38)	ALTA-1L	NCT02737501	Start: 26/05/16, completion: 29/01/21, data cut-off: 19/02/18	Brigatinib and crizotinib in ITT population of IC-TTP
Camidge, D.R., Kim, H.R., Ahn, M.-J., Yang, J.C.H., Han, J.-Y., Hochmair, M.J. et al. 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. J Clin Oncol 2020; 38: 3592-3603. (39)	ALTA-1L	NCT02737501	Start: 26/05/16, completion: 29/01/21, data cut-off: 28/06/19	Brigatinib and crizotinib in ITT population
Camidge, D.R., Kim, H.R., Ahn, M.-J., Yang, J.C.H., Han, J.-Y., Hochmiar, J., et al. Brigatinib Versus Criziotinib in ALK inhibitor-Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. J Thora Oncol 2021; 16(12): 2091-2108. (19)	ALTA-1L	NCT02737501	Start: 26/05/16 completion: 29/01/21, data cut-off: 29/01/21	Brigatinib and crizotinib in ITT population of PFS(BIRC), PFS(INV), OS, Grade 3-4 AEs, Discontinuation rate due to AEs, HRQOL

Alunbrig-H-C-4248-II-0003: EPAR Assessment report- Variation, 2020 European Medicines Agency. Ref. No.EMA/140650/2020	ALTA-1L	NCT02737501	Start: 26/05/16, completion: 29/01/21, data cut-off: 28/06/19	Brigatinib and crizotinib for SAE
Ignatius Ou S-H, Solomon BJ, Besse B, Bearz A, Lin C-C, Chiari R, Camidge DR, Lin JJ, Abbattista A, Toffalorio F, et Soo RA. Brief Report: Final overall survival and long-term safety of lorlatinib in patients with ALK-positive non-small cell lung cancer from the pivotal phase 2 study. J of Thora Oncol 2024, https://doi.org/10.1016/j.jtho.2024.11.021 (40)	Study 1001	NCT01970865	Start: 08/01/14, completion: 24/05/23. Data cutoff: 27/07/23	Lorlatinib efficacy

* If there are several publications connected to a trial, include all publications used

5.2 Literature used for the assessment of health-related quality of life

A systematic literature search was conducted to obtain further health state utility values to supplement the utility data from the CROWN study with a comparator relevant to Danish clinical practice. The literature search is described in Appendix I. Literature used for HRQoL inputs are listed in Table 7.

Table 7 Relevant literature included for documentation of health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
National Institute for Health and Care excellence Technology appraisal guidance 670. Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor (6)	The utility data was based on patients with ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor for the following: • Utility values for progression-free and progressed patients • Disutilities for adverse events	Described in section 10.3
Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. Health Qual Life Outcomes. 2008; 6(1): (41)	The utility data was based on metastatic NSCLC patients on second-line treatment for the following: • Disutilities for adverse events	Described in section 10.3

Roughley A, Damonte E, Taylor-Stokes G, et al. Impact of Brain Metastases on Quality of Life and Estimated Life Expectancy in Patients with Advanced Non-Small Cell Lung Cancer. Value Health. 2014; 17(7):A650 (42)	Used to model a utility multiplier in order to estimate the effect of CNS-progression on HRQoL (disutility).	Described in section 10.3

5.3 Literature used for inputs for the health economic model

A systematic literature search was conducted to obtain further literature input for the health economic model to supplement the CROWN data. However, most inputs were identified in targeted literature review in NICE technical appraisals (TA) or in the clinical SLR. The literature search is described in Appendix J. The literature references used for input to the economic model are listed in Table 8. Modelling of comparators alectinib and brigatinib was based on the comparative analysis presented in section 7, therefore, publications related to alectinib and brigatinib efficacy are not presented below in Table 8.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Solomon, J.S., Liu, G., Felip, E., Mok, T.S.K., Soo, R.A., Mazieres, J. et al. Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. J Clin Oncol 2024 (17)	Efficacy data	Clinical systematic literature review	Section 6.1.4
Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. The Lancet Oncology. 2018;19(12):1654-1667. Expansion cohort EXP3B-5' from Study 1001 (5)	Post-progression survival for alectinib and brigatinib	Clinical systematic literature review	Section 8.2
Ignatius Ou SH, Jänne PA, Bartlett CH, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. Annals of oncology: official journal of the European Society for Medical Oncology. 2014;25(2):415-422. (43)	Post-progression survival for lorlatinib (only used in scenario analysis)	Targeted literature review via NICE TA628	Section 12.2.1

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE SINGLE TECHNOLOGY APPRAISAL - Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer TA536 (44)	Inputs for alectinib including RDI, adverse events and subsequent treatments	Targeted literature	Section 11
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE SINGLE TECHNOLOGY APPRAISAL - Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor TA670 (6)	Inputs for brigatinib including RDI, adverse events and subsequent treatments, resource use	Targeted literature	Section 11
Le H, Montero D, Lowry C, et al. [Data on file] Cost of managing brain metastases in patients with ALK+ advanced NSCLC with first-line tyrosine kinase inhibitors in the UK. 2024. (45)	Resource use for CNS progression	Data on file – soon to be published	Section 11.4
Ignatius Ou S-H, Solomon BJ, Besse B, Bearz A, Lin C-C, Chiari R, Camidge DR, Lin JJ, Abbattista A, Toffalorio F, et Soo RA. Brief Report: Final overall survival and long-term safety of lorlatinib in patients with ALK-positive non-small cell lung cancer from the pivotal phase 2 study. J of Thora Oncol 2024, https://doi.org/10.1016/j.jtho.2024.11.021 (40)	Efficacy data. Lorlatinib OS	Published after initial submission	Section 6.1.6

6. Efficacy

6.1 Efficacy of lorlatinib compared to alectinib for advanced ALK positive NSCLC adult patients.

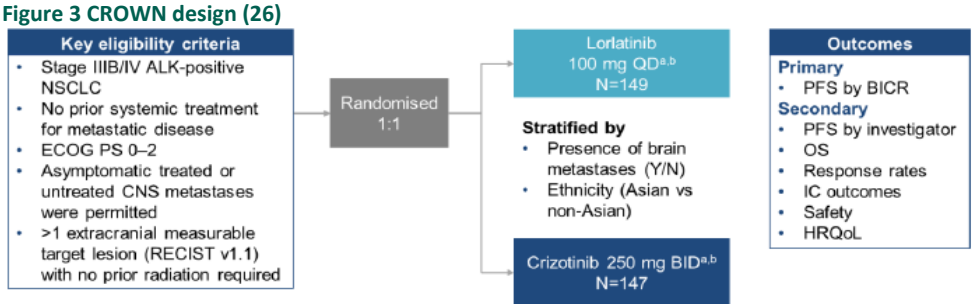
6.1.1 Relevant studies

We have chosen to compare lorlatinib with alectinib, as alectinib is one of three equal options for first-line treatment of ALK+ lung cancer in Denmark. It is our opinion that the ALEX study, which investigated the effect of alectinib versus crizotinib, is broadly comparable to CROWN in terms of design and patient population and thus provides the best opportunities to make a statistically valid comparison. Alectinib has been the first choice in daily clinical practice for ALK positive advanced NSCLC patients for some years before brigatinib.

ALESIA, a smaller study with an exclusively Asian population (46), was also identified. The patient population in ALESIA does not correspond to the Danish population, although baseline characteristics – apart from geographical origin – are reasonably balanced and correspond to ALEX. It cannot be excluded that the origin of the patients has an impact on the effect of the medicines. ALESIA was not included as a literature basis for the first application of lorlatinib into current treatment guidelines and this approach was accepted by DMC. Therefore, we have excluded ALESIA from the comparison (29).

CROWN: CROWN is an ongoing Phase III, multinational, multicenter, randomized, open-label, parallel, two-arm study in which patients with previously untreated ALK-positive advanced NSCLC were randomized 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy (17) as first-line treatment to compare efficacy and safety between treatment arms. Patients were stratified by presence of brain metastases (yes/no) and ethnicity (Asian/non-Asian). Brain lesions could be either measurable or non-measurable. Testing for ALK positivity could be done locally or centrally. Patients received lorlatinib 100 mg once daily (n=149) or crizotinib 250 mg twice daily (n= 147). Cross-over was not permitted (32).

Figure 3 CROWN design (26)

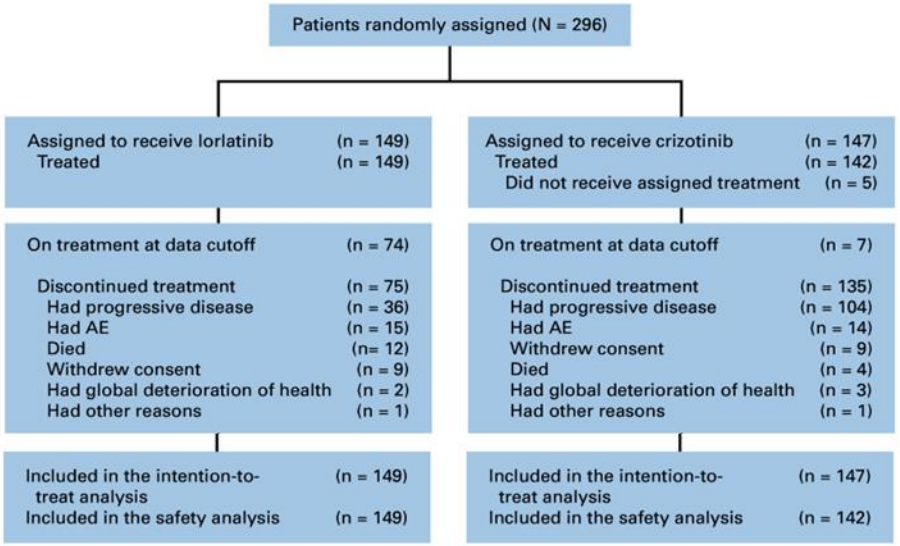


CONSORT diagram of patient flow is presented in Figure 4. All 149 patients in the lorlatinib arm received treatment, however five patients in the crizotinib arm did not receive treatment. At the data cut-off October 31, 2023, 74 patients remained on treatment in the lorlatinib-arm and seven in the crizotinib-arm. The most common

reason for discontinuation was disease progression in both arms (36 patients in lorlatinib/104 patients in crizotinib-arm) (17). Other reasons for discontinuation were AEs (15 in lorlatinib and 14 in crizotinib), and withdrawal of consent (9 in both arms) (17). Patients could withdraw from the study at any time on request or be withdrawn at any time at the discretion of the investigator or sponsor for safety or for behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

The primary endpoint for CROWN was PFS by BIRC (RECIST v1.1) (PFS-BIRC). Key secondary endpoints included PFS by investigator (PFS-INV), overall survival, objective response rate, duration of response, objective intracranial response, safety, biomarker analysis and patient reported outcomes (PRO) (17).

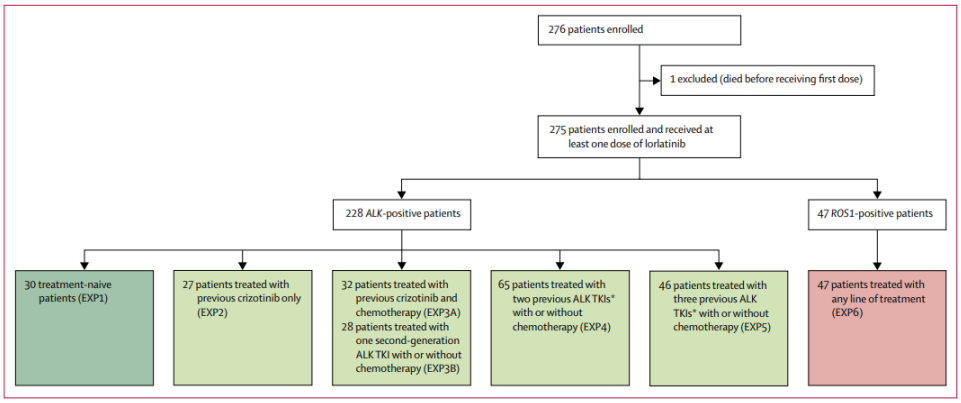
Figure 4 CONSORT diagram CROWN (17)



Study 1001: Lorlatinib is investigated in a phase I/II study with the title: "Phase 1/2 Study of PF-06463922 (An ALK/ROS1 Tyrosine Kinase Inhibitor) in Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations". The purpose was to study the safety, pharmacokinetics, pharmacodynamics, patient reported outcomes and efficacy of lorlatinib in ALK + advanced NSCLC patients and ROS1+ advanced NSCLC patients.

In the global single-arm phase II part of the study, lorlatinib is investigated in both treatment-naïve and previously treated adult patients (aged ≥18 years) with histologically or cytologically ALK or ROS1-positive advanced NSCLC with or without asymptomatic central nervous system (CNS) metastases and with an Eastern Cooperative Oncology Group performance status of 0-2.(40) A total of 6 expansions cohorts are included: EXP1: ALK+ treatment naive NSCLC and EXP2-3A, EXP3B, and EXP4-5: ALK+ NSCLC patients treated with 1. or 2. Generation ALK-TKI +/- CT or later lines. Expansion cohort 6 is ROS1 positive patients. EXP1-6 cover all patients treated with lorlatinib for safety reporting. A total of 275 patients are enrolled in the phase 2 study and received at least 1 dose of lorlatinib. Of these, 228 are ALK positive: 30 patients in EXP1, 59 in EXP2-3A, 28 in EXP3B, and 111 patients in EXP4-5.(40)

Figure 5 Summary of expansions cohorts (40)



Lorlatinib was administered orally in a tablet form at a starting dose of 100 mg once daily continuously in 21-day cycles. Treatment continued until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients were allowed to continue treatment with lorlatinib after objective progression as long as there was evidence of clinical benefit in the investigator's opinion. (40)

ALEX: ALEX is a randomized, multicentre, open label, phase 3 study that investigated the effect and safety of first-line treatment with alectinib compared to crizotinib in patients with incurable ALK-positive NSCLC, who had not previously received treatment for their disease. Patients were randomised 1:1 to alectinib, 600 mg twice daily (n=152), or crizotinib, 250 mg twice daily (n=151). The randomization was stratified by performance status (PS 0/1 vs. 2), race (Asian vs. non-Asian), and the presence of CNS metastases (yes or no). Cross-over between the arms was not allowed per protocol. Subsequent treatment at progression was up to the treating physician and could include alectinib after crizotinib in countries where alectinib treatment was approved. Testing for ALK protein expression positivity of tissue samples was done centrally (30). At the latest OS analysis, 53 patients (34.9%) in the alectinib arm and 13 patients (8.6%) in the crizotinib arm were still in treatment with the original study treatment (47).

The study's primary endpoint was INV-PFS (RECIST v.1.1). Secondary endpoints included IRC- PFS, IRC-rated time to CNS progression, OS, safety, and quality of life (measured with EORTC-QLQ-C30). See Table 9 for more information. Efficacy analyses were calculated for intention-to-treat (ITT) population, and safety analyses were calculated for all patients who received at least one study dose (24).

Table 9 Overview of study design for studies included in the comparison.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
CROWN, NCT03052608, (17)	Open-label, multinational, randomized 2 arm phase III trial comparing lorlatinib with crizotinib	From May 2017 to February 2019, 296 patients were randomized. Study is ongoing and latest cut off October 31,2023.	ALK positive advanced NSCLC treatment naïve adult patients	Lorlatinib tablets 100 mg once daily and treated until disease progression, death, withdrawal of consent or unacceptable toxic effects. Study treatment beyond progression was allowed. Participants who develop radiological disease progression but are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with the treatment they have been assigned to, provided that the treating physician has determined that the benefit/risk for doing so is favourable.	Crizotinib capsules 250 mg twice daily and treated until disease progression, death, withdrawal of consent or unacceptable toxic effects.	Primary outcome: PFS based on BIRC assessment (RECIST v1.1): Unplanned analysis after 3 years: Median duration of follow-up for PFS by BIRC: 36.7 month for lorlatinib and 29.3 month for crizotinib. Secondary outcomes: PFS based on INV assessment (RECIST v1.1): Post hoc analysis after 5 years: Follow-up time 60.2 months for lorlatinib and 55.1 months for crizotinib. OS: Interim analysis: Median duration of follow-up: 18.3 months in lorlatinib group and 14.8 in crizotinib group. ORR and DOR based on BIRC and on INV (RECIST v1.1): BIRC: Unplanned analysis: Median duration of follow-up: 36.7 month for lorlatinib and 29.3 month for crizotinib. INV: Post hoc analysis after 5 years: Follow-up time 60.2 months for lorlatinib and 55.1 months for crizotinib. IC-TTP, IC-OR and IC-DOR, all based on BIRC and on INV (modified RESIST v1.1): BIRC: Unplanned analysis after 3 years by BIRC: Median duration of follow-up: 36.7 month for lorlatinib and 29.3 month for crizotinib. INV: Post hoc analysis after 5 years: Follow-up time 60.2 months for lorlatinib and 55.1 months for crizotinib. Adverse events: Are classified using NCI-CTC AE version 4.03 classification system and reported at each analysis, follow-up time 60.2 months for lorlatinib and 55.1 months for crizotinib. Health related Quality of Life: Treatment arms evaluated based on EORTC QLQ-C30, EORTC QLQ-LC-13 and EQ-5D-5L utility and VAS scores and was reported at following time point: First interim analysis and unplanned analysis at 3 years.

ALEX NCT02075840 (16) (48)	Randomized, multicenter, open-label, phase III study of alectinib versus crizotinib.	From August 2014 till January 2016, 303 patients were randomized. Study not finalized, and latest cut off November 29, 2019.	ALK positive advanced NSCLC treatment-naïve adult patients	Alectinib 600 mg (4 capsules of 150 mg) twice daily. Patients were randomized to lorlatinib or crizotinib and treated until disease progression, death, withdrawal of consent or unacceptable toxic effects.	Crizotinib capsules 250 mg twice daily	Primary outcome: PFS by INV assessment (RECIST v1.1): Final analysis: median duration of follow-up 37.8 month for alectinib and 23.0 months for crizotinib. Secondary outcomes: PFS based on IRC assessment (RECIST v1.1): Median duration of follow- up: 18.6 months for alectinib and 17.6 months for crizotinib. Time to CNS progression by IRC (RECIST v1.1 and RANO): Median duration of follow-up: 18.6 months for alectinib and 17,6 months for crizotinib. ORR and DOR based on INV assessment (RECIST v1.1): Follow-up 27.8 months for alectinib and 22.8 months for crizotinib. Overall survival: Final analysis: Median duration of follow-up: 48.2 months for alectinib and 23.3 months for crizotinib. CNS-ORR and CNS-DOR based on IRC): Follow-up 27.8 months for alectinib and 22.8 months for crizotinib Adverse events: Are categorized using NCI-CTC for AE version classification system and reported at each analysis, median follow-up time 48.2 months. Health related Quality of Life: Treatment arms evaluated based on EORTC QLQ-C30, EORTC QLQ-LC-13. Evaluate time to deterioration: First interim analysis and unplanned analysis at 3 years.
B7461001: Study 1001 NCT01970865 (5)	Global, multicenter, open, single-arm phase II trial with lorlatinib in 6 different cohorts: EXP1, EXP2-3A, EXP3B,	Between September 15, 2015, and October 3, 2016, 276 patients were enrolled. Study is finalized	ALK positive advanced NSCLC treatment: 30 ALK+ and treatment naive (EXP1); 59 ALK+ and received	Lorlatinib 100 mg once daily continuously in 21-day cycles. Treatment continued until investigator-assessed disease progression unacceptable toxicity, withdrawal of consent, or death. Patients were allowed to continue	None	Primary endpoint: Objective tumour response (ORR) (defined as a confirmed CR or PR) and intracranial tumour response (IC-ORR) according to modified RECIST version 1.1, which allowed for up to five CNS target lesions, as assessed by independent central radiology review (ICR) and assessed in pooled subgroups of ALK-positive patients (EXP1, EXP2–3A, EXP3B, EXP4–5 and EXP2–5). Data cutoff for this analysis was March 15, 2017. Secondary endpoints:

EXP4-5 and EXP1-6	and latest cut off October 31,2023.	previous crizotinib without (n=27; EXP2) or with (n=32; EXP3A) previous chemotherapy; 28 ALK+ and received one previous non-crizotinib ALK TKI +/- chemotherapy (EXP3B); 112 ALK+ with two (n=66; EXP4) or three (n=46; EXP5) previous ALK TKIs +/- chemotherapy; and 47 ROS1+ with any previous treatment (EXP6).	treatment with lorlatinib after objective progression as long as there was evidence of clinical benefit in the investigator's opinion.	Progressions-free survival (PFS), Overall survival (OS) and safety, data cut-off July 27, 2023. The median follow-up for OS was 72.7 months (95% CI, 69.3-76.3) in EXP1, 69.3 months (95% CI, 65.1-75.3) in EXP2-3A, 66.7 months (95% CI, 58.6-69.6) in EXP3B, 66.7 months (95% CI, 63.0-68.8) in EXP4-5, and 66.7 months (95% CI, 63.0-67.7) in EXP3B-5.

6.1.2 Comparability of studies

Head-to-head data between lorlatinib and alectinib is not available, but CROWN and ALEX have crizotinib as a common comparator, which makes an indirect comparison possible.

The ALEX- and CROWN study is similar in design and patient population: both studies randomize experimental drug versus crizotinib, and cross-over is not allowed. In addition, patients who have previously received chemotherapy for metastatic disease are excluded in both studies, and all patients are treatment naïve for advanced ALK+ disease, like EXP1 in Study 1001.

Patients included in the CROWN study have had several available drugs post progression as the study was initiated at a later timepoint than ALEX, and in the meantime several treatments have been approved for subsequent treatment. A proportion of the progressed patients received several lines of subsequent treatment which potentially can influence overall survival, especially in the comparator arm.

Since the last comparison between lorlatinib and alectinib was made, the median follow-up has changed for CROWN, which is important when evaluating the OS and PFS endpoints. Median follow-up for CROWN outcomes is now 60.2 months for lorlatinib and 55.1 months for crizotinib (17), opposite to the ALEX trial with a latest follow-up for alectinib of 48.2 months and 23.3 months for crizotinib (16).

Study 1001 was also included to provide the longest possible follow-up on lorlatinib OS. The study 1001 is a phase II study, and thus less comparable to ALEX, but cohort EXP1 patients add to the number of treatment naïve lorlatinib treated 1L patients.

6.1.2.1 Comparability of patients across studies

A summary of the baseline characteristics of patients in the CROWN and ALEX trials are shown in Table 10. The baseline patient demographics were well-balanced between treatment arms in both studies with comparable median age, number of males and race. There were numerically slightly fewer female patients in the lorlatinib arm compared with the crizotinib arm in CROWN (32). Patient population in EXP1 from Study 1001 is included in Table 10 and are comparable with CROWN population.

There is a difference in the patient population between the two phase III studies in terms of the proportion of patients who had brain metastases at baseline (26% in CROWN, 38% in ALEX). Both alectinib and lorlatinib are expected to have a significant effect in the central nervous system (CNS), while the comparator in both studies, crizotinib, does not cross the blood-brain barrier to any significant extent and therefore does not have much activity in the CNS. Therefore, a relative efficacy difference between crizotinib and an experimental drug can be expected to be greater in a population that has more patients with brain metastases at baseline. The consequence of this may be an overestimation of the effect of alectinib on brain metastases by an indirect comparison with lorlatinib.

In CROWN, [redacted] patients treated with lorlatinib had progressed and were on subsequent treatment. [redacted] of these patients were treated with a subsequent ALK TKI therapy,

[redacted] of the lorlatinib treated patients in second-line. For crizotinib [redacted] received second-line treatment, [redacted] of these received ALK TKI [redacted].

In ALEX a greater use of pemetrexed-based chemotherapy as subsequent therapy was observed in patients who died in the alectinib arm versus the crizotinib arm (37.3% versus 12.9%, respectively) was observed. Subsequent ALK TKIs were given to the same extent in both treatment arms, 35.3% and 37.1%, respectively. The proportion of patients who received more than one subsequent line of therapy were also similar in the two arms, (15.7% in the alectinib arm and 11.1% in the crizotinib arm) (16).

The baseline characteristics from cohort EXP1 study 1001 is included in Table 10. However, as study 1001 consists of different cohorts, the baseline characteristics for each cohort in Study 1001 are also presented in Table 11.

Table 10 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (5, 32, 47)

	CROWN		Study 1001 EXP1	ALEX	
	Lorlatinib (n=149)	**Crizotinib (n=147)**	**Lorlatinib (n=30)**	**Alectinib (n=152)**	**Crizotinib (n=151)**
Age, years mean+/- SD	59.1 ± 13.1	55.6 ±13.5	57.4 ± 12.1	56.3 ± 12.0	53.8 ± 13.5
Male, n (%)	65 (44)	56 (38)	17 (57)	68 (45)	64 (42)
Ethnic group, n (%)					
Non-Asian	72 (48)	73 (50)	12 (40)	83 (55)	82 (54)
Asian	65 (44)	65 (44)	17 (57)	69 (45)	69 (46)
Missing	12 (8)	9 (6)	1 (3)		
ECOG PS, n (%)					
0/1	146 (98)	138 (94)	29 (97)	142 (93)	141 (93)
2	3 (2)	9(6)	1 (3)	10 (7)	10 (7)
Smoking status, n (%)					
Never	81 (54)	94 (64)	NA	92 (61)	98 (65)
Previous	55 (37)	43 (29)	NA	48 (32)	48 (32)
Current	13 (9)	9(6)	NA	12 (8)	5 (3)
Stage of disease, n (%)					
IIIA	1 (1)	0	NA		
IIIB	12 (8)	8 (5)	NA	4 (3)	6(4)

IV	135 (91)	139 (95)	NA	148 (97)	145 (96)
Other*	1 (1)	0	NA		
Histological type, n (%)					
Adenocarcinoma	140 (94)	140 (95)	NA	137 (90)	142 (94)
Other**	9 (6)	7 (5)	NA	15 (10)	9 (6)
Brain metastases at baseline, n (%)***	38 (26)	40 (27)	8 (27)	64 (42)	58 (38)
Previous brain radiotherapy, n (%)	9 (6)	10 (7)	2 (7)	26 (17)	21 (14)

* AJCC-version 8.0 instead of AJCC-version 7.0 for all other patients
**Include adenosquamous carcinoma, large-cell carcinoma, squamous carcinoma and other
***assessed by IRC/BIRC

Table 11 Baseline characteristic: Study 1001 (5)

	B7461001				
	Lorlatinib EXP1 (n=30)	**Lorlatinib EXP2-3A (n= 59)**	**Lorlatinib EXP3B (n=28)**	**Lorlatinib EXP4-5 (n=111)**	**Pooled safety, EXP1-6 (n=275)**
Age, years mean+/- SD/range	57.4 ± 12.1 (27-75)	54.9 ± 12.5 (30-85)	55.0 ± 11.6 (33-77)	51.9 ± 11.5 (29-83)	53.6 ±12.1 (19-85)
Male, n (%)	17 (57)	20 (34)	12 (43)	49 (44)	118 (43)
Ethnic group, n (%)					
Non Asian	12 (40)	33 (56)	9 (33)	64 (58)	147 (53)
Asian	17 (57)	17 (29)	16 (57)	37 (33)	103 (37)
Missing	1 (3)	9 (15)	3 (11)	10 (9)	25 (9)
ECOG PS, n (%)					
0/1	29 (97)	58 (98)	28 (100)	105 (95)	265 (96)
2	1 (3)	1 (2)	0	6 (5)	10 (4)
Smoking status, n (%)	NA	NA	NA	NA	NA
Never	NA	NA	NA	NA	NA
Previous	NA	NA	NA	NA	NA
Current	NA	NA	NA	NA	NA
Stage of disease, n (%)	NA	NA	NA	NA	NA

IIIA	NA	NA	NA	NA	NA
IIIB	NA	NA	NA	NA	NA
IV	NA	NA	NA	NA	NA
Other	NA	NA	NA	NA	NA
Histological type, n (%)	NA	NA	NA	NA	NA
Adeno-carcinoma	NA	NA	NA	NA	NA
Other	NA	NA	NA	NA	NA
Brain metastases at baseline, n (%) *	8 (27)	37 (63)	13 (46)	83 (75)	166 (60)
Previous brain radiotherapy, n (%)	2 (7)	19 (32)	8 (29)	59 (53)	103 (37)
Previous chemotherapy in la/mNSCLC, n (%)	1 (3)	35 (59)	13 (47)	85 (77)	232 (84)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

A real-world study of ALK+ NSCLC patients diagnosed between 2011-2018 by Hansen et al. (2), regardless of stage, gives some characteristics of the Danish population, Table 12. The Danish patient population appear to be some years older than the populations in the included clinical trials. The proportion of patients who had brain metastases at baseline in the clinical trials (26% in CROWN and 40% in ALEX) (32, 47) also differs when compared to the Danish population, in which 10% has a confirmed brain metastases at diagnosis. The number is likely underestimated in the Danish RW-study as scans for brain metastases was not routinely done during the studied period from 2011-2018. The rest of the characteristics are comparable between the Danish Real-World population and the patients included in the chosen studies. (2, 32, 47)

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population N= 209(2)	Value used in health economic model (32)
Age, mean/SD, years	61.6 ± 14.2	57.45
Gender, male, n (%)	91 (43.5)	41%
ECOG PS, n (%)		
0/1	165 (79)	NA

2	26 (13)	NA
Smoking status, n (%)		
Never	104 (50)	NA
Previous	79 (38)	NA
Current	23 (11)	NA
Stage of disease, n (%)		
IIIA	20 (10)	NA
IIIB	15 (7)	NA
IV	131 (63)	NA
Other	43 (20)	NA
Histological type, n (%)		
Adenocarcinoma	204 (97.5)	NA
Other	5 (2.5)	NA
Brain metastases at baseline, n (%)	21 (10)	NA

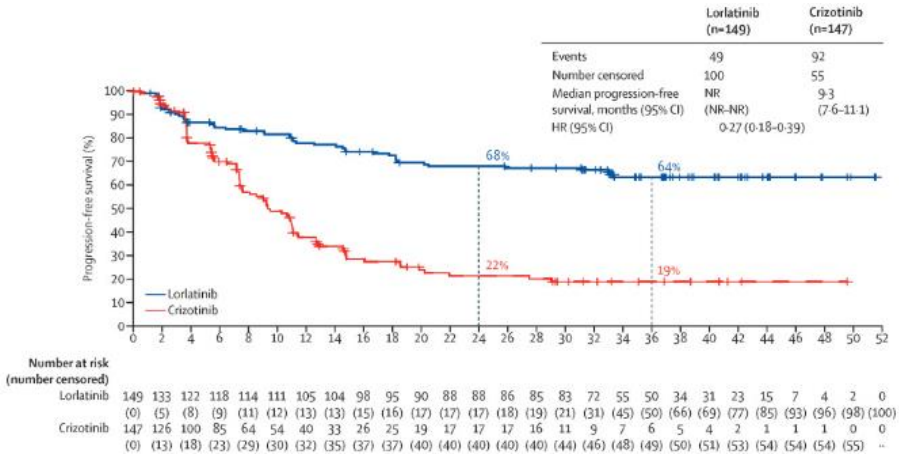
Abbreviations: NA not applicable in the health economic model

6.1.4 Efficacy – results per CROWN

Three different data cut-offs are available for the pivotal Phase III CROWN trial, corresponding to up to 5 years of follow-up for selected outcomes. The planned interim analysis at 18-month data cut off (March 2020) is used for OS, as OS has not yet reached maturity at the 5-year data cut-off. Data from the unplanned 3-year analysis (data cut-off September 2021), include primary outcomes of PFS- BICR (RECIST v1.1) (33). This submission focuses on the latest, 5-year post hoc analysis (data cut-off October 2023) for median PFS-INV (follow-up 60.2 months (95% CI: 57.4 to 61.6) for lorlatinib and 55.1 months (95% CI: 36.8 to 62.5) for crizotinib) (17). Updated results from 5-years analysis are not part of EPAR for lorlatinib.

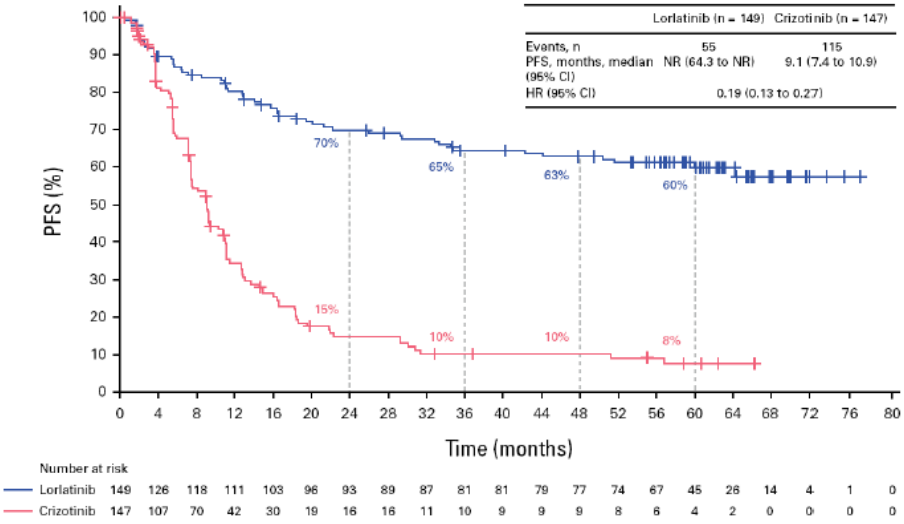
Progression free survival: At the interim analysis the primary endpoint for PFS -BICR using RECIST v1.1 was met, hazard ratio HR; 0.28 (95% CI, 0.19-0.41) (32). PFS-BIRC was reported up to the unplanned 3-year data analysis. Median PFS-BICR was not reached (NR, (95% CI: NR, NR)) in the lorlatinib arm and was 9.3 months (95% CI: 7.6, 11.1) in the crizotinib arm. This resulted in a substantial 73% reduction in risk of progression or death between the lorlatinib arm and crizotinib arm (hazard ratio [HR] 0.27; 95% CI: 0.18, 0.39) (33), Kaplan-Meier curve for PFS-BIRC in CROWN, Figure 6.

Figure 6 Progression free survival by BIRC, ITT population, data cut off September 2021



At the latest 5-year data cut-off, the median follow-up for PFS-INV (RECIST v1.1) was 60.2 months (95% CI: 57.4 to 61.6) for lorlatinib and 55.1 months (95% CI: 36.8 to 62.5) for crizotinib (17). Median PFS was not reached for lorlatinib (95% CI: 64.3, NR) and was 9.1 months (95% CI: 7.4, 10.9) for crizotinib. There was an 81% reduction in the risk of progression or death in favour of lorlatinib (HR: 0.19; (95% CI: 0.13, 0.27)) (17). The 4- and 5-year PFS rate was 63% and 60% (95% CI: 51 to 68) with lorlatinib, respectively, and 10% and 8% (95% CI: 3 to 14) with crizotinib (17). Kaplan-Meier curves for PFS-INV in CROWN, Figure 7, (17). Only 6 patients in the lorlatinib arm progressed in the 2 years period between 3- and 5- years analysis versus 23 patients in crizotinib arm (17).

Figure 7 Kaplan-Meier curve for PFS by INV in CROWN. Data cut-off October 30, 2023. (17)

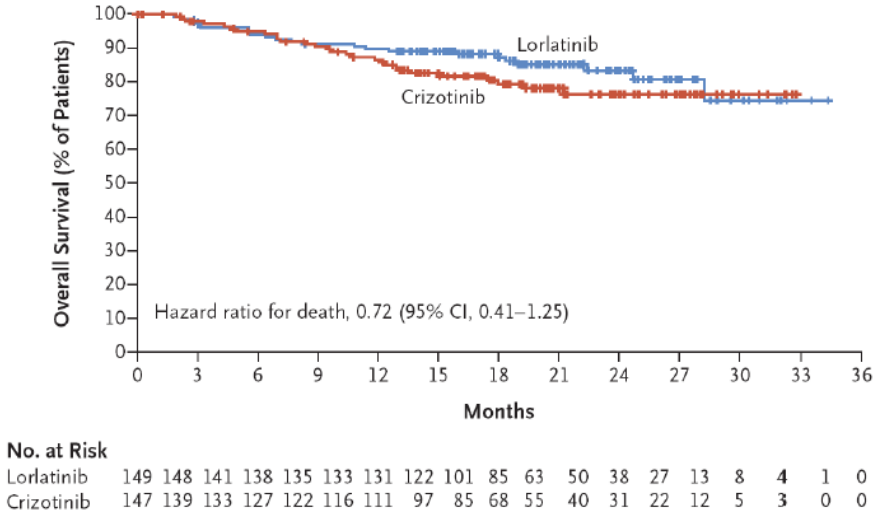


Overall survival: As per protocol, a total of 198 deaths are required to achieve 70% power using a one-sided stratified log-rank test, which has not yet been met in the CROWN trial. As such, OS data were not analysed as of the October 2023 nor September 2021 data cut-off, and therefore, only OS data from the March 2020 data cut-off are presented here (32).

At the March 2020 data cut-off, the majority of patients in both treatment arms were still alive, and only 51 (26%) of the total 198 deaths required for the final OS analysis had occurred. The efficacy boundary for OS was not crossed. The HR for OS showed a 28%

reduction in the risk of death in the lorlatinib arm compared with the crizotinib arm (HR: 0.72 (95% CI: 0.41, 1.25)) (32). Deaths had occurred in 15.4% and 19.0% of patients in the lorlatinib and crizotinib arms, respectively (32). The median OS was not evaluable in either treatment arm. Despite the immaturity of OS data, the HR is in favour of lorlatinib. In the Kaplan–Meier curve shown in Figure 6, a separation between the curves can be seen from 10 months, indicating an improvement in OS in the lorlatinib arm, and is sustained until substantial censoring occurs at later time points due to the immaturity of the data (17).

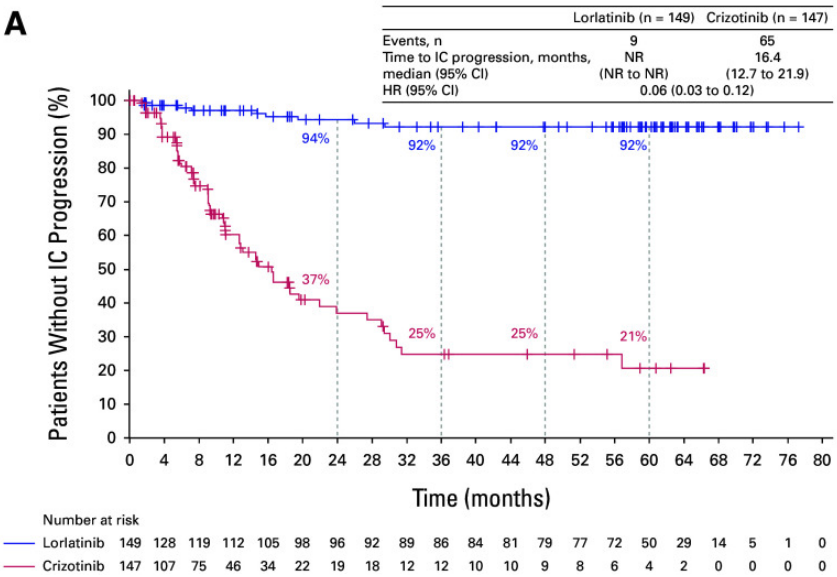
Figure 6: Kaplan-Meier curve for OS in CROWN, ITT population. Data cut off March 2020. (32)



Due to the immaturity of the trial data, no robust conclusions can yet be drawn from the OS data. Further OS analyses are event-driven, planned when 70% and 100% of the 198 OS events needed for the final OS analysis have occurred, and therefore their date is unknown.

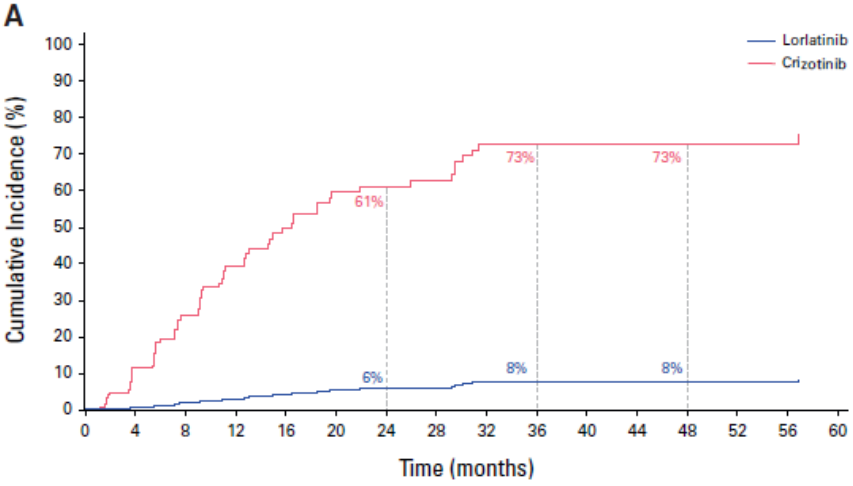
Intracranial efficacy: Intracranial time to progression (IC-TTP) was analysed by BIRC at 3-years analysis and by INV at the October 2023 data cut-off. Results from the latest analysis showed substantially longer IC-TTP with lorlatinib than with crizotinib, with an HR of 0.06 (95% CI: 0.03, 0.12) showing a 94% reduction in the risk of intracranial progression in the lorlatinib arm compared with the crizotinib arm censored for patients who receive systemic therapy that is not lorlatinib and death. (Figure 8). Median IC-TTP was not reached (NR) (95% CI: NR, NR) with lorlatinib and 16.4 months (95% CI: 12.7, 21.9) with crizotinib (17). Furthermore, the probability of being free of intracranial progression at 5-year was 92% (95% CI: 85, 96) with lorlatinib and 21% (95% CI: 10, 33) with crizotinib. No new patients have had a CNS event since last data cut-off at 3 years in lorlatinib arm.

Figure 8 Kaplan-Meier plot of time to intracranial progression by INV (modified RECIST, v1.1) in ITT population, data cut-off October 2023 (17), censored for patients who receive systemic therapy that is not lorlatinib and death.



The cumulative incidence of progression of brain metastases as the first event, with adjustment for the competing risks of progression other than brain metastases and death, was lower in the lorlatinib group than in the crizotinib group. (17). At 48 month the cumulative incidence of CNS progression as first event was 8 % with lorlatinib, and 73 % with crizotinib (17).

Figure 9 Cumulative incidence of progression of brain metastases as the first event adjusted for competing risks of progression



Responses: Objective response rate (ORR, RECIST v1.1; by INV): At the October 2023 data cut-off, the proportion of patients with a confirmed objective response by INV was 81% (95% CI: 73, 87) with lorlatinib and 63% (95% CI: 54, 70) with crizotinib (17). Duration of response (DOR, RECIST v1.1, by INV): At the October 2023 data cut-off, the median DOR was not reached (NR) (95% CI: NR, NR) with lorlatinib and 9.2 months (95% CI: 7.5, 11.1) with crizotinib (17). In the lorlatinib arm, 74% of patients had a DOR ≥ 2 years compared with 15% of patients in the crizotinib arm (17).

IC-OR and IC-DOR based on INV (modified RECIST v1.1) were reported at the October 2023 data cut-off in patients with measurable and/or non-measurable baseline brain metastases (n = 35 patients in the lorlatinib arm and n = 38 in the crizotinib arm). IC-OR was greater with lorlatinib than with crizotinib (60% versus 11%, respectively (17). Intracranial complete response was reported in 49% and 5% of patients, respectively. Median duration of intracranial response was NR (95% CI: NR, NR) and 12.8 months (95% CI: 7.5, NR), respectively.

PFS, OS, IC-TTP and DOR times associated with each treatment arm were summarised using the Kaplan–Meier method. 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.

Subgroup analysis: The PFS benefit in the lorlatinib arm compared with the crizotinib arm was consistently observed across all pre-specified subgroups based on baseline patient demographics and disease characteristics, supporting the robustness of PFS findings within the study population (17) (33).

- Among patients with baseline brain metastases (measurable and/or non-measurable; n = 35 in the lorlatinib group and n = 38 in the crizotinib group), the HR for PFS with lorlatinib versus crizotinib was 0.08 (95% CI: 0.04, 0.19) (17). Median PFS was NR (95% CI: 32.9, NR) with lorlatinib and 6.0 months (95% CI: 3.7, 7.6) with crizotinib (17).
- Among patients without baseline brain metastases (n = 114 in the lorlatinib group; n = 109 in the crizotinib group), the HR for PFS with lorlatinib versus crizotinib was 0.24 (95% CI: 0.16, 0.36) (17). Median PFS was NR (95% CI, 64.3, NR) with lorlatinib and 10.8 months (95% CI: 9.0, 12.8) with crizotinib. (17)
- Time to intracranial progression (IC-TTP) based on INV (modified RECIST v1.1) was analysed in the updated analysis, and among patients with baseline brain metastases, there were only five events of intracranial progression in the lorlatinib arm, all occurring in the first 3 years of treatment. The HR for IC-TTP favoured lorlatinib over crizotinib at 0.03 (95% CI: 0.01, 0.13) (10). Median IC-TTP was NR (95% CI: NR, NR) in the lorlatinib arm and 7.2 months (95% CI: 3.7, 11.0) in the crizotinib arm.
- Among patients without baseline brain metastases, only four patients developed intracranial lesions in the lorlatinib arm, all of them occurring in the first 16 months of treatment. The HR for IC-TTP was 0.05 (95% CI, 0.02 to 0.13), favouring lorlatinib over crizotinib (17). Median IC-TTP was NR (95% CI: NR, NR) in the lorlatinib arm and 23.9 months (95% CI: 16.4, 30.8) in the crizotinib arm. The probability of preventing development of brain metastases at 5-years was 96% (95% CI: 89, 98) with lorlatinib versus 27% (95% CI: 14, 43) with crizotinib. (17).

Biomarker analysis: Baseline plasma samples were available from 134 lorlatinib-treated patients and 129 crizotinib treated patients. In a subgroup of patients with EML4::ALK variant 3a/b treated with lorlatinib (n=18), median PFS was 60.0 months (95% CI, 33.3 to NR), and in the crizotinib subgroup (n=23) the median PFS was 5.6 months (95% CI, 5.3 to 7.6) (17). In the TP53 mutation-positive subgroup treated with lorlatinib (n = 41), the

median PFS was 51.6 months (95% CI: 16.4, NR) and in the TP53 mutation negative subgroup treated with lorlatinib (n=56), the median PFS was NR (95% CI, 60.0, NR). For TP53 mutation-positive and -negative patients treated with crizotinib (n =100) the median PFS was 5.7 months (95% CI: 5.4, 7.2) and 9.1 months (95% CI: 7.6, 11.1), respectively, supporting lorlatinib's efficacy in ALK-positive patients with poor prognostic disease (17).

End of treatment ctDNA samples were available for 31 patients in lorlatinib group and no new single ALK or ALK compound mutations were detected. Paired baseline and end-of treatment ctDNA samples indicated that bypass mechanism aberrations were main resistance mechanism (17).

Health-related Quality of Life: In CROWN EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-LC13 were collected. HRQoL was collected until the September 2021 data cut-off as per CROWN protocol, HRQL data was not collected after the 3-year follow-up. In Global quality of life from QLQ-C30, improvements were seen as early as cycle 2 and were maintained over time in both treatment groups. However, in a post-hoc analysis, median time to deterioration in global quality of life from EORTC QLQ-C30 was 24.7 months (95% CI 6.5–not reached) for lorlatinib and 12.0 months (6.5–not reached) for crizotinib (33). Patients in the lorlatinib group had greater overall improvement from baseline in global quality of life and emotional functioning and showed a non-significant improvement in physical and role functioning, except cognitive functioning, compared with those who received crizotinib. Symptom scales for fatigue, nausea and vomiting, insomnia, appetite loss, constipation, diarrhoea, and coughing favoured lorlatinib, whereas scales for pain, dyspnoea, haemoptysis, sore mouth, peripheral neuropathy, and pain in other parts did not favour lorlatinib over crizotinib (33). More information and figures related to HRQoL in section 10 and appendix F.

6.1.5 Efficacy – results per Study 1001

Progression-free survival: The median time to disease progression was 17.7 months (95% CI, 12.5-40.5) in EXP1 (treatment naïve), 12.5 months (95% CI: 8.2–22.2) in EXP2-3A, 5.5 months (95% CI: 3.2–9.0) in EXP3B, 7.1 months (95% CI: 5.5–11.0) in EXP4-5, and 6.9 months (95% CI: 5.5–8.4) in EXP3B-5. At the data cutoff for this analysis (July 27, 2023), median duration of treatment with lorlatinib was 64.6 months (range, 1.68-88.21), 47.6 months (range: 0.36–89.19) in EXP2-3A, 8.7 months (range: 0.26–83.02) in EXP3B, 10.1 months (range: 0.23–9.65) in EXP4-5, and 10.1 months (range: 0.23–89.65) in EXP3B-5.(40) The median relative dose intensity was 98% (range, 23%-110%) in all treated patients, EXP1-6.(40)

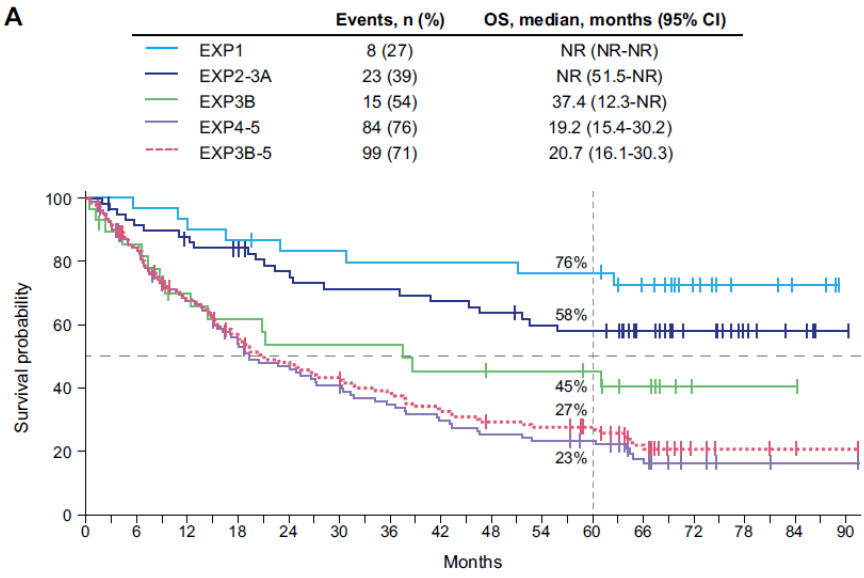
Overall survival: The median follow-up for OS was 72.7 months (95% CI, 69.3-76.3) in EXP1 cohort, 69.3 months (95% CI: 65.1–75.3) in EXP2-3A, 66.7 months (95% CI: 58.6–69.6) in EXP3B, 66.7 months (95% CI: 63.0–68.8) in EXP4-5, and finally 66.7 months (95% CI: 63.0–67.7) in EXP3B-5 cohort. The median OS was not reached (NR; 95% CI, NR-NR) in EXP1 cohort, NR (95% CI: 51.5–NR) in EXP2-3A, 37.4 months (95% CI: 12.3–NR) in EXP3B, 19.2 months (95% CI: 15.4–30.2) in EXP4-5, and 20.7 months (95% CI: 16.1–30.3) in EXP3B-5 cohort.

Five-year OS probabilities were 76%, 58%, 45%, 23%, and 27%, respectively. See Figure 10

In patients with baseline CNS metastases (measurable and non-measurable), the median OS was NR (95% CI, 51.0-NR) in EXP1 (n = 8), NR (95% CI: 51.5–NR) in EXP2-3A (n = 37), NR (95% CI: 14.4–NR) in EXP3B (n = 13), 18.6 months (95% CI: 15.0–30.2) in EXP4-5 (n= 82), and 19.2 months (95% CI: 15.1–37.4) in EXP3B-5 (n = 95). (40)

In patients without baseline CNS metastases, the median OS was NR (95% CI, NR-NR) in EXP1 (n = 22), NR (95% CI: 24.4–NR) in EXP2-3A (n = 22), 20.7 months (95% CI: 6.5–NR) in EXP3B (n = 15), 26.5 months (95% CI: 9.1–36.4) in EXP4-5 (n = 29), and 25.3 months (95% CI: 9.1–35.5) in EXP3B-5 (n = 44). (40)

Figure 10 Kaplan-Meier curves of OS in ALK-positive patients in EXP1, EXP2-3A, EXP3B, EXP4-5, and EXP3B-5 after at least 5 years of follow-up. OS in (A) ITT population. (40)



No. at risk

EXP1	30	30	29	29	27	27	26	25	24	24	24	23	23	23	23	23	23	22	22	22	19	18	16	11	8	6	6	4	4	0
EXP2-3A	59	56	53	52	50	48	46	42	41	39	38	38	37	36	36	34	34	33	31	30	30	28	22	19	16	13	8	6	5	1	1
EXP3B	28	24	22	19	17	15	15	14	13	13	13	13	11	11	11	10	10	10	10	10	9	6	6	3	1	1	1	1	0		
EXP4-5	111	99	89	76	70	63	54	47	45	42	39	35	33	30	28	26	24	24	22	22	20	18	10	5	4	2	2	1	1	1	1
EXP3B-5	139	123	111	95	87	78	69	61	58	55	52	48	46	41	39	37	34	34	32	32	29	24	16	8	5	3	3	2	1	1	1

Responses: Of the 30 patients in EXP1, 27 (90.0%; 95% CI 73.5–97.9) had an objective response, with one patient achieving a complete response and 26 achieving a partial response. Of these 27 confirmed responses, 23 (85%) were ongoing and the median duration of response was not reached (95% CI: 10·0 months–NR). Median time to first tumour response was 1.4 months (IQR 1.3–2.7). The estimated median duration of follow-up for response was 6.9 months (IQR 5.6–12.5). Three patients in EXP1 had measurable baseline CNS lesions per ICR, and objective intracranial responses (both partial responses) were observed in two (66.7%; 95% CI: 9.4–99.2). Median intracranial duration of response was not reached (95% CI: NR–NR). (5)

Of the 59 patients in EXP2–3A cohort, 41 (69.5%; 95% CI: 56.1–80.8) achieved an objective response, with one patient achieving a complete response and 40 patients achieving a partial response. Median duration of response had not been reached (95% CI: 11.1–NR). The median duration of follow-up for response was 6.9 months (IQR 4.2–7.0). 37 patients had baseline CNS lesions per ICR, with a median of five CNS lesions (both target and non-target) per patient (IQR 3–7). Of 23 patients with measurable baseline CNS lesions per ICR, intracranial responses were observed in 20 (87.0%; 95% CI 66.4–97.2). Median intracranial duration of response was not reached (95% CI: 8.4–NR) at the time of analysis. The median time to first tumour response was 1.4 months (IQR 1.3–2.6) and the median time to first intracranial response was 1·4 months (1.3–1.4). (5)

Of the 28 patients in EXP3B, nine patients (32.1%; 95% CI: 15.9–52.4) had an objective response, including one complete response and eight partial responses. The median duration of follow-up for response was 7.0 months (IQR 5.6–8.3). 13 patients in EXP3B had baseline CNS lesions per ICR, with a median of six CNS lesions per patient (IQR 3–6). Of nine patients with measurable baseline CNS lesions per ICR, intracranial responses were observed in five (55.6%; 95% CI: 21.2–86.3). Median intracranial duration of response was not reached (95% CI: 4·1–NR) at the time of analysis. The median time to first tumour response was 1.4 months (IQR 1.4–2.7) and the median time to first intracranial response was 1.4 months (IQR 1.4–2.6). (5)

Of the 111 patients in EXP4-5 cohort, responses were observed in 43 (38.7%; 95% CI 29.6–48.5), with two complete responses and 41 partial responses. The median duration of follow-up for response was 7.2 months (IQR 5.6–9.8). 83 patients in this cohort had baseline CNS lesions per ICR, with a median of four CNS lesions per patient (IQR 2–7). Of the 49 patients with measurable baseline CNS lesions per ICR, 26 (53.1%; 95% CI: 38.3–67.5) had objective intracranial response, with ten complete responses and 16 partial responses. The median intracranial duration of response was 14.5 months (95% CI: 6.9–14.5). The median time to first tumour response was 1.4 months (IQR 1.4–2.9), the median time to first intracranial tumour response was 1.4 months (1.3–3.1), and the median progression-free survival was 6.9 months (95% CI: 5.4–9.5). (5)

Prior therapies: Of the 28 patients in EXP3B, 13 (46%) each received alectinib and ceritinib as the last ALK-TKI before lorlatinib, one (4%) received brigatinib, and one (4%) received another experimental ALK-TKI (entrectinib). Of the 111 patients in EXP4–5, 49 (44%) received alectinib as their last ALK-TKI before starting lorlatinib treatment, 34 (31%) received ceritinib, 18 (16%) received crizotinib, seven (6%) received brigatinib, and three (3%) received another ALK tyrosine kinase inhibitor. (40)

Subsequent therapies: At least 1 type of subsequent anticancer therapy was received by 9 (30%) patients in EXP1, 22 patients (37%) in EXP2-3A, 14 patients (50%) in EXP3B, 70 patients (63%) in EXP4-5, and 84 patients (60%) in EXP3B-5. At least one subsequent systemic anticancer therapy was received by eight patients (27%) in EXP1, 19 patients (32%) in EXP2-3A, 14 patients (50%) in EXP3B, 69 patients (62%) in EXP4-5, and 83 patients (60%) in EXP3B-5.

At least one subsequent anticancer radiotherapy was received by two patients (7%) in EXP1, seven patients (12%) in EXP2-3A, five patients (18%) in EXP3B, 19 patients (17%) in

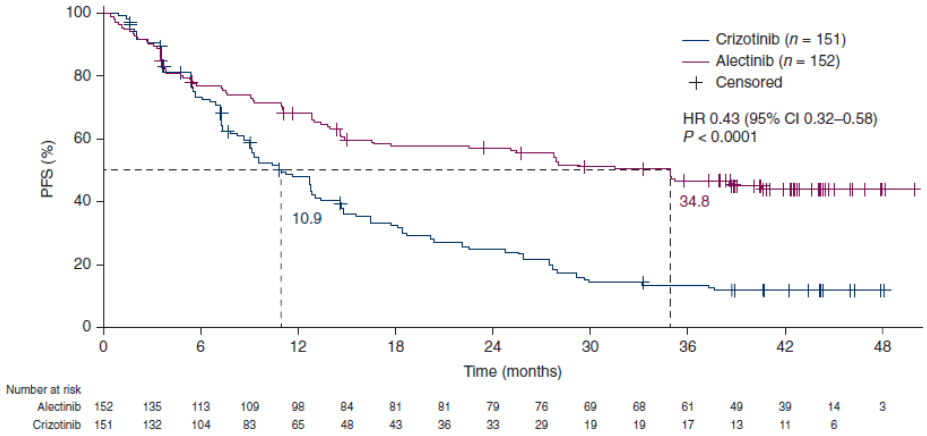
EXP4-5, and 24 patients (17%) in EXP3B-5. At least one subsequent anticancer surgery was received by two patients (7%) in EXP1, five patients (8%) in EXP2-3A, four patients (14%) in EXP3B, five patients (5%) in EXP4-5, and nine patients (6%) in EXP3B-5 cohort. The most common first subsequent systemic therapy was an ALK TKI in all cohorts. (40)

6.1.6 Efficacy – results per ALEX

The trial met its primary endpoint at the primary analysis, demonstrating a statistically significant PFS-INV. The most recent updated study data from the ALEX study is the final analysis with median follow-up of 48.2 months (16).

Progression-free survival: The final PFS-INV using RECIST v1.1 was reported after a median duration of follow-up of 37.8 (0.5-50.7) months for alectinib and 23.0 (0.3-49.8) months for crizotinib at cut-off date November 30, 2018. Median PFS-INV was 34.8 (95% CI: 17.7, NE) in the alectinib arm and was 10.9 months (95% CI: 9.1, 12.9) in the crizotinib arm. This resulted in a 57% reduction in risk of progression or death between the alectinib arm and crizotinib arm (hazard ratio [HR] 0.43; 95% CI: 0.32, 0.58) (16). For ITT population the 4 years PFS rate was 43.7% for alectinib and couldn't be estimated for crizotinib.

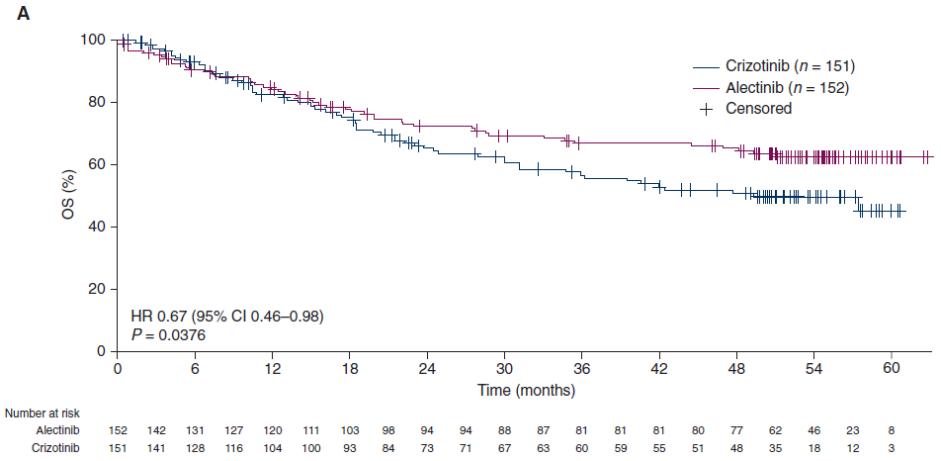
Figure 11 Kaplan-Meier plot of investigator-assessed progression-free survival (RECIST, v1.1) in ITT population, data cut-off November 30, 2018 (17)



Independent review committee–assessed PFS (PFS-IRC) done at primary analysis with median duration of follow-up of 17.6 (0.3-27.0) months for crizotinib and 18.6 (0.5-29.0) for alectinib group, was significantly longer with alectinib than with crizotinib. For alectinib median PFS was 25.7 months (95% CI, 19.9 to NE) vs. 10.4 months (95% CI, 7.7 to 14.6) for crizotinib. Hazard ratio for disease progression or death was 0.50 (95% CI, 0.36 to 0.70); P<0.001 (47).

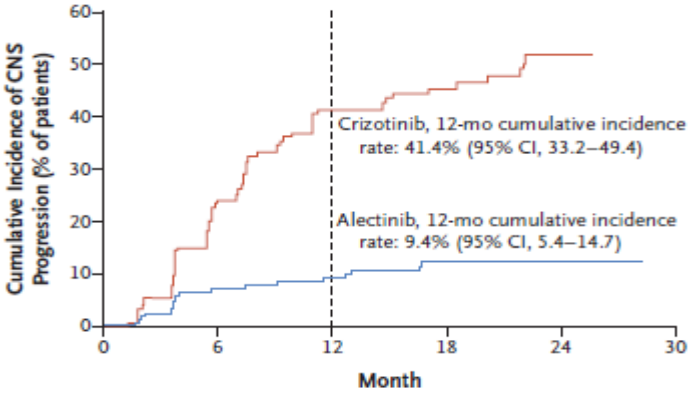
Overall survival: Updated OS results based on 29 November 2019 data cut-off provided a median duration of survival follow-up of 48.2 months (range 0.5–62.7) with alectinib and 23.3 months (range 0.3–60.6) with crizotinib. OS data remained immature with 37% of events recorded (stratified HR 0.67, 95% CI: 0.46–0.98). Median OS was NR with alectinib and was 57.4 months with crizotinib (95% CI: 34.6–NR) (8). The 5-year OS rate was 62.5% (95% CI: 54.3–70.8) with alectinib and 45.5% (95% CI: 33.6–57.4) with crizotinib (16).

Figure 12 Kaplan-Meier plot of investigator-assessed overall survival in ITT population, data cut-off November 29, 2019 (17)



Intracranial activity: The time to CNS progression was significantly longer in the alectinib-arm vs the crizotinib-arm in the ITT population (cause-specific hazard ratio, 0.16; 95% CI: 0.10 to 0.28; P<0.001); 18 patients (12%) in the alectinib group had an event of CNS progression, as compared with 68 patients (45%) in the crizotinib group (47). Cause-specific stratified HRs and 95% CI were estimated by Cox regression where patients with competing events were censored at the time of these events. P values are from two-sided stratified cause-specific log-rank tests. Time to CNS progression had a median duration of follow-up of 17.6 (0.3-27.0) months for crizotinib and 18.6 (0.5-29.0) months for alectinib. The cumulative incidence rate of CNS progression, with adjustment for the competing risks of non-CNS progression and death, was consistently lower over time with alectinib than with crizotinib, and the 12-month cumulative incidence rate of CNS progression was 9.4% (95% CI: 5.4- 14.7) versus 41.4% (95% CI: 33.2- 49.4) (47).

Figure 13 Cumulative incidence of CNS progression ALEX



Responses: Overall response (ORR) was reported with median durations of follow-up of 27.8 months (range 0.5–38.7) with alectinib and 22.8 months (range 0.3–36.7) with crizotinib, and was consistent with that reported in the primary analysis; 82.9% for alectinib arm (95% CI: 75.95–88.51) versus 75.5% for crizotinib arm (95% CI: 67.84–82.12) (36). The median DOR was 33.1 months (95% CI: 31.3–NE) with alectinib versus 11.1 months (95% CI: 7.5–13.0) with crizotinib (36).

CNS-OR, among patients with measurable CNS lesions at baseline, occurred in 17 of 21 patients in the alectinib group (81%; 95% CI: 58-95) and in 11 of 22 patients in the crizotinib group (50%; 95% CI: 2 -72) (47). DOR- IC was 17.3 months (95% CI: 14.8 -NE) for alectinib and 5.5 months (95% CI, 2.1 to 17.3) for crizotinib group. Among patients with measurable or non-measurable CNS lesions at baseline, a CNS response occurred in 38 of 64 patients in the alectinib group (CNS-RR, 59%; 95% CI: 46 -71) and in 15 of 58 patients in the crizotinib group (CNS-RR, 26%; 95% CI: 15- 39) (47).

Subgroups:

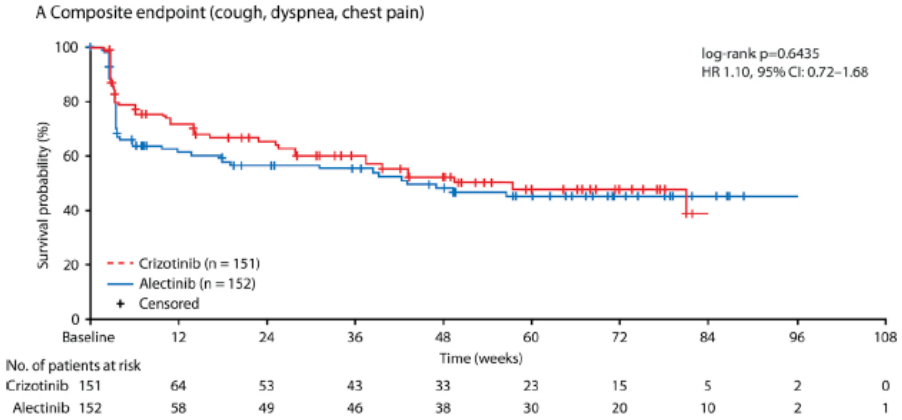
- The median PFS in patients with baseline CNS metastases, for alectinib versus for crizotinib were 27.7 months (95% CI: 9.2–NE) and 7.4 months (95% CI: 6.6–9.6) (HR = 0.35, 95% CI: 0.22–0.56), respectively (32).
- For patients without baseline CNS metastases, the median PFS were 34.8 months (95% CI: 22.4–NE) versus 14.7 months (95% CI: 10.8–20.3)(HR= 0.47, 95% CI: 0.32–0.71), respectively (36).

Biomarker: In an exploratory analysis of biomarker-evaluable subgroup, the PFS-INV for each of the EML4-ALK fusion variant populations was analysed and was longer for alectinib than for crizotinib based on both plasma and tissue samples. In the plasma biomarker subgroup, the median PFS in patients treated with alectinib versus with crizotinib were 34.8 months versus 7.4 for variant 1; 24.8 months versus 8.8 months for variant 2; and 17.7 months versus 9.1 months for variant 3a/b, respectively (27). The median DOR-INV was longer with alectinib than with crizotinib in all three EML4-ALK fusion variant populations using both plasma and tissue samples (36).

Health-related Quality of Life: In ALEX Patient-Reported outcomes (PRO) data were collected using EORTC QLQ-C30 and QLQ-LC13 questionnaires and pre-specified PRO endpoints were: mean change from baseline in symptoms, HRQoL, and functioning; and time to deterioration (TTD) in cough, dyspnea, chest pain, arm/shoulder pain, fatigue, and a composite of three symptoms (cough, dyspnea, chest pain). Time to deterioration (TTD) was defined as the time from randomization until confirmed clinically meaningful deterioration (i.e., a $\geq$10-point score change from baseline). Questionnaires were completed using a self-administered electronic device at the patient's home, at baseline, every 4 weeks until disease progression and during post-progression on treatment in case of isolated, asymptomatic CNS progression. Data were also collected at the post-treatment visit (4 weeks after permanent treatment discontinuation) and at 8-weekly survival follow-up visits for a period of 6 months. PRO completion population and rate were 197 patients (65%): alectinib n=100 (66%) and for crizotinib n=97 (64%). The reasons for noncompliance were not recorded. (37)

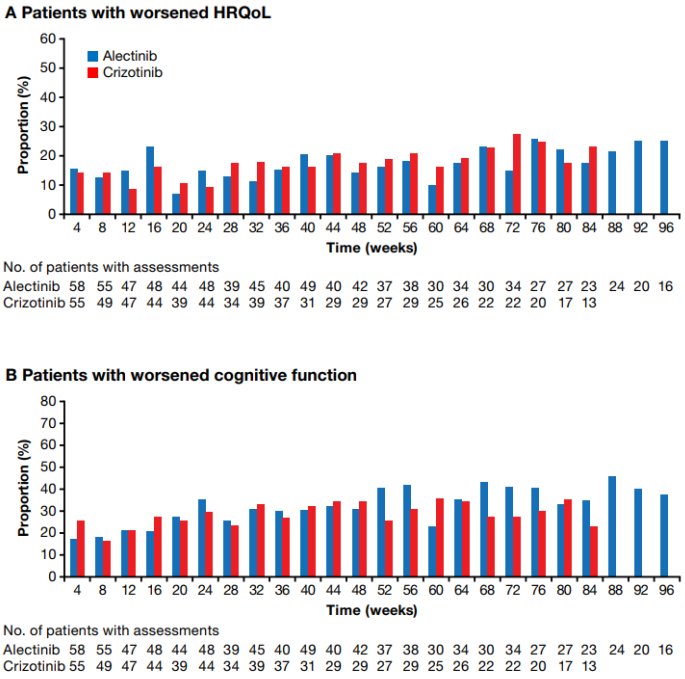
Patients in both treatment arms reported clinically meaningful improvement for multiple lung cancer symptom scores while on treatment. However, differences in lung cancer symptoms tended to favor alectinib from 11.1 months (45 weeks) onwards, around the time of median PFS with crizotinib (11.1 months). Time to Deterioration (TTD) in lung cancer symptoms was similar between treatment arms, despite longer duration of symptom improvement with alectinib; composite symptom endpoint (hazard ratio 1.10 [95% confidence interval: 0.72–1.68]), Figure 14. (37)

Figure 14 Composite symptom endpoint (37)



For global health status no differences between treatment arms were observed within the TTD analyses in the ITT population; median TTD in global health status (HR 0.72, 95% CI: 0.38–1.39) and cognitive function (HR 0.85, 95% CI: 0.55–1.33). (37)

Figure 15 Patients with worsened HRQoL and worsened cognitive function (37)



6.2 Efficacy of lorlatinib compared to brigatinib for ALK positive advanced NSCLC adult patients.

6.2.1 Relevant studies

In this submission lorlatinib is compared with brigatinib, as brigatinib is one of three equal treatment options for first-line treatment of ALK+ NSCLC. Due to price, brigatinib is

currently the recommended first choice in daily clinical practice for ALK+ advanced NSCLC patients by the DMC (7). ALTA-1 is the registration study for brigatinib (19). ALTA-1L investigated the efficacy and safety of brigatinib versus crizotinib, and is less comparable to CROWN than ALEX, in terms of design and patient population. CROWN and Study 1001 were described earlier in this application, so only ALTA-1L is described below.

ALTA-1L evaluated brigatinib versus crizotinib in adult patients with advanced ALK+ NSCLC who had not previously received an ALK- targeted therapy. ALTA-1L is a randomised (1:1), open-label, phase III multicentre trial including 275 adult patients. Eligibility criteria permitted enrolment of patients with a documented ALK rearrangement based on a local standard of care testing and an ECOG performance status of 0-2. Patients were allowed to have up to 1 prior regimen of chemotherapy in the locally advanced or metastatic setting. Neurologically stable patients with treated or untreated CNS metastases, including leptomeningeal metastases, were eligible. Patients with a history of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis were excluded (25, 38).

Patients were randomised to receive brigatinib 180 mg once daily with a 7-day lead-in at 90 mg once daily (N = 137) or crizotinib 250 mg orally twice daily (N = 138). Randomisation was stratified by brain metastases (present, absent) and prior chemotherapy use for locally advanced or metastatic disease (yes, no). Patients in the crizotinib arm who experienced disease progression were offered crossover to receive treatment with brigatinib. Among all 121 patients who were randomised to the crizotinib arm and discontinued study treatment by the time of the final analysis, 99 (82%) patients received subsequent treatment with ALK TKIs. Eighty (66%) patients who were randomised to the crizotinib arm received subsequent brigatinib treatment, including 65 (54%) patients who crossed over in the study (25).

The major outcome measure was PFS-BIRC according to (RECIST v1.1). Additional outcome measures evaluated by the BIRC include confirmed-ORR, DOR, time to response (TTR), disease control rate (DCR), IC-ORR, IC-PFS and IC-DOR. INV-assessed outcomes include PFS and OS (25). The primary analysis was performed at a median follow-up duration of 11 months in the brigatinib arm (38). A protocol-specified second interim analysis with cut-off date of 28 June 2019 was performed at a median follow-up duration of 24.9 months in the brigatinib arm (39). The protocol-specified final analysis, with last patient last contact date of 29 January 2021, was performed at a median follow-up duration of 40.4 months in the brigatinib arm (19).

Table 13 Overview of study design for studies included in the comparison.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
CROWN, NCT03052608, (17)	Listed in Table 9					Listed in Table 9
B7461001, NCT01970865, (5)	Listed in Table 9					Listed in Table 9
ALTA-1L, NCT02737501, (38)	Open-label, multi-national, randomized 2 arm phase III trial comparing brigatinib with crizotinib.	From April 2016 to August 2017, 275 patients were randomized. Study is finalized with study end January 2021.	ALK positive advanced NSCLC, ALK-inhibitor naïve adult patients	Brigatinib 180 mg once daily, after a 7-day lead in period at 90 mg once daily.	Crizotinib capsules 250 mg twice daily. Cross-over to brigatinib allowed after progresssion by BIRC	Primary outcome: PFS based on BIRC assessment (RECIST v1.1): Study end analysis: median follow-up 40.4 months for brigatinib. Secondary outcomes: OS: Study end analysis: median follow-up 40.4 months for brigatinib and 15.2 months for crizotinib. PFS by INV assessment (RECIST v1.1): Study end analysis: median follow-up 40.4 months for brigatinib and 15.2 months for crizotinib. ORR and DOR assessed by BIRC (RECIST v1.1): Study end analysis: median follow-up 40.4 months for brigatinib. IC-ORR based on BIRC (RECIST v1.1): Study end analysis: median follow-up 40.4 months for brigatinib and 15.2 months for crizotinib. IC-PFS assessed by BIRC (RECIST v1.1): Study end analysis: median follow-up 40.4 months for brigatinib and 15.2 months for crizotinib. Adverse events: 4 years follow-up. For each treatment arm, the incidence rates of treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), and serious treatment-emergent adverse events (SAEs) will be described by MedDRA System Organ Class (SOC) and Preferred Term. PRO: Assessed by EORTC QLQ-C30 (v3.0) and QLQ-LC13 (v3.0): Study end analysis: median follow-up 40.4 months for brigatinib.

6.2.2 Comparability of studies

There are no head-to-head data between lorlatinib and brigatinib, but both CROWN and ALTA-1L studies have crizotinib as a common comparator and an indirect comparison is therefore possible, even though the study designs are not the same and the NMA results should be interpreted with caution. Both studies randomized experimental drug versus crizotinib, but the patients in the ALTA-1L study were allowed to have received one previous systemic anticancer treatment for their advanced disease. That is not in accordance with Danish clinical practice, where ALK+ NSCLC patients in 1st line will receive ALK-TKI.

Patients were stratified for presence of brain metastases in both trials, and in CROWN patients were also stratified by ethnic group. For ALTA-1L patients were also stratified for completion of a full cycle of chemotherapy or not. PFS-BIRC was primary endpoint in ALTA-1L, but assessment of progression included also local radiotherapy for CNS lesions together with progression or death. IC-PFS was per protocol analyzed in patients with and without baseline brain metastases.

Cross-over was not allowed in CROWN study but allowed in ALTA-1L for the crizotinib group after progression assessed by BIRC. At final analysis, 80 patients (66%) in crizotinib arm had crossed over to brigatinib and 28 patients (23%) to alectinib. (19).

Subsequent therapy by treating physicians choice, was recorded in CROWN (26). Of [redacted] patients treated with lorlatinib and progressed and received subsequent treatment, [redacted] were treated with a subsequent ALK TKI therapy, [redacted]. In ALTA-1L a greater proportion of patients in the crizotinib arm received subsequent anticancer treatment after discontinuation compared with the brigatinib arm. Among 121 patients who discontinued crizotinib before study end, 103 (85%) received subsequent anticancer treatment with 99 (82%) receiving subsequent ALK TKI treatment, most often brigatinib (66%) and alectinib (23%). Among 78 patients who discontinued brigatinib, 46 (59%) received subsequent systemic anticancer treatment with 42 (54%) receiving a subsequent ALK TKI, most often lorlatinib (28%) and alectinib (21%) (19). Increased availability of targeting treatments can potentially increase the patients' overall survival outcomes, especially in the comparator arm, and minimize the OS-difference between arms.

Study 1001 was also included to provide the longest possible follow-up on lorlatinib OS. Study 1001 was a phase II study, and thus less comparable to ALTA-1L than CROWN, but patient population in EXP1 are treatment naïve 1L NSCLC lorlatinib treated patients with long follow up.

6.2.2.1 Comparability of patients across studies

The patient population in the CROWN study is not comparable to the ALTA-1L population, as ALTA-1L allowed patients with one previous systematic treatment to be included and 26% of brigatinib treated patients had received prior treatment. In comparison, CROWN only included treatment naïve patients. More patients in ALTA-1L

were of non-Asian ethnicity and more had previously received brain radiotherapy than patients in CROWN. There is a no difference in the patient population of the two phase III studies in terms of the proportion of patients who had brain metastases at baseline (26% in CROWN, 29% in ALTA-1L), Table 14. (32, 38)

The study 1001 EXP1 baseline characteristics was also included in Table 14. However, as Study 1001 consists of different cohorts, the baseline characteristics for each cohort are also presented in Table 11 in section 6.1.2.1.

Table 14 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (5, 32, 38)

	CROWN		Study 1001 EXP1	ALTA-1L	
	Lorlatinib (n=149)	**Crizotinib (n=147)**	**Lorlatinib (n=30)**	**Brigatinib (n=137)**	**Crizotinib (n=138)**
Age, years mean+/- SD/range	59.1 ± 13.1	55.6 ±13.5	57.4 ± 12.1	58 (27-86)	60 (29-89)
Male, n (%)	65 (44)	56 (38)	17 (57)	68 (50)	57 (41)
Ethnic group, n (%)					
Non-Asian	72 (48)	73 (50)	12 (40)	78 (57)	89 (64)
Asian	65 (44)	65 (44)	17 (57)	59 (43)	49 (36)
Missing	12 (8)	9 (6)	1 (3)		
ECOG PS, n (%)					
0/1	146 (98)	138 (94)	29 (97)	131(96)	132 (96)
2	3 (2)	9(6)	1 (3)	6 (4)	6 (4)
Smoking status, n (%)					
Never	81 (54)	94 (64)	NA	84 (61)	75 (54)
Previous	55 (37)	43 (29)	NA	49 (36)	56 (41)
Current	13 (9)	9(6)	NA	4 (3)	7 (5)
Stage of disease, n (%)					
IIIA	1 (1)	0	NA		
IIIB	12 (8)	8 (5)	NA	8 (6)	12(9)
IV	135 (91)	139 (95)	NA	129 (94)	126 (91)
Other	1 (1)	0	NA		
Histological type, n (%)					
Adenocarcinoma	140 (95)	140 (95)	NA	126 (92)	137 (99)

Other	9 (6)	7 (5)	NA	11 (8)	1 (1)
Brain metastases at baseline, n (%) *	38 (26)	40 (27)	8 (27)	40 (29)	41 (30)
Previous brain radiotherapy, n (%)	9 (6)	10 (7)	2 (7)	18 (13)	19 (14)
Previous chemotherapy in la/mNSCLC, n (%)	NA	NA	1 (3)	36 (26)	37(27)

*include adenosquamous carcinoma, large-cell carcinoma, squamous carcinoma and other

6.2.3 Comparability of the study population(s) with Danish patients eligible for treatment

See section 6.1.3 for comparability of the study population with Danish patients eligible for treatment.

6.2.4 Efficacy – results per CROWN

See section 6.1.4 for efficacy results per CROWN.

6.2.5 Efficacy – results per Study 1001

See section 6.1.5 for efficacy results per CROWN.

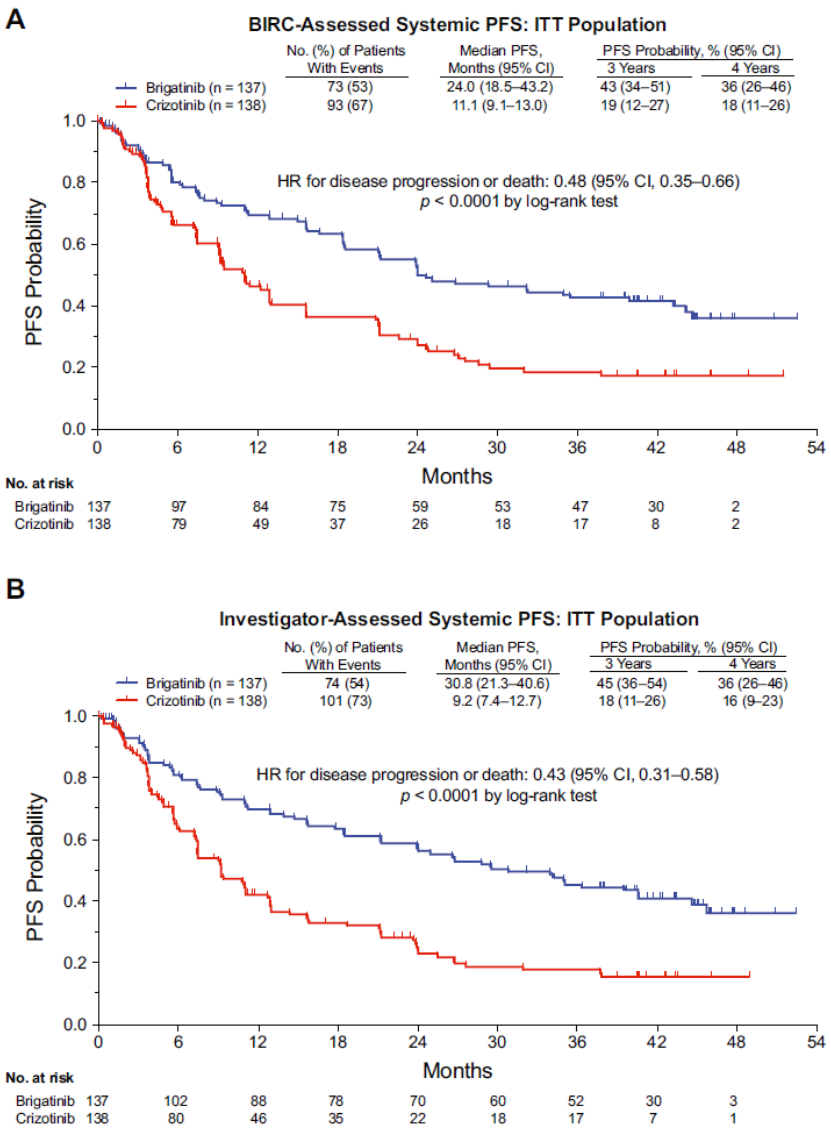
6.2.6 Efficacy – results per ALTA-1L

The trial met its primary endpoint at the primary analysis, demonstrating a statistically significant improvement in PFS(BIRC). The most recent updated study data of the ALTA-1L study is the final analysis with data after 40.4 months median follow-up. Mature PFS, OS, ORR, DOR and safety data are derived from the final analysis (19).

Progression-free survival: The primary endpoint was PFS(BIRC) per RECIST v.1.1 in the ITT population. Median PFS was 24.0 (95% CI: 18.5-43.2) months for the brigatinib arm and 11.1 (95% CI: 9.1-13.0) months in the crizotinib arm; HR = 0.48, (95% CI: 0.35-0.66), log-rank p<0,0001 (19). At 4 years, the PFS(BIRC) rate was 36% (95% CI:26–46) in the brigatinib arm and 18% (95% CI:11–26) in the crizotinib arm, although the 4-year data were limited by a high rate of censoring and small sample size (two patients at risk in each group) (19).

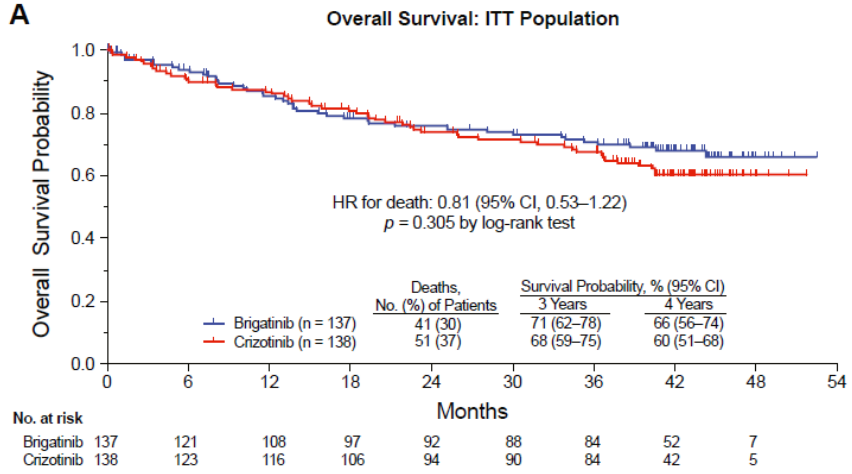
Median PFS (INV) for brigatinib was 30.8 (95% CI: 21.3–40.6) months versus 9.2 (95% CI:7.4–12.7) months for crizotinib; HR = 0.43, (95% CI: 0.31–0.58, log-rank p < 0.0001) (9). Improvements in BIRC-assessed PFS were consistent across all subgroups (19).

Figure 16 Kaplan-Meier plot of investigator-assessed progression-free survival (RECIST, v1.1) in ITT population A) by BIRC and B) Investigator assessed, follow-up 40,4 months (17)



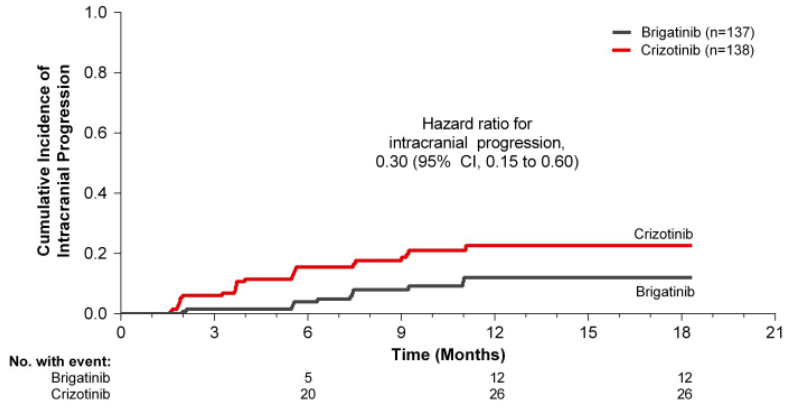
Overall survival: At study end, 92 patients had died (brigatinib, 41 (30%); crizotinib, 51 (37%)). OS rate at 3-years was 71% (95% CI:62%–78%) in the brigatinib arm and 68% (59%–75%) in the crizotinib arm without adjustment for patients who crossed over from crizotinib to brigatinib (HR = 0.81, 95% CI: 0.53–1.22, log-rank p = 0.331) (21). At 4 years, the KM-estimated OS was 66% (95% CI: 56%–74%; 7 patients at risk) in the brigatinib arm and 60% (51%–68%; 5 patients at risk) in the crizotinib arm. To adjust for potential time-dependent confounding effects of cross- over after patients discontinued crizotinib, a marginal structural model (MSM) and an inverse probability of censoring weight Cox model were constructed. In these sensitivity analyses the OS HR was 0.54 (95% CI: 0.31–0.92, p = 0.023) by the MSM method and 0.50 (95% CI: 0.28–0.87, p = 0.014) by the inverse probability of censoring weight approach (19).

Figure 17 Kaplan-Meier plot of overall survival in ITT population without adjustments for crossover, follow-up 40,4 months (17)



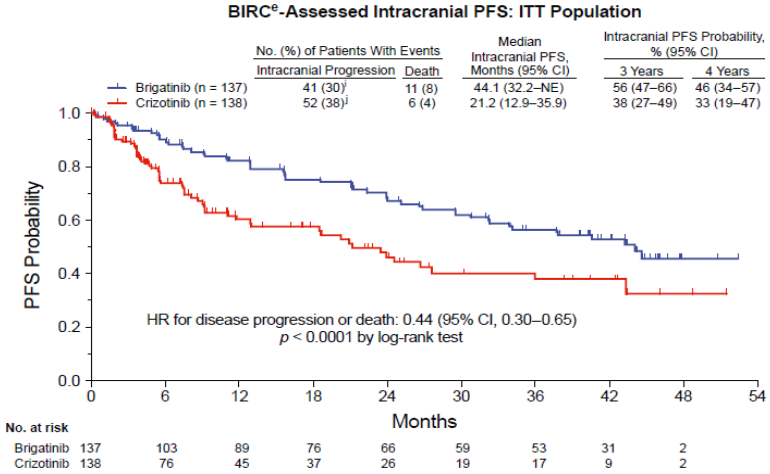
Intracranial activity: In ALTA-1L intracranial PFS was analysed in patients with and patients without brain metastases at baseline, but in latest analysis IC-PFS in ITT population was analysed. An exploratory competing-risks analysis of intracranial disease progression in the intention-to-treat population showed that the cause-specific hazard ratio (HR) for time to progression of intracranial disease was 0.30 (95% CI, 0.15 to 0.60) at first interim analysis with median follow-up of 11.0 months for brigatinib and 9.3 months for crizotinib (38).

Figure 18 Cumulative incidence of intracranial progression ALTA-1L



In the ITT population, the 4-year intracranial PFS rate was 46% (95% CI: 34%–57%; two patients at risk) with brigatinib and 33% (95% CI: 19%–47%; two patients at risk) with crizotinib (19).

Figure 19 BICR-assessed intracranial PFS ALTA-1L



Responses: The BIRC-assessed confirmed ORR was 74% (95% CI: 66% to 82%) with brigatinib and 62% (95%CI: 54% to 70%) with crizotinib. The median DOR in confirmed responders was 33.2 months (95% CI:22.1–NR) with brigatinib and 13.8 months (95% CI:10.4–22.1) with crizotinib (19). The confirmed ORR-BIRC in patients with brain metastases at baseline was 78% (95% CI:52% to 94%) with brigatinib and 26% (95% CI:10% to 48%) with crizotinib (19). The median intracranial DOR in patients with measurable brain metastases at baseline by BIRC assessment was 27.9 months (95% CI:5.7 –NE) in the brigatinib arm and 9.2 months (95% CI: 3.9 –NE) in the crizotinib arm (19).

Subgroups:

- Among 65 patients who crossed over to brigatinib (47% of total crizotinib arm, 65% of patients with PD on crizotinib), the median PFS-BIRC was 16.8 months (95% CI: 10.1–23.9) with a median follow-up of 22.7 months (95% CI:0.2–37.6). Confirmed ORR-BIRC was 57% (95% CI: 44%–69%), with median DOR in confirmed responders of 19.1 months (95% CI: 10.9–23.5) (19) .
- Among patients with brain metastases at baseline per INV, 33 patients had died (brigatinib, 11 of 40 [28%]; crizotinib, 22 of 41 [54%]). The HR for death was 0.43 (95% CI: 0.21–0.89, log-rank p = 0.020). The survival benefit of brigatinib versus crizotinib in this subset of patients was greater in patients without previous radiotherapy to the brain (HR = 0.25, 95% CI: 0.08–0.75, log-rank p = 0.008) than in patients with previous radiotherapy to the brain (HR = 0.76, 95% CI: 0.27–2.12, log-rank p = 0.637).
- Among patients without baseline brain metastases assessed by INV (brigatinib, n = 97; crizotinib, n = 97), 59 patients died (brigatinib, 30 [31%]; crizotinib, 29 [30%]; HR = 1.16, 95% CI: 0.69–1.93, log-rank p = 0.603) (19).
- In patients with any brain metastases at baseline by BIRC assessment, the 4-year rate was 22% (95% CI:9%–39%; two patients at risk) with brigatinib and NE (zero patients at risk) with crizotinib (19).

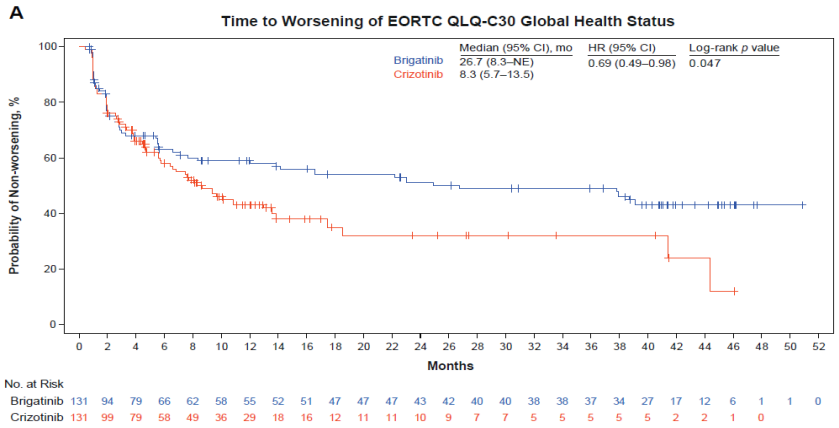
Biomarker: EML4-ALK fusions were detected in 57 of 123 patients (46%) in the brigatinib arm and 64 of 127 patients (50%) in the crizotinib arm. Patients with EML-ALK fusion v3 had worse PFS compared with patients with v1 or v2, regardless of the treatment group

(19). Although the OS data were immature, there was the suggestion of a trend for worse OS in patients with v3 compared with v1 for death, HR: 1.45 (95% CI:0.54–3.91) for brigatinib; 1.58 (95% CI:0.65, 3.83) for crizotinib. Brigatinib exhibited a higher ORR and longer median PFS compared with crizotinib in all variant subgroups (19).
Among patients with EML4-ALK fusions detected at screening, the TP53 mutation was detected in 22 out of 57 patients (39%) in the brigatinib arm and 23 out of 64 patients (36%) in the crizotinib arm. Patients with the TP53 mutation exhibited a trend toward lower ORR and worse PFS compared with patients with wild type (WT) in both treatment arms (19). The TP53 mutation maintained a strong prognostic trend toward worse PFS in the multivariate analysis HR for PD, TP53 mutation versus WT = 1.76 (95%CI: 0.81–3.83) for brigatinib; 1.77 (95% CI:0.90–3.49) for crizotinib. Brigatinib exhibited superior ORR and PFS compared with crizotinib in patients with and without the TP53 mutation (19).

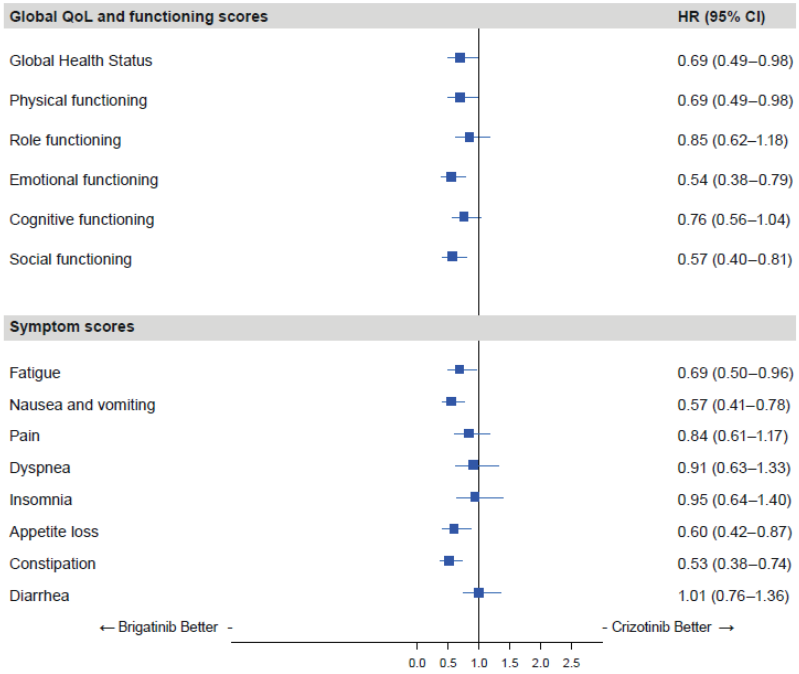
Health-related Quality of Life: In ALTA-1L Patient-reported Quality of Life was assessed by using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. They were administered at baseline, day 1 of every 4 weeks cycle, at end of treatment and 30 days after last dose of treatment. Time to worsening in EORTC QLQ-C30 Global health score, Quality of Life and other functioning and symptom scores, defined as a ≥10-point decrease from baseline, in patients with baseline and any postbaseline EORTC assessment were compared between treatment arms using a two-sided stratified log-rank test (19).

The median time to worsening in Global Health Score/QoL for brigatinib was 26.7 months, and for crizotinib was 8.3 months (HR = 0.69, 95% CI: 0.49–0.98, log-rank p = 0.047), Figure 20A). Compared with crizotinib, brigatinib significantly delayed the time to worsening of emotional (HR= 0.54 (0.38-0.79)) and social functioning (HR= 0.57 (0.40-0.81)) and symptoms of fatigue (HR= 0.69 (0.50-0.96)), nausea and vomiting (HR= 0.57(0.41-0.78)), appetite loss (HR= 0.60 (0.42-0.87)), and constipation (HR= 0.53 (0.38-0.74)) (log-rank p < 0.05). No domain significantly favored crizotinib (19), Figure 20B.

Figure 20 Time to worsening in EORTC QLQ-C30 scores among PRO-ITT population. (A) Kaplan-Meier plot of time to worsening in EORTC QLQ-C30 GHS score, B) Forest plot of HRs for time to worsening in global QoL and functioning and symptom scores in the brigatinib arm versus the crizotinib arm.



B



7. Comparative analyses of efficacy

As no head-to-head trial was available versus alectinib or brigatinib, an indirect comparison was necessary. As all included trials had the common comparator of crizotinib, an NMA was carried out to assess the comparative efficacy between lorlatinib, alectinib and brigatinib. Baseline patient characteristics are compared across ALEX, ALTA-1L, and CROWN trials in Table 62 presented in appendix C.1.

7.1.1 Differences in definitions of outcomes between studies

The relevant efficacy outcomes for this submission reported in the ALEX, ALTA-1L, and CROWN trials are PFS (INV), PFS (BICR), OS, and IC-TTP. Grade 3/4 adverse events and discontinuation due to adverse events were also included in the NMA, but these are presented in section 9.1. The definitions of the outcomes were considered sufficiently similar for inclusion in an NMA. The definitions and sources for all outcomes for all trials are presented in section 3.7.

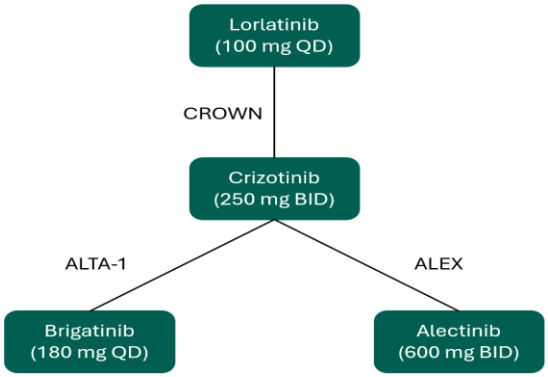
Analyses of IC-TTP between trials differ slightly; with competing risk HRs used for the brigatinib and alectinib trials, competing risks analysis calculates HR by treating systemic (i.e. 'PFS') progression as a competing event, whereas the lorlatinib CROWN HR censors patients who receive systemic therapy that is not lorlatinib. The published competing risk analysis HRs from CROWN were 0.06 at 18 months, which aligns with the IC-TTP HR from the 5-year data cut off (32,17). Median follow-up time differs for analysis of IC-TTP,

ALTA-1L is 11.0 months, ALEX 18.6 months and finally CROWN with median 60 months follow-up.

7.1.2 Method of synthesis

The methods used for the NMA are briefly described here; details on the methods of synthesis are provided in Appendix C.

Figure 21 Network graph for NMA of lorlatinib versus brigatinib and alectinib



Abbreviations: BID: Twice a day; NMA: Network meta-analysis; QD: Once a day

For PFS (INV), PFS (BICR), OS, and IC-TTP, hazard ratios of lorlatinib, alectinib, and brigatinib against crizotinib in ALK-positive NSCLC patients were extracted. These were then combined using frequentist NMA methodology, using the *netmeta* package in the freely available software R. The *netmeta* package adopts the approach proposed by Rücker, which relies on graph-theoretical methods(49). To fit fixed and random effect models, treatment estimates and corresponding standard errors of all pairwise comparisons must be available. As is common in meta-analysis, standard errors are assumed to be known and fixed(50). As the conducted NMA included only one study per comparison, there was no within-comparison heterogeneity, meaning that fixed- and random effect models provided exactly similar estimates; therefore, only results from the fixed effect model are presented. Similarly, as the network graph (shown in Figure 21) contained no closed loops (and thus no NMA estimates were informed by different designs), no inconsistency was observed.

7.1.3 Results from the comparative analysis

The results of the random effect NMA of lorlatinib versus brigatinib and alectinib for ALK-positive NSCLC patients are shown in Table 15. All analyses are done using the ITT populations of the included trials.

Table 15 Results from the comparative analysis of lorlatinib versus alectinib and brigatinib for ALK-positive NSCLC patients

Outcome measure	CROWN(32, 33, 51) (Lorlatinib = 149 Crizotinib = 147)	ALTA-1L(19, 38) (Brigatinib = 137 Crizotinib = 138)	ALEX(16, 47) (Alectinib = 152 Crizotinib = 147)	NMA Results (fixed effects, frequentist NMA)
OS	Lorlatinib median OS: NR, 95% CI: NE	Brigatinib median OS: NR, 95% CI: NE	Alectinib median OS: NR, 95% CI: NE	**Lorlatinib vs. brigatinib HR:**

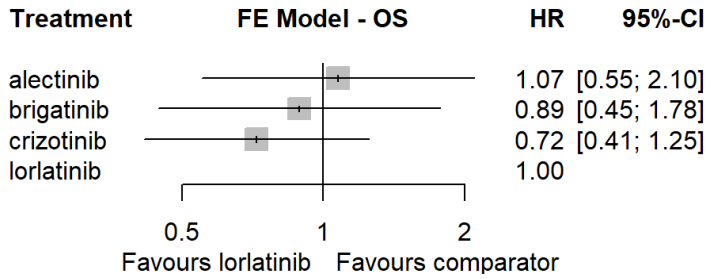
	Crizotinib median OS: NR, 95% CI: NE **Lorlatinib vs. crizotinib HR: 0.72** 95% CI: 0.41 to 1.25	Crizotinib median OS: NR, 95% CI: NE **Brigatinib vs. crizotinib HR: 0.81** 95% CI: 0.53 to 1.22	Crizotinib median OS: 57.4 months, 95% CI: 34.6 – NE **Alectinib vs. crizotinib HR: 0.67** 95% CI: 0.46 to 0.98	**0.89,** 95% CI: 0.45 to 1.78 **Lorlatinib vs. alectinib HR: 1.07,** 95% CI: 0.55 to 2.09
PFS (INV)	Lorlatinib median PFS: NR, 95% CI: 64.3 – NE Crizotinib median PFS: 9.1 months, 95% CI: 7.4 – 10.9 **Lorlatinib vs. crizotinib HR: 0.19,** 95% CI: 0.13 to 0.27	Brigatinib median PFS: 30. 8 months, 95% CI: 21.3 – 40.6 Crizotinib median PFS: 9.2 months, 95% CI: 7.4 – 12.7 **Brigatinib vs. crizotinib HR: 0.43** 95% CI: 0.31 to 0.58	Alectinib median PFS: 34.8 months, 95% CI: 17.7 – NE Crizotinib median PFS: 10.9 months 95% CI: 9.1 – 12.9 **Alectinib vs. crizotinib HR: 0.43** 95% CI: 0.32 to 0.58	**Lorlatinib vs. brigatinib HR: 0.44,** 95% CI: 0.27 to 0.71 **Lorlatinib vs. alectinib HR: 0.44,** 95% CI: 0.28 to 0.71
PFS (BICR)	Lorlatinib median PFS: NR, 95% CI: NE Crizotinib median PFS: 9.3 months, 95% CI: 7.6 – 11.1 **Lorlatinib vs. crizotinib HR: 0.27,** 95% CI: 0.18 to 0.39	Brigatinib median PFS: 24.0 months, 95% CI: 18.5 – 43.2 Crizotinib median PFS: 10.4 months, 95% CI: 7.7 – 14.6 **Brigatinib vs. crizotinib HR: 0.48** 95% CI: 0.35 to 0.66	Alectinib median PFS: 25.7 months, 95% CI: 19.9 – NE Crizotinib median PFS: 10.4 months, 95% CI: 7.7 – 14.6 **Alectinib vs. crizotinib HR: 0.50** 95% CI: 0.36 to 0.70	**Lorlatinib vs. brigatinib HR: 0.40** 95% CI: 0.24 to 0.64 **Lorlatinib vs. alectinib HR: 0.38,** 95% CI: 0.24 to 0.61
IC-TTP	Lorlatinib median IC-TTP: NR, 95% CI: NE Crizotinib median IC-TTP: 16.4 months, 95% CI: 12.7 – 21.9 **Lorlatinib vs. crizotinib HR: 0.06,** 95% CI: 0.03 to 0.12	Brigatinib median IC-TTP: NR, 95% CI: NE Crizotinib median IC-TTP: NR, 95% CI: NE **Brigatinib vs. crizotinib HR: 0.30** 95% CI: 0.15 to 0.60	Alectinib median IC-TTP: NR, 95% CI: NE Crizotinib median IC-TTP: NR, 95% CI: NE **Alectinib vs. crizotinib HR: 0.16** 95% CI: 0.10 to 0.28	**Lorlatinib vs. brigatinib HR: 0.20,** 95% CI: 0.07 to 0.53 **Lorlatinib vs. alectinib HR: 0.37,** 95% CI: 0.16 to 0.89

Abbreviations: BICR: Blinded independent central review; CI: Confidence interval; HR: Hazard ratio; IC-TTP: Intracranial time-to-progression; NE: Not Estimatable; NMA: Network meta-analysis; NR: Not reached; OS: Overall survival; PFS: Progression-free survival

7.1.4 Efficacy – results per overall survival

For OS, in the NMA, lorlatinib was numerically superior to brigatinib with an HR for lorlatinib versus brigatinib of 0.89 (95% CI: 0.45 to 1.78). The hazard ratio of lorlatinib versus alectinib was 1.07 (95% CI: 0.55 to 2.10). None of the differences were statistically significant; this may be explained by the low number of OS events observed in the included studies. Figure 22 presents the forest plot for overall survival.

Figure 22 Fixed effects meta-analysis of overall survival

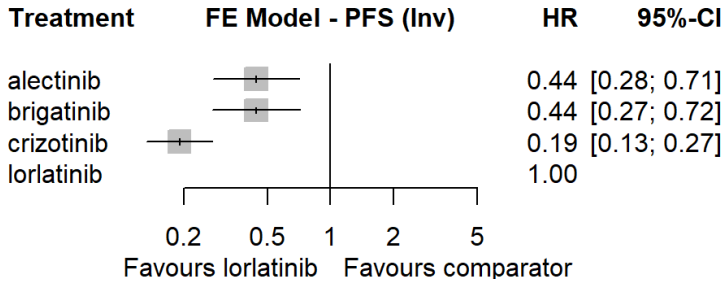


Abbreviations: RE: random effect; OS: overall survival; HR: hazard ratio; CI: confidence interval

7.1.5 Efficacy – results per progression free survival (investigator assessed)

For PFS by investigator, in the NMA, lorlatinib was statistically significantly superior to both alectinib and brigatinib with HRs (lorlatinib versus comparator) of 0.44 (95% CI: 0.28 to 0.71) and 0.44 (95% CI: 0.27 to 0.72), respectively. Figure 23 presents the forest plot for PFS (assessed by investigator).

Figure 23 Fixed effects meta-analysis of progression free survival (investigator)

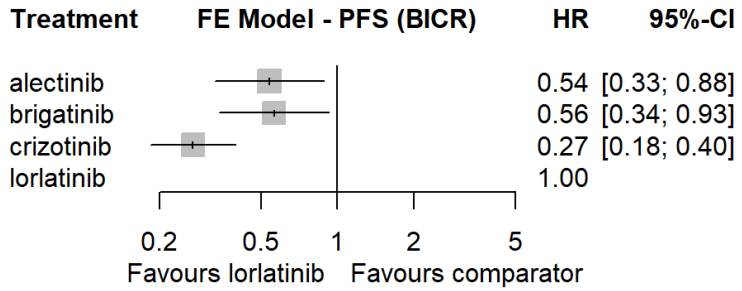


Abbreviations: FE: Fixed effect; PFS: progression free survival; Inv: investigator; HR: hazard ratio; CI: confidence interval

7.1.6 Efficacy – results per progression free survival (BICR)

Similarly to PFS by investigator, in the fixed effects NMA of PFS by BICR, lorlatinib was statistically significantly superior to both alectinib and brigatinib with HRs (lorlatinib versus comparator) of 0.54 (95% CI: 0.33 to 0.88) and 0.56 (95% CI: 0.34 to 0.93), respectively. Figure 24 presents the forest plot for PFS (BICR).

Figure 24 Fixed effects meta-analysis of progression free survival (BICR)

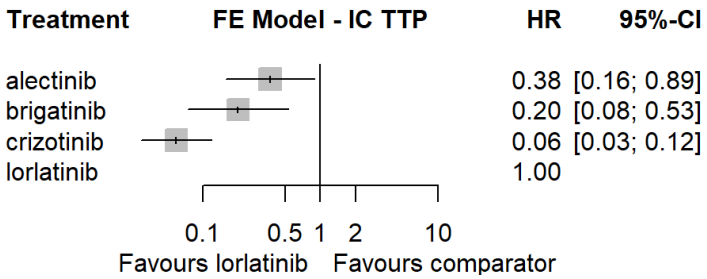


Abbreviations: FE: fixed effect; PFS: progression free survival; BICR: blinded independent central review; HR: hazard ratio; CI: confidence interval

7.1.7 Efficacy – results per intra-cranial time to progression

As discussed in section 7.1.1, IC-TPP was defined differently in ALTA-1L compared to ALEX and CROWN, however, to compare intracranial progression ALTA-1L results were still included in the ITC. For intra-cranial time to progression, in the NMA, lorlatinib was statistically significantly superior to both alectinib and brigatinib with HRs (lorlatinib versus comparator) of 0.38 (95% CI: 0.16 to 0.89) and 0.20 (95% CI: 0.08 to 0.53), respectively. Figure 25 presents the forest plot for the intra-cranial time to progression.

Figure 25 Fixed effects meta-analysis of IC-TTP



Abbreviations: FE: fixed effect; IC TTP: intra-cranial time to progression; HR: hazard ratio; CI: confidence interval.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The primary source of efficacy data in the model was the CROWN trial for lorlatinib and the NMA (section 7) for alectinib and brigatinib. Due to the immaturity of the OS data, the CROWN OS KM data was pooled with the Study 1001 cohort EXP1 (see section 8.2 for a thorough description) (40). To model post-progression survival of alectinib and brigatinib, the EXP3B-5 cohort from Study 1001 was used (40).

Based on feedback from a Danish clinical expert, the superior PFS of lorlatinib versus comparators was expected to result in increased OS for lorlatinib patients, despite current immature OS data. This is reflected in the model results.

8.1.1 Extrapolation of efficacy data

As mentioned above, the CROWN data and the NMA results were the main evidence used to model and extrapolate efficacy. Proportional hazards testing was carried out to assess whether joint- or independent extrapolation models were more appropriate. The proportional hazards assessment suggests that broadly, the proportional hazards assumption holds between crizotinib, alectinib and brigatinib. Whereas the proportional hazards assumption between lorlatinib and crizotinib is unlikely to hold.

Due to 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 and crizotinib arms of the model. Given that there was no clear evidence that the proportional hazards assumption was violated in the ALEX and ALTA-1L trials (see Table 71), alectinib and brigatinib was modelled by applying a HR from the NMA to parametric survival curves of the crizotinib treatment arm from the CROWN trial. Therefore, assumptions on the approach to extrapolations are presented for both lorlatinib and crizotinib in Table 16 and Table 17.

Both standard parametric models and more flexible modelling approaches were explored. Of the flexible modelling approaches, the piecewise models seemed to provide the most reliable results, which was used to model lorlatinib PFS. Flexible modelling approaches were not found to bring any clear benefit over the standard parametric models for the remaining extrapolations. Extrapolations are explained in section 8.1.1.1 and 8.1.1.2, and further detailed in Appendix D.

8.1.1.1 Extrapolation of progression-free survival

The CROWN October 2023 data cut did not include PFS BICR. Therefore, PFS INV was applied in the base case. Separate models were fitted for the lorlatinib and crizotinib arm, as the proportional hazards assumption seemed to be violated.

For lorlatinib PFS, a piecewise model was chosen in the base case, as standard parametric models were not considered to fit the KM data and the hazard profile of the lorlatinib arm properly. The piecewise function models PFS solely based on the KM data until a pre-determined time point. From that timepoint and onwards, a parametric curve was applied based on the KM data. The pre-determined timepoint was based on the smoothed hazard plot (section D.1.6), from which it was seen that PFS hazards seem to decrease at 23 months and again at 36 months. Therefore, piecewise models were constructed using either 23 months or 36 months as the pre-determined timepoint. These are referred to as 23-month piecewise and 36-month piecewise models in the remainder of the document.

The lorlatinib 36-months piecewise models were prioritized over the 23-months piecewise models, as the 36-months piecewise models provide a better statistical fit. Most of the 36-months piecewise models provided a reasonable statistical fit, as all models were within >5 point difference in AIC and BIC, except for the Gompertz model. The 36-months piecewise exponential, generalized gamma, log-logistic, and log-normal curves all provided very optimistic PFS results, with more than 13% alive and progression-free after 30 years, which is expected to be clinically implausible.

Both the 36-month piecewise gamma and 36-month piecewise Weibull models provided reasonable statistical fit and seemed clinically plausible. However, the 36-month piecewise gamma model led to extrapolations above the equivalent parametric OS during most of the time horizon. Therefore, the 36-month piecewise Weibull curve was selected for the lorlatinib base case as this curve represents the second-best statistical fit to observed data combined with plausible long-term extrapolation for lorlatinib compared with the other curves, while the 36-month piecewise gamma model was

explored in scenario analysis. Lorlatinib KM data along with the piecewise extrapolations are presented in Figure 26.

As alectinib and brigatinib arms were modelled by applying a HR to the crizotinib arm, it was also necessary to model the crizotinib arm. The applied HRs are presented in section 7. For the crizotinib arm, the standard log-logistic model provided the best statistical fit, while the Weibull provided the worst statical fit. Given the best statical fit, the log-logistic curve was selected for crizotinib, which was also expected to better align with the flexibility of the piecewise model used for lorlatinib. The choice of crizotinib PFS extrapolation does not have a large impact on the modelled PFS estimate, as Kaplan–Meier PFS data were more complete with a PFS rate of 8% after 5 years. All parametric extrapolations for crizotinib PFS resulted in ≤1% of patients being alive and progression-free after 10 years except for generalized gamma and Gompertz. Other parametric curves to model crizotinib were tested in scenario analysis. Crizotinib KM data along with the standard parametric extrapolations are presented in Figure 27. Base case extrapolations for lorlatinib, crizotinib, alectinib and brigatinib is presented in Figure 28.

Table 16 Summary of assumptions associated with extrapolation of progression-free survival

Method/approach	Description/assumption
Data input	CROWN October 2023 data cut, PFS (INV).
Model	Both standard parametric models and piecewise models were considered. 23- and 36-month piecewise models were available for the lorlatinib arm.
Assumption of proportional hazards between intervention and comparator	Proportional hazards assumption between lorlatinib and crizotinib was likely violated.
Function with best AIC fit	Lorlatinib: 36-months exponential Crizotinib: Log-logistic
Function with best BIC fit	Lorlatinib: 36-months exponential Crizotinib: Log-logistic
Function with best visual fit	Lorlatinib: 36-months Weibull Crizotinib: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Lorlatinib: 36-months Weibull Crizotinib: Log-logistic
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinions on clinical plausibility
Function with the best fit according to external evidence	Lorlatinib: 36-months Weibull Crizotinib: Log-logistic
Selected parametric function in base case analysis	Lorlatinib: 36-months Weibull Crizotinib: Log-logistic

Adjustment of background mortality with data from Statistics Denmark	OS was adjusted for background mortality.
Adjustment for treatment switching/cross-over	Not relevant
Assumptions of waning effect	Only explored in scenario analysis.
Assumptions of cure point	No

Figure 26 Investigator assessed PFS KM data and 36-months piecewise models for lorlatinib

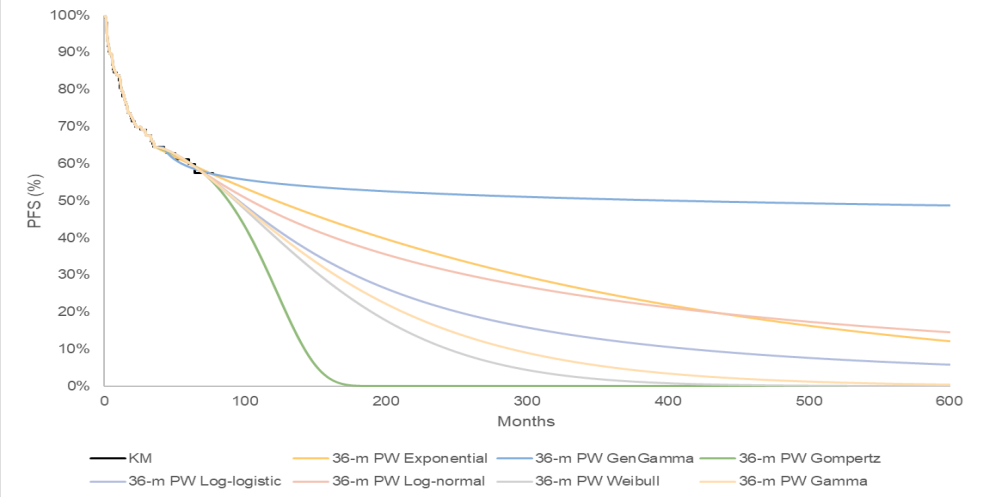


Figure 27 Investigator assessed PFS KM data and standard parametric models for crizotinib

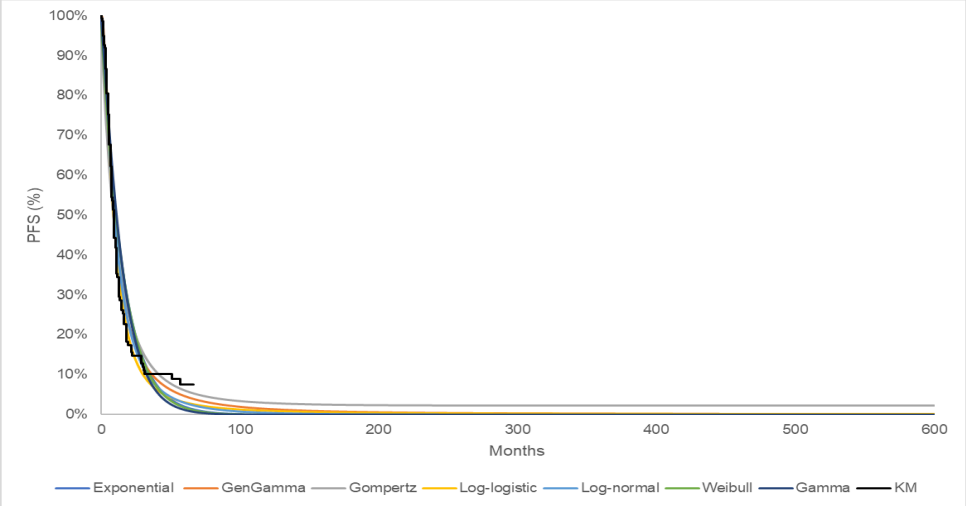
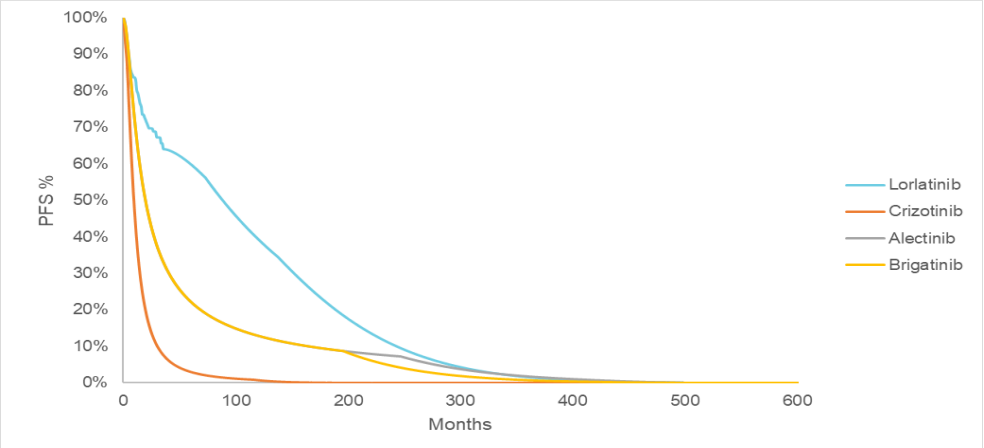
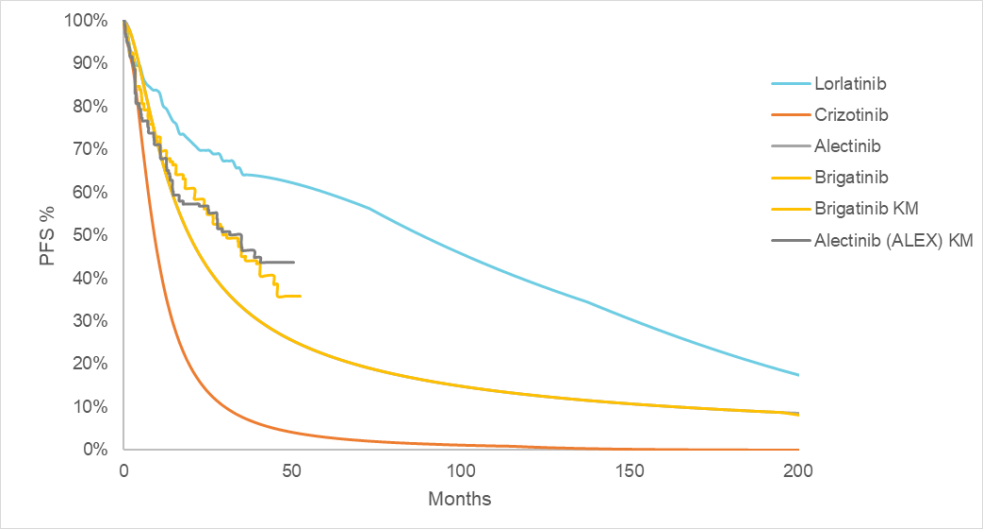


Figure 28 Base case PFS extrapolations for lorlatinib, crizotinib, alectinib, brigatinib



Note: Alectinib and brigatinib are cut by their own OS curve at approximately 200 and 250 months. This is to ensure plausibility between the health states.

Figure 29 Base case PFS extrapolations for lorlatinib, crizotinib, alectinib, brigatinib compared with the PFS KM data for alectinib and brigatinib



Note: Due to similar hazards ratios, the alectinib and brigatinib extrapolations are overlayed.

8.1.1.2 Extrapolation of overall survival

As highlighted in section 6.1.4, only OS data from the March 2020 data cut-off is available, highlighting the key challenge of the CROWN survival analyses, the immaturity of the OS data. To mitigate the immaturity of CROWN OS data, the KM data were pooled with study 1001 EXP1 (40) to ensure more mature OS data for the lorlatinib arm.

Study 1001 is a Phase II open-label, single-arm trial of lorlatinib in patients with ALK-positive NSCLC with varying prior treatment exposure, including a the EXP1 cohort of 30 patients who were treatment naïve. The results are presented in section 6.1.5. The mean OS results of Study 1001 EXP1 were presented in the discussion sections of Solomon et al., 2024 (17): Median follow-up for OS of 72.7 months (95% CI, 69.3 to 76.3), and 5-year OS was 76% (95% CI, 57 to 88) in patients with treatment-naïve *ALK*-positive NSCLC. Both CROWN and study 1001 EXP1 include lorlatinib patients with similar baseline

characteristics and subsequent therapies. Pooling both populations provides a longer follow-up, as the patients in EXP1 had up to 90 months of follow-up (40). The impact of data pooling moderately increases the survival predictions of the parametric fittings versus the CROWN only fittings. More details on the pooled analysis can be found in Appendix K.

Independently fitted curves were fitted to lorlatinib using pooled CROWN + Study 1001 Kaplan–Meier data. Piecewise models were also considered for OS extrapolation; however, this did not add any value over standard approaches, as no unique hazard profile was observed. Thus, the standard parametric models were fitted to the pooled CROWN + Study 1001 data, while extrapolations of OS solely based on CROWN trial data was explored in scenario analysis.

Table 17 Summary of assumptions associated with extrapolation of overall survival

Method/approach	Description/assumption
Data input	Pooled CROWN (March 2020 data cut-off) + Study 1001 EXP1
Model	Standard parametric models
Assumption of proportional hazards between intervention and comparator	Proportional hazards assumption between lorlatinib and crizotinib was likely violated.
Function with best AIC fit	Lorlatinib: Generalized gamma Crizotinib: Generalized gamma
Function with best BIC fit	Lorlatinib: Exponential Crizotinib: Exponential
Function with best visual fit	Lorlatinib: Weibull Crizotinib: Weibull
Function with best fit according to evaluation of smoothed hazard assumptions	Lorlatinib: Generalized gamma Crizotinib: Generalized gamma
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Lorlatinib: Weibull Crizotinib: Weibull
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	Only explored in scenario analysis.

Assumptions of cure point	No

Figure 30 Overall survival KM data and standard parametric models for lorlatinib (CROWN + 1001 EXP1 pooled OS analysis)

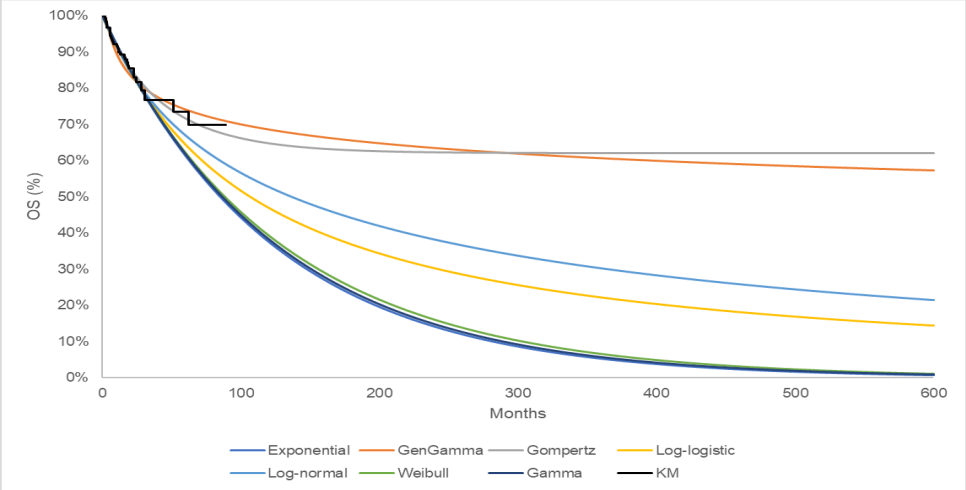
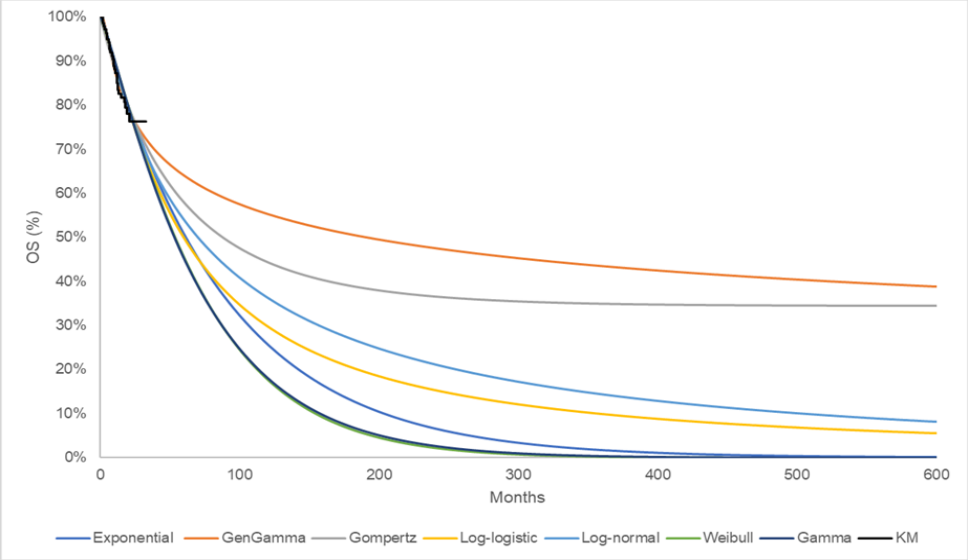


Figure 31 Overall survival KM data and standard parametric models for crizotinib (CROWN)



8.1.2 Calculation of transition probabilities

Not applicable.

Table 18 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Not applicable.			

8.2 Presentation of efficacy data from second-line lorlatinib OS (Study 1001 - EXP:3B-5 cohorts pooled)

In ALEX, only 13.1% of progressed patients received second-line lorlatinib, while 2.4% received alectinib and 9.5% brigatinib, while in ALTA-1L, 28% received second-line lorlatinib, compared to 21% receiving alectinib and 3% brigatinib (16, 52). Full overview of subsequent treatments in CROWN, ALEX and ALTA-1L is provided in Table 63 in Appendix C.1. Lorlatinib is currently recommended as second-line and third-line treatment by the DMC, and therefore, the post-progression survival of the ALEX and ALTA-1L trials is not expected to reflect Danish clinical practice(30).

For alectinib and brigatinib 'the expansion cohort (EXP) 3B-5' from Study 1001 is used to model the post progression survival necessary for the pseudo transition modelling approach. EXP3B-5 from Study 1001 includes 139 patients with disease progression following one or more second generation ALK inhibitors (5). This data is used to model the survival following progression on first-line treatment, under the assumption that patients are treated with lorlatinib in second-line.

8.2.1 Extrapolation of efficacy data

Not applicable.

8.2.2 Calculation of transition probabilities

The standard PSM model was not found appropriate to apply for alectinib and brigatinib due to concerns related to the confounding effects introduced by subsequent TKIs in the ALEX and ALTA-1L trials, which are informing the relative efficacy of comparators in the model, as outlined above in section 8.2.

Therefore, alectinib and brigatinib post progression survival was modelled using 'the expansion cohort EXP3B-5' from Study 1001, which includes 139 patients with disease progression following one or more second generation ALK inhibitors (5). Incorporation of time-varying post-progression would have required multiple tunnel states. Therefore, a simple approach was taken to use utilize an exponential curve based on the data from Study 1001; EXP3B-5 (5) to model a constant post-progression transition rate. The method provided a per cycle transition rate of 2.47% from the progressed health state to death for alectinib and brigatinib.

Table 19 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Progressed disease	Death	Exponential curves using data on lorlatinib following another ALK inhibitor	Study 1001; EXP3B-5 (5)

Note: This transition only applied for alectininb and brigatinib.

8.3 Modelling effects of subsequent treatments

Effects of the subsequent treatments were not modelled directly. However, post-progression survival was modelled separately for alectinib and brigatinib, due to the differences between subsequent treatments in the ALEX and ALTA-1L trial and the expected Danish clinical practice. As the post-progression survival was based on external literature, this is described in section 8.2.

8.4 Other assumptions regarding efficacy in the model

8.4.1 CNS-progression as an intercurrent event

A simple approach was taken to account for the additional costs and QoL implications of brain metastases, by including the CNS-progression as an intercurrent event. The CNS-progression events were modelled based on IC-TPP, which was presented in section 6.1.4 with the KM data presented in Figure 8.

To simplify the modelling of IC-TPP, a constant rate was modelled based on the exponential function based on the IC-TTP data. Alectinib and brigatinib rates were calculated based on applying HRs to the crizotinib hazard, which is then converted into rates. HRs are presented in section 7.1.7. The model applies the per cycle rates of CNS progression presented in Table 20. Rates applied to patients in the model who are alive and on treatment – including patients who stop treatment before progression – in each cycle to calculate the incidence of CNS progression.

Table 20 IC-TTP rates by treatment

Treatment	Rate
Lorlatinib	0.15%
Crizotinib	3.35%
Alectinib	0.55%
Brigatinib	1.02%

Abbreviations: IC-TTP, intracranial time to progression.

8.4.2 Treatment waning

Longer-term extrapolations remain highly uncertain and therefore treatment effect waning remains as an option in the model. However, treatment waning was not applied the base case given that the median PFS has not been reached after a median follow-up of 60 months, and clinical experts did not expect the effect to suddenly wane off. Treatment waning is only explored in scenario analysis. In those scenarios, hazards are waned down to the base crizotinib hazards from the waning point and forward.

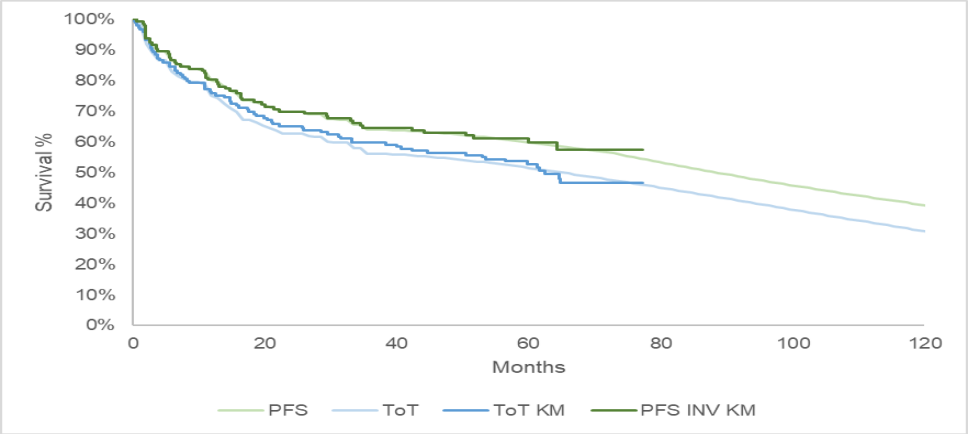
8.4.3 Time on treatment (ToT)

Figure 32 presents the PFS and ToT Kaplan–Meier curves showing that the ToT curve is consistently below the PFS curve in CROWN. This is likely due to the unusually long

duration of treatment for lorlatinib compared with second generation ALK inhibitors; the greater the duration of treatment with an ALK inhibitor, the higher the likelihood of stopping treatment. Lorlatinib is the most effective ALK inhibitor, so patients may stay on the treatment (median ToT 62 months) much longer compared with alectinib (median ToT 28.1 months) or brigatinib (median ToT 24.3 months), despite the higher rate of AEs.

As the relationship between the CROWN lorlatinib PFS and ToT was consistent, a HR was applied to the PFS arm to calculate the ToT rather than relying on parametric curves. The HR (HR=1.295, 95% CI: 0.914 - 1.834) was estimated for the observed ToT versus the observed PFS from CROWN using a Cox model with a variable for outcome type. ToT for lorlatinib was therefore estimated by applying the HR of 1.295 to the lorlatinib PFS curve.

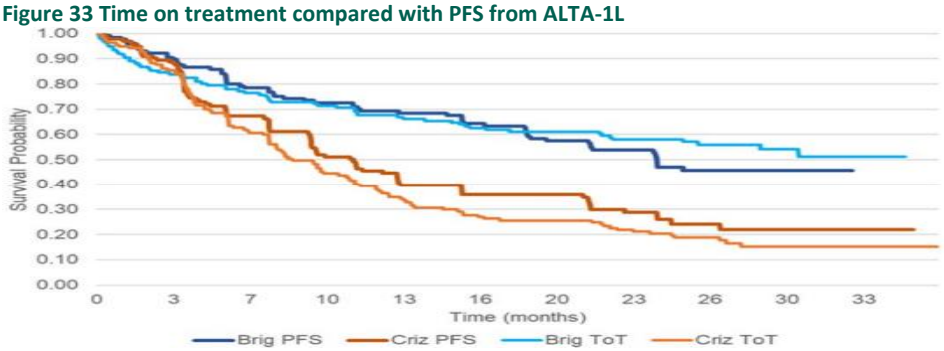
Figure 32 Time on treatment and investigator assessed progression free survival curves



Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival; ToT, time on treatment.

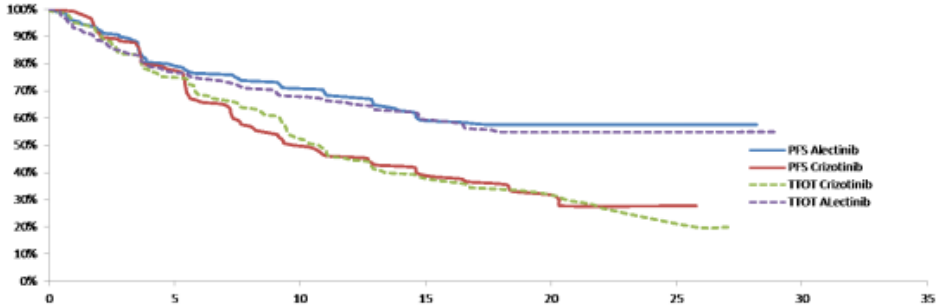
For alectinib and brigatinib, the observed PFS from pivotal trial overlayed with ToT almost perfectly and so in line with appraisals TA536 and TA670, ToT is assumed to equal PFS (i.e. HR of 1 is applied) (6, 44), illustrated in Figure 33 and Figure 34.

Figure 33 Time on treatment compared with PFS from ALTA-1L



Abbreviations: BIRC, blinded independent review committee; Brig, brigatinib; Criz, crizotinib; PFS, progression-free survival; ToT, time on treatment

Figure 34 Time on treatment compared with PFS from ALEX



As the parametric curves were not used for the base case, these are not presented in section 8.1. However, the extrapolations are presented in appendix D.3, and applying ToT using parametric curves is explored in scenario analysis.

8.5 Overview of modelled average treatment length and time in model health state

The PFS and OS estimates without discounting and half-cycle correction are presented in Table 21 and Table 22. Time in model states is presented in Table 23.

Table 21 PFS (investigator assessed) estimates in the model

	Modelled average PFS ('Partitioned Survival model O20, O22, 024')	Modelled median PFS ('Partitioned Survival model O21, O23, 025')	Observed median from relevant study
Lorlatinib	8.84 years	7.39 years	Median not reached (17)
Alectinib	4.50 years	1.64 years	2.90 years (16)
Brigatinib	4.25 years	1.64 years	2.57 years (19)

Table 22 Overall survival estimates in the model

	Modelled average OS ('Partitioned Survival model P20, P22, P24')	Modelled median OS ('Partitioned Survival model P21, P23, P25')	Observed median from relevant study
Lorlatinib	10.13 years	7.39 years	Median not reached (32)
Alectinib	7.58 years	5.01 years	Median not reached (16)
Brigatinib	7.38 years	5.01 years	Median not reached (19)

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length (years)	PFS (years)	OS (years)
Lorlatinib	7.06	8.84	10.13

Alectinib	4.50	4.50	7.58
Brigatinib	4.25	4.25	7.38

9. Safety

9.1 Safety data from the clinical documentation

The safety population consists of patients with advanced ALK+ NSCLC who received at least one dose of study drug in either in the intervention or comparator arm in the included studies, CROWN, ALEX and ALTA-1L. 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.

The review of the adverse reaction profiles is based on the summaries of product characteristics (SmPC), where the adverse reaction profiles are aggregated from the underlying studies (1, 24, 25) and are supplemented with adverse events data from the registrational studies (16, 17, 19). CROWN included patients from May 2017 to February 2019, and the study is still ongoing. ALEX included patients from August 2014 till January 2016, and the study is not finalized (47). ALTA-1L included patients from April 2016 till August 2017, and the study is finalized with study end January 2021 (19).

A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition), CTCAE version 4.03 used. Adverse reactions are drug related events.

Comparison lorlatinib and alectinib

Lorlatinib: The most frequently reported all grades adverse reactions with lorlatinib treatment are hypercholesterolaemia (81.1%), hypertriglyceridemia (67.2%), oedema (55.7%), peripheral neuropathy (43.7%), weight gain (30.9%), cognitive effects (27.7%), fatigue (27.3%), joint pain (arthralgia, 23.5%), diarrhoea (22.9%) and effects on mood (21.0%) (22). In the lorlatinib SmPC, special warning and precautions are described regarding hyperlipidaemia, central nervous system effects, atrioventricular block, left ventricular ejection fraction decrease, lipase and amylase increase, interstitial lung disease (ILD)/pneumonitis, high blood pressure and hyperglycaemia, drug interaction, fertility & pregnancy, lactose intolerance, and dietary sodium (1).

The safety data from CROWN are reported as all-causality adverse events in the latest analysis with a 60.2-month follow-up period (17). The safety profile remains similar to that reported in previous analyses of the CROWN study. Median duration of treatment (DOT) in the lorlatinib arm was 57.0 months (IQR: 13.9–63.3) versus 9.6 months (IQR: 4.7–17.1) in the crizotinib arm (17).

Number and proportion of grade 3-4 AEs of all causalities in CROWN are lorlatinib 115 patients (77%) and for crizotinib 81 patients (57%) (17). The most common grade 3-4 all causality adverse events in the CROWN study during treatment with lorlatinib were hypercholesterolaemia (21%), hypertriglyceridemia (25%), weight gain (23%) and high blood pressure (12%) (17). Sixteen patients (11%) treated with lorlatinib, and 15 patients (11%) treated with crizotinib discontinued treatment due to AE of all causalities in CROWN. Eight patients (5%) in both arms in CROWN were seen as treatment-related AEs (17).

Among all treated patients in the phase II Study 1001 trial, any-grade all-cause AEs were reported in 274 (100%) patients and grade 3/4 AEs were reported in 209 (76%). (40)

The most common all-cause AEs reported in patients were hypercholesterolemia (84%), hypertriglyceridemia (69%), edema (56%), peripheral neuropathy (49%) and dyspnea (31%). The most common TRAEs were hypercholesterolemia (84%), hypertriglyceridemia (68%), edema (45%) and peripheral neuropathy (35%), (40)

All cause AEs leading to dose reduction were reported in 77 (28%) patients, temporary treatment discontinuation in 158 (57%), and permanent discontinuation in 35 (13%). Any grade treatment-related AEs (TRAEs) were reported in 262 (95%) patients; grade 3/4 TRAEs were reported in 137 (50%). TRAEs leading to dose reduction were reported in 72 (26%) patients, temporary treatment discontinuation in 100 (36%), and permanent discontinuation in 13 (5%). No treatment related deaths occurred. (40)

Alectinib: The most common adverse reactions (≥ 20%) with treatment with alectinib are constipation, muscle pain (myalgia), oedema, anaemia, rash, increased bilirubin and nausea (24). In alectinib's SmPC, special warnings and precautions are described regarding ILD/pneumonitis, bradycardia, hepatotoxicity, severe myalgia and increased creatine kinase, gastrointestinal perforation, photosensitivity, haemolytic anaemia, women of child-bearing potential, lactose intolerance and sodium content (24).

The ALEX trial reported safety summary in an updated analysis with 48.2-month follow - up (16) . The number and proportion of grade 3-4 AEs of all causalities in ALEX are for alectinib 72 patients (47%) and for crizotinib 78 patients (52%) (16) . The most common grade ≥ 3 adverse events in the ALEX study when treated with alectinib was anaemia (5.9%), increased aspartate transaminase (5.3%), elevated alanine aminotransferase (4.6%) and pneumonia (4.6%). Median DOT in ALEX at second interim analysis were 27.0 (range 0.0-39.0) months with alectinib versus 10.8 (range 0.0-29.0) months with crizotinib (36) and at the latest analysis, median DOT was 28.1 months with alectinib and 10.8 months for crizotinib (16). In ALEX, 22 patients (14.5%) discontinued due to AEs in both arms (16).

Overview of safety events show more patients with grade 3-4 AEs in lorlatinib arm than alectinib arm, but the longer treatment length in CROWN together with other AE types than expected from an ALK-TKI, might account for part of the difference. In the alectinib group more patients have stopped treatment regardless of reason, mainly because of progression and adverse events. Less lorlatinib patients had stopped treatment at 60 months versus alectinib at 48 months, because of longer PFS benefit.

The number of patients that discontinue due to AEs are similar between treatments. Interestingly, only 2 grade 3-4 AEs have been reported since the previous analysis after 36 months follow-up in lorlatinib arm.

Table 24 Overview of safety events - ITT population (Follow-up time: 60 months for lorlatinib (17, 35)) and 48.2 months for alectinib (16)).

	Lorlatinib (N=149) (CROWN)	Crizotinib (N=142) (CROWN)	Difference, % (95 % CI)	Alectinib (n=152) ALEX	Crizotinib (n=151) ALEX	Difference % (95 % CI)
Number of adverse events, n	[redacted]	[redacted]		NF	NF	
Number and proportion of patients with ≥1 adverse events, n (%)	149 (100%)	140 (99%)	1% (NA)	147 (97%)	147 (97%)	0% (NA)
Number of serious adverse events*, n	NF	NF		NF	NF	
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	65 (44%)	45 (32%)	12% (NA)	59 (39%)	48 (32%)	7% (NA)
Number of CTCAE grade ≥ 3 events, n						
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	129 (86%)	88 (62%)	24% (NA)	79 (52%)	85 (56%)	4% (NA)
Number of adverse reactions, n	[redacted]	[redacted]		NF	NF	
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	145 (97%)	133 (94%)	3% (NA)	123 (81%)	134 (89%)	8% (NA)
Number and proportion of patients who had a dose reduction, n (%)	34 (23%)	21 (15%)	8% (NA)	31 (20%)	30 (20%)	0%
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	75 (50%)	135 (92%)	42% (NA)	99 (65%)	138 (91.4%)	26%
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	16 (11%)	15 (11%)	0%(NA)	22 (14.5%)	22 (14.5%)	0%

Serious adverse reactions were reported in 7.4% of patients receiving lorlatinib (1). The most frequent serious adverse drug reactions were cognitive effects and pneumonia (1). The most common serious adverse reactions occurring in at least 2 patients in patients treated with alectinib are pneumonia, pneumonitis, ALAT increase and pulmonary embolism (35).

The frequency of all SAEs with frequency of ≥ 5% recorded in the studies are listed in Table 25 below. For CROWN the listed SAEs are from latest 60-month analysis (35). For ALEX the listed SAEs are from the EMA assessment report 2017 and only SAEs occurring in at least 2 patients are listed and none were more than 5% (53). It has not been possible to identify later SAE data for ALEX. Number of patients with SAEs with alectinib and crizotinib are from the updated analysis of ALEX with 48,2 months follow-up (16).

Table 25 Serious adverse events, ITT population (60 months for lorlatinib (17, 35) and 48.2 months for alectinib (16))

Adverse events	Lorlatinib (N=149)		Crizotinib (N=142)		Alectinib (N=152)		Crizotinib (N=151)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Serious adverse event, n (%)	65 (43.6)		45 (31.7)		59 (38.8)		48 (31.8)	
[redacted]								

Comparison between lorlatinib and brigatinib

The most common adverse reactions (≥ 25%) reported in patients treated with brigatinib at the recommended dosing regimen were increased aspartate aminotransferase (AST), increased creatinine phosphokinase (CPK), hyperglycaemia, increased lipase, hyperinsulinemia, diarrhoea, increased alanine aminotransferase (ALT), increased amylase, anaemia, nausea, fatigue, hypophosphatemia, decreased lymphocyte count, cough, increased alkaline phosphatase, rash, increased Activated Partial Thromboplastin Clotting Time (APTT), myalgia, headache, hypertension, decreased white blood cell count, dyspnoea, and vomiting. (25). In brigatinib SmPC special warnings and precautions are described for pulmonary adverse reactions, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, elevations of pancreatic enzymes, hepatotoxicity, hyperglycemia, drug- drug interactions, photosensitivity, fertility, lactose and sodium.

ALTA-1L trial reported a safety summary in final analysis with 40.4 months follow-up (19) In ALTA-1L sign and symptoms of progression of the underlying disease were also

collected as AEs and could lead to a higher number of AEs reported for brigatinib. Median duration of assigned treatment in ALTA-1L at final analysis were 34.9 (0.1-52.4) months with brigatinib versus 9.3 (0.1-51.5) months with crizotinib (19).

The most common grade ≥ 3 adverse events in the ALTA-1L study in treatment with brigatinib were increased blood creatine phosphokinase (26%), lipase increased (15%), hypertension (14%) and amylase increased (6%) (21).

The number and proportion of patients who discontinue treatment due to adverse events of all causalities in ALTA-1L are 18 patients (13%) treated with brigatinib and 12 patients (9%) treated with crizotinib. (19) Number and proportion of grade 3-4 AEs of all causalities in ALTA-1L are for brigatinib 95 (70%) and for crizotinib 77 patients (56%).

The safety population consisting of patients with advanced ALK positive NSCLC patients from CROWN and ALTA-1L are listed below, Table 26. It's not been possible to find total number of adverse events with alectinib. Results show a few more patients with grade 3-4 AEs in lorlatinib arm than brigatinib arm, but longer treatment length in CROWN could result in more events being reported and hence result in a difference. For brigatinib 44% of patients had dose reduction, and for lorlatinib it was 23%, indicating that more adverse events were manageable without dose reductions for lorlatinib. Less lorlatinib patients had stopped treatment at 60 months versus brigatinib at 40 months, because of longer PFS benefit.

Table 26 Overview of safety events. ITT population (Follow-up time: 60 months for lorlatinib (17) (35) and 40.4 months for brigatinib (19)).

	Lorlatinib (N=149) (CROWN)	Crizotinib (N=142) (CROWN)	Difference, % (95 % CI)	Brigatinib (n=136) (ALTA-1L)	Crizotinib (n=137) (ALTA-1L)	Difference % (95 % CI)
Number of adverse events, n	[redacted]	[redacted]		NF	NF	
Number and proportion of patients with ≥1 adverse events, n (%)	149 (100%)	140 (99%)	1% (NA)	136 (100%)	137 (100%)	0% (NA) (9)
Number of serious adverse events*, n	NF	NF		NF	NF	
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	65 (44%)	45 (32%)	12% (NA)	NR	NR	NR
Number of CTCAE grade ≥ 3 events, n	NF	NF		NF	NF	
Number and proportion of patients	129	88	24% (NA)	106	88	14% (NA)

with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	(86%)	(62%)		(78%)	(64%)	
Number of adverse reactions, n	[redacted]	[redacted]		NF	NF	
Number and proportion of patients with ≥ 1 adverse reaction, n (%)	145 (97%)	133 (94%)	3% (NA)	0	0	NA
Number and proportion of patients who had a dose reduction, n (%)	34 (23%)	21 (15%)	8% (NA)	60 (44%)	34 (25%)	19% NA)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	75 (50%)	135 (92%)	42% (NA)	78 (58%)	121 (88%)	30%(NA)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	16 (11%)	15 (11%)	0% (NA)	18 (13%)	12 (9%)	4%

The frequency of all serious adverse events (SAEs) with a frequency of ≥ 5% recorded in the studies are listed in Table 27 below. For CROWN SAEs from latest 60-month analysis are listed (35). For ALTA-1L data from EMA assessment report 2020 is used for event terms (54) with a median follow-up of 24.9 month (0-34.1) for brigatinib and 15.2 (0.1-36.0) months for crizotinib. It has not been possible to identify later SAE data for ALTA-1L. Number of patients with SAEs with brigatinib and crizotinib are from the final result analysis of ALTA-1L (19).

Data for ALTA-1L treatment-emergent SAEs are from the second interim analysis, June 2019 as listed in Table 72 in the EMA assessment report for brigatinib (54).

Table 27 Serious adverse events (60 months follow-up for lorlatinib (35) and 24.9 months for brigatinib(19)).

Adverse events	Lorlatinib (N=149)		Crizotinib (N=142)		Brigatinib (N=137)		Crizotinib (N=138)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events

Serious Adverse event, n (%)	65 (43.6)	45 (31.7)	45 (33.1)	51 (37.2)
[redacted]	[redacted]	[redacted]	6 (4.4)	5 (3.6)

The adverse event profile of lorlatinib differs from other ALK inhibitors as hypercholesterolemia and hypertriglyceridemia are mostly reported together with adverse events related to the central nervous system. Among 237 treatment emergent hyperlipidaemia events in the lorlatinib group, 68% required concurrent medication only, 22% required no intervention and 9% required dose interruption or dose reduction and concurrent medication (32).

Cognitive side effects and mood effects of grade 3-4 were experienced by 3% and 1% of patients in the lorlatinib arm in the CROWN study, respectively (17). In a post hoc analysis of 103 treatment emergent CNS adverse events 59% didn't require intervention, 15% required dose reduction only and 14% required concurrent medication only (32). According to a Danish clinical expert these adverse events are manageable and well known based on experience with lorlatinib second-line treatment. Only two patients stopped treatment due to CNS side effects in CROWN (17). As mentioned by DMC in a previous assessment, a published retrospective report has shown that psychiatric adverse reactions also are related to the other ALK inhibitors brigatinib, alectinib, ceritinib and crizotinib. The incidence of these was higher for lorlatinib (2.8%) than for the other ALK TKIs (1.2% for brigatinib, 0.7% for alectinib, 0.6% for ceritinib and 0.3% for crizotinib, indicating increased CNS penetration of blood-brain barrier (55).

Comparative analysis

Comparative safety was analyzed for grade 3/4 adverse events (Figure 35) and discontinuation due to adverse events (Figure 36). The methods used for the NMA are described in Appendix C.

Grade 3/4 adverse events were more common with lorlatinib than with any of the other treatments; however, the difference was only statistically significant for alectinib and crizotinib. For discontinuations due to adverse events, lorlatinib was numerically superior to brigatinib; however, the difference was not statistically significant. Rates of discontinuations were very similar between lorlatinib, alectinib, and crizotinib.

Figure 35 Results of the NMA of grade 3/4 adverse events

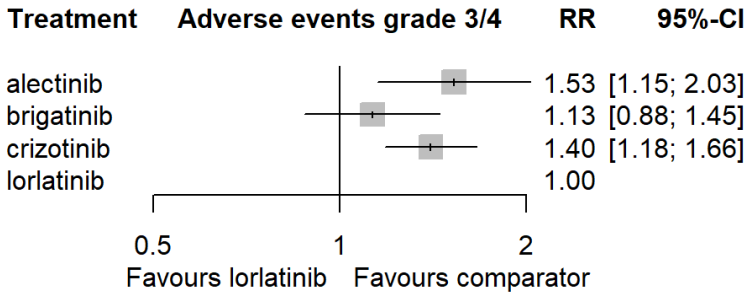
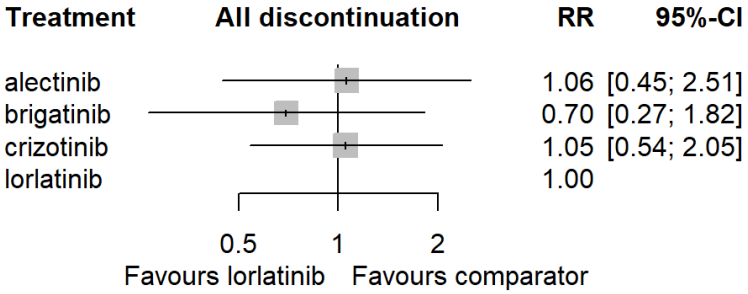


Figure 36 Results of the NMA of discontinuation due to adverse events



AE used in the health economic model

The model includes grade 3 or higher all-cause AEs observed in at least 5% of patients in the lorlatinib arm of CROWN, in the alectinib arm of ALEX, or in the brigatinib arm of ALTA-1L as reported in TA670. Peripheral neuropathy, cognitive effects and mood effects grade 3 or higher were also included, despite less than 5% had these event. However, these were thought to be events of interest. This is a conservative assumption against lorlatinib as we have not included relevant AEs of special interest for alectinib and brigatinib. Adverse event proportions are presented in Table 28.

Rather than applying AE management costs as a one-off, the model uses average treatment exposure to calculate yearly AE rates, to avoid biasing in favour of treatments with a shorter trial follow-up. The patient numbers and treatment exposure for each treatment are presented in Table 29.

Table 28 Adverse events used in the health economic model

Adverse events	Lorlatinib	Alectinib	Brigatinib		
	Frequency used in economic model			Source	Justification
Adverse event, n (%)					
Hypertriglyceridemia	24.83%	0.00%	0.00%	For lorlatinib: CROWN. For alectinib: ALEX. For brigatinib: ALTA-1L as reported in TA670.	The model includes Grade 3 or higher all-cause AEs observed in at least 5% of patients in the lorlatinib or crizotinib arms of CROWN, in the alectinib arm of ALEX, or in the brigatinib arm of ALTA-1L as reported in TA670.
Weight increased	22.82%	0.00%	0.00%		
Increased lipase level	6.04%	0.00%	12.50%		
Hypercholesterolemia	21.48%	0.00%	0.00%		
Aspartate amino-transferase increased	2.01%	5.26%	2.21%		
Gamma glutamy-ltransferase increased	6.04%	0.00%	0.74%		
Hypertension	12.08%	0.00%	7.35%		
Anaemia	4.03%	5.92%	1.47%		
Amylase increased	0.00%	0.00%	5.88%		

Adverse events	Lorlatinib	Alectinib	Brigatinib
Neutropenia	0.67%	0.00%	0.00%
Blood creatine phosphokinase increased	2.68%	3.29%	23.53%
Neutrophil count decreased	0.00%	0.00%	0.00%
Peripheral neuropathy	1.34%	0.00%	0.00%
Cognitive effects	3.36%	0.00%	0.00%
Mood effects	1.34%	0.00%	0.00%

Table 29 Patient numbers and treatment exposure

Treatment	N	Treatment exposure	Source	Notes
Lorlatinib	149	3.99 years	CROWN 2023 (17)	Mean duration, calculated using ToT KM
Alectinib	152	2.34 years	ALEX 2020 (16)	Median treatment duration, 28.1 months
Brigatinib	136	2.03 years	TA670 (ALTA-1L) (6)	Median duration of exposure, 24.3 months

Abbreviations: KM, Kaplan–Meier; N, number of patients in trial; ToT, time on treatment.

9.2 Safety data from external literature applied in the health economic model

Not applicable.

Table 30 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)	Comparator (N=x)	Difference, % (95 % CI)
Adverse event, n	Not applicable		

10. Documentation of health-related quality of life (HRQoL)

In the CROWN trial, patient-reported outcomes were assessed using the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L. Only EQ-5D-5L data will be presented here, while information on

EORTC QLQ-C30 and EORTC QLQ-LC13 is summarized in Appendix F. Base case utility values for the health economic model are presented in Table 40 Adverse event duration estimatation

Adverse event	Duration (days)	Source
Hypertriglyceridemia	714	CROWN
Weight increased	778	CROWN
Hypercholesterolemia	770.5	CROWN
Neutropenia	30	Nafees et al. (41)
Increased lipase, Aspartate aminotransferase increased, Gamma-glutamyl transferase increased, Hypertension, Anaemia, Amylase increased, Blood creatine phosphokinase increased, and Neutrophil count decreased	30	Assumed same as neutropenia
Peripheral neuropathy	380	CROWN
Cognitive effects	221	CROWN
Mood effects	218	CROWN

Table 41.

Table 31 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	CROWN(22, 33, 56)	Utilities
EORTC QLQ-C30	CROWN(33, 56)	Clinical effect. Detailed in Appendix F. Not presented here in section 10.
EORTC QLQ-LC13	CROWN(33, 56)	

10.1.1 Study design and measuring instrument

The CROWN trial study design is described in detail in section 6.1.1. EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-LC13 was collected in the trial. EQ-5D-5L was collected as to explore generic utility, while EORTC QLQ-C30 and EORTC QLQ-LC13 were collected with disease-specific utility in mind. HRQL data are presented up to the September 2021 data cut-off as per CROWN protocol, HRQL data was not collected after the 3-year follow-up.

10.1.2 Data collection

Utility data was collected on Day 1 of each cycle, at the end of treatment, and at post-treatment follow-up in CROWN. Completion rates for the EORTC QLQ-C30 and QLQ-LC13 were ≥96% through Cycle 18, with similar completion rates for the EQ-5D-5L. Unscheduled visits were excluded from the analysis. The last measurement prior to or on the day of first dose of study treatment was used as the baseline measurement. If no

observations meet these criteria, then baseline is considered missing. Data was evaluated as observed, and no imputation method for missing values will be used. It was not possible to describe and compare the patients who had missing values and their characteristics with the population who did not have missing vales. Relevant data collection time points are reported in Table 32 with missing observations, number and percentage missing since randomization, and number and percentage completed.

Table 32 Pattern of missing data and completion EQ-5D-5L data for lorlatinib

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 33 Pattern of missing data and completion EQ-5D-5L data for crizotinib

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.1.3 HRQoL results

Table 34 provides results at baseline and at relevant data collection timepoints for EQ-VAS, while EQ-5D-5L is presented in Table 35. Baseline, cycle 2 and every 8th cycle was presented in the tables. Plots with change from baseline are available for EQ-VAS and EQ-5D-5L index scores in Figure 37 and Figure 38. The graphs were not available using Danish preference weights.

Table 34 HRQoL EQ-VAS summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 35 HRQoL EQ-5D-5L summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 37

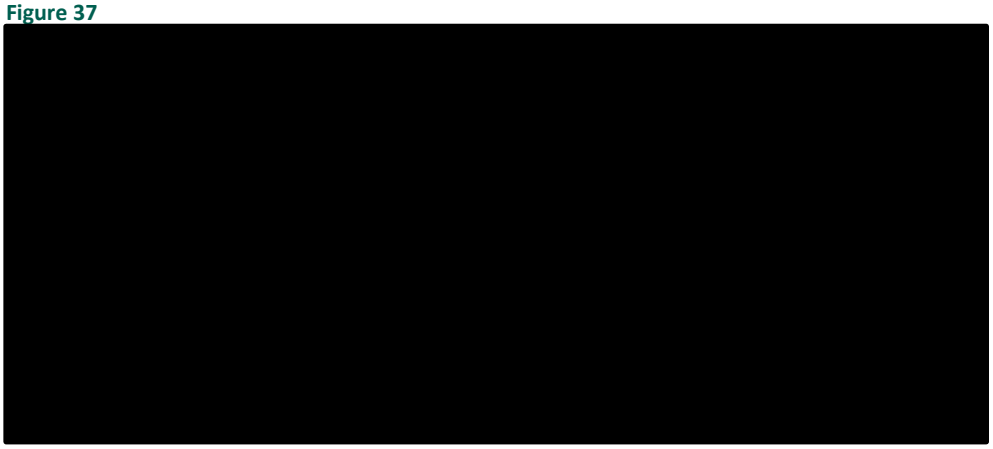
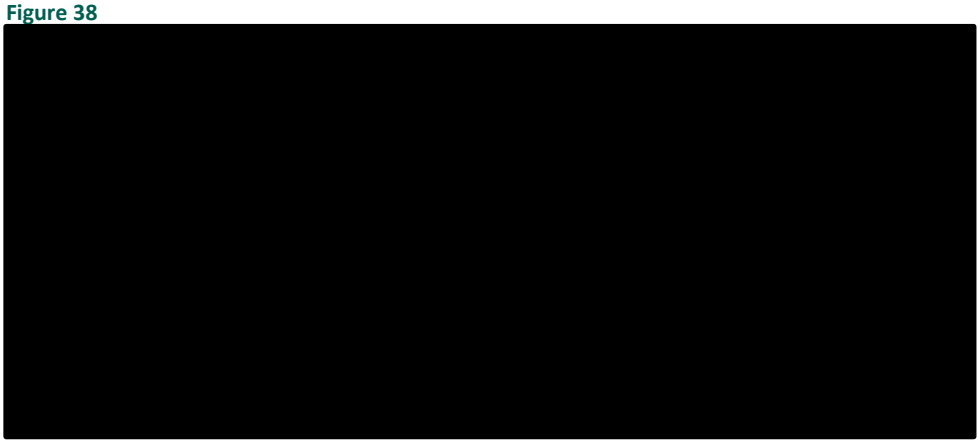


Figure 38



10.2 Health state utility values (HSUVs) used in the health economic model

The CROWN EQ-5D data indicates that patients have a slight decrease in utility after progression, with the greatest difference between pre- and post-progression seen in the crizotinib arm. A substantial proportion of records in CROWN occur pre-progression, while post-progression HRQL data for patients who received lorlatinib were collected on a small number of patients (n=36). Of the post-progression utilities, most were close to the date of progression, indicating that the post-progression utility in the trial may not be reflective of the true value of post-progression utility over time after the progression

event as they could not capture deterioration in HRQL. Due to these limitations, the utilities applied in the model were a mix of the utility values derived from CROWN and literature-based utilities identified in the NICE submission for brigatinib in 1st line ALK-positive NSCLC patients. The impact of this was explored in scenario analysis. For good measures, all CROWN-derived health state utility values are presented in this section.

Model base case health state utility values are presented in Table 40 Adverse event duration estimatation

Adverse event	Duration (days)	Source
Hypertriglyceridemia	714	CROWN
Weight increased	778	CROWN
Hypercholesterolemia	770.5	CROWN
Neutropenia	30	Nafees et al. (41)
Increased lipase, Aspartate aminotransferase increased, Gamma-glutamyl transferase increased, Hypertension, Anaemia, Amylase increased, Blood creatine phosphokinase increased, and Neutrophil count decreased	30	Assumed same as neutropenia
Peripheral neuropathy	380	CROWN
Cognitive effects	221	CROWN
Mood effects	218	CROWN

Table 41 (Section 10.3.4.)

10.2.1 HSUV calculation

EQ-5D-5L from the CROWN trial was used to derive a set of health state utility values, which could potentially be used in the health-economic model. The derivation of Danish specific utility scores from the EQ-5D-5L questionnaire data recorded in CROWN was based on the value set developed by Jensen et al.(57)

Stepwise backward variable selection was used to determine which patient demographics and disease characteristics should be included in a final regression model to be used in the economic model. Stepwise backward variable selection was chosen to avoid unnecessary complexity in the models. A final mixed effects model was selected via the stepwise regression. Using a backwards selection algorithm, the least-contributing predictors were removed in iteration until a final model was found with all predictors being statistically significant. Variables and values are presented in Table 36.

Table 36 Final mixed effects models with included variables

Parameter	Value
[redacted]	[redacted]

[redacted]

Furthermore, HSUVs were age-adjusted in accordance with the DMC guidelines. This was done using the Wittrup-Jensen et al., publication.

10.2.1.1 Mapping

No mapping was necessary for the CROWN utility data, as the data was collected as EQ-5D-5L.

10.2.2 Disutility calculation

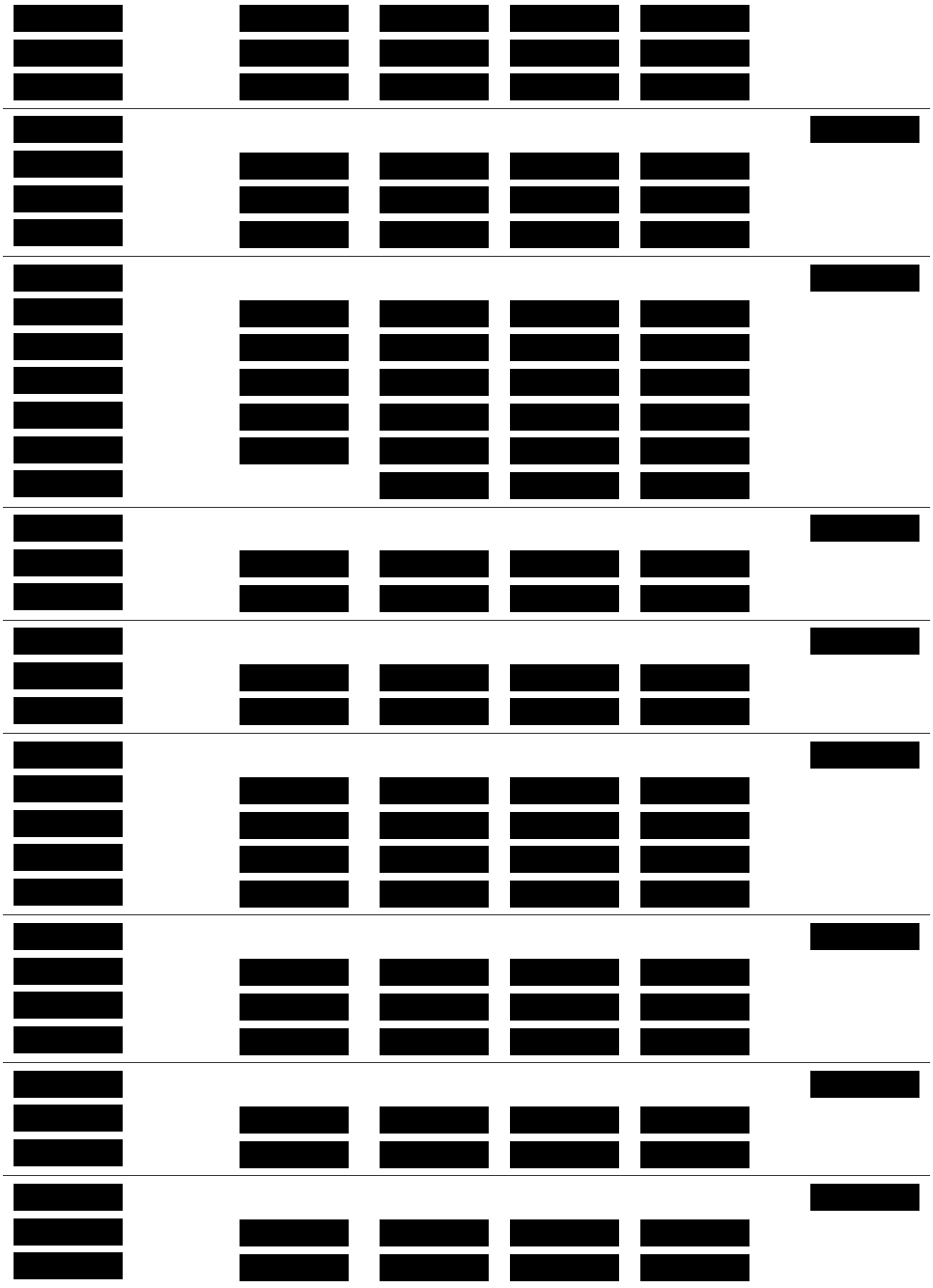
Disutilities were applied in the model to account for the impact of a Grade 3/4 AE on HRQoL. Disutilities were derived from the literature, and hence these are presented in section 10.3.

10.2.3 HSUV results

The results of the univariate mixed effects models and naïve means are presented in Table 37 with the number of patients and observations for each variable.

Table 37 Univariate naïve mean utility and mixed effects least square mean utility score results from CROWN - Denmark

Category	N patients	N records	Naïve mean (SD)	LS mean (95% CI)	p-value
[redacted]					

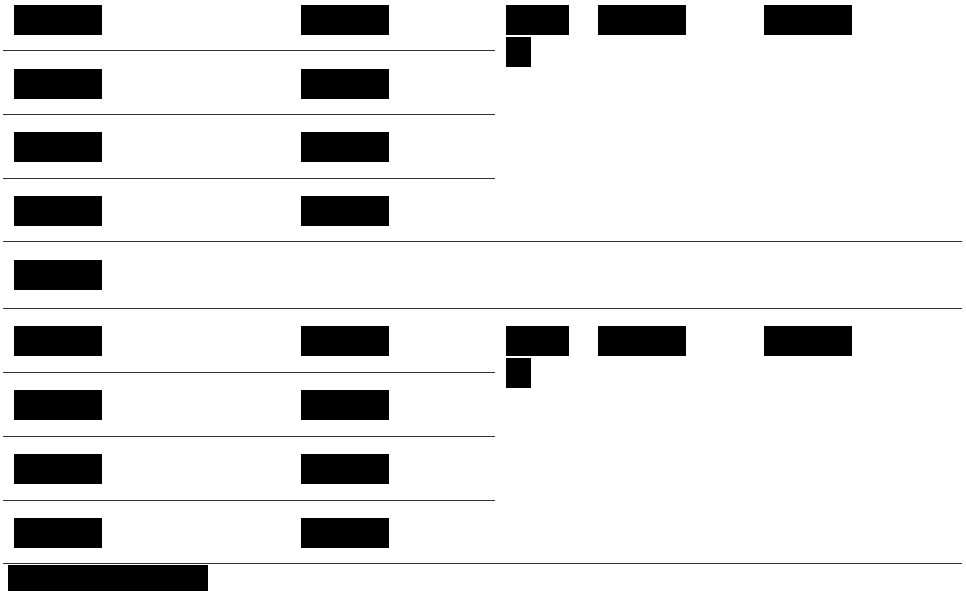


Abbreviations: CI, confidence interval; LS, least-squares; SD, standard deviation.

The health state utility values are presented in Table 38. Only the PFS (on treatment) and PFS (off treatment) health states were applied in the base case of the health economic model, due to the limitations in the CROWN utility data. This is further described in section 10.3.

Table 38 Overview of health state utility values derived from the CROWN trial

	Results [95% CI]	Instrument	Tariff (value set) used	Comments



10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Due to the limitations mentioned in section 10.2, alternative utility sources were considered. Based on the utility SLR, health state utility values and adverse event disutilities were derived from the NICE appraisal of brigatinib TA670 (6). Remaining disutilities were derived from Nafees et al (41).

10.3.1 Study design

The phase 3 ALTA-1L study design is described in more detail in section 6.2.2. A secondary objective of the ALTA-1 L study was to compare HRQOL in ALK-positive NSCLC patients treated with brigatinib or crizotinib. The PROs evaluated included the EORTC QLQ-C30 version 3 (v3) and the EORTC QLQ-LC13. A summary of the data collection and HRQoL results are presented in the subsections below, while the details were described in publication by Campelo et al., 2021.(58)

10.3.2 Data collection

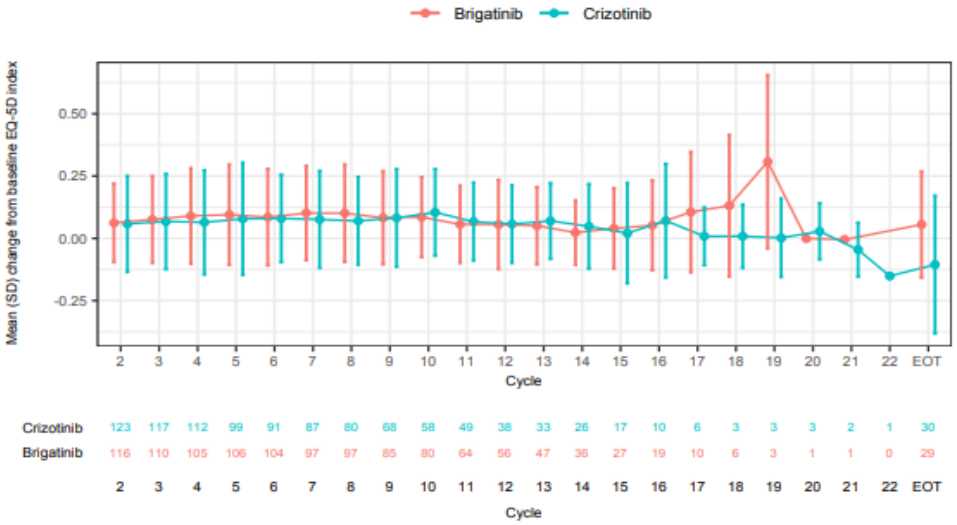
The EORTC measures were administered using pen-and-paper approaches only; measures were completed independently at study sites prior to any medical testing or discussions with the treating physicians. The measures were administered at screening, day 1 of each 4-week cycle, end of treatment, and 30 days after the last dose of study drug. The prespecified study objectives in the study protocol were to examine time to worsening, change from baseline, and duration of improvement in QoL and other functional and symptom scales assessed with the EORTC QLQ-C30, and time to worsening and duration of improvement in core symptoms of lung cancer (dyspnea, cough, and chest pain), assessed with the EORTC QLQ-LC13.(58)

10.3.3 HRQoL Results

Data were available from 131/137 (95.6%) patients in the brigatinib arm and from 131/138 (94.9%) patients in the crizotinib arm. Based on the overall least squares mean difference in change from baseline across different time points using linear mixed models, brigatinib showed numerically greater improvements compared with crizotinib in scores for HRQoL and most functional and symptom scales with between-arm differences of ≥5 points in favour of the brigatinib arm for appetite loss and constipation. In the pattern mixture models, conducted as a sensitivity analysis for missing data, the treatment differences across the treatment groups were not statistically significant or clinically meaningful (58).

The utilities were derived from the EORTC QLQ C30 completed by patients enrolled in the ALTA-1L clinical trial. The algorithm published in Longworth et al. was used to map the EORTC QLQ C30 values to EQ-5D-3L. Mean change from baseline results are presented in Figure 39 (6).

Figure 39 Change from Baseline Treatment Cycle EQ-5D in ALTA-1L



Reference: ALTA-1L identified in NICE techinical appraisal 670(6)

10.3.4 HSUV and disutility results

A mixed-effects model was fitted to the data which accounts for the longitudinal nature of the data, whereby patients have multiple utility scores, measured over time. Health state utility values from the TA670(6) are presented in Table 39 along with the disutilities for adverse events. Nafees et al.(41) and Roughley et al.(59) was not described in detail, as these were only used to model disutilities. Excluding disutilities was explored in scenario analysis. Nafees et al.(41) was used to model AE disutilities, while Roughley et al.(59) was used to model the disutility of CNS progression. In Roughley et al.(59), EQ-5D was found to be significantly lower for patients with brain metastases (mean 0.52, n=29) compared with contralateral lung metastases (0.69, n=111, p=0.0196). This was used to calculate the CNS-progression multiplier of 75.36%. Where possible, the duration of AEs is informed by evidence from CROWN. Neutropenia AE duration is informed by Nafees et

al. 2017. (41) For the rest of the AEs, it is assumed that the duration is equal to neutropenia duration. Durations of disutilities are presented in Table 40.

Table 39 Overview of literature-based health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
PFS	0.793 [0.774-0.812]	EORTC QLQ C30 mapped to EQ-5D-3L.	UK	Derived from the EORTC QLQ C30 completed by patients enrolled in the ALTA-1L clinical trial. TA670(6)
Progressed disease	0.624 [0.582-0.665]	EORTC QLQ C30 mapped to EQ-5D-3L.	UK	Derived from the EORTC QLQ C30 completed by patients enrolled in the ALTA-1L clinical trial. TA670(6)
Disutilities				
Hypertriglyceridemia, Weight increased, Increased lipase level, Hyper-cholesterolemia, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hypertension, Anaemia, Amylase increased, Blood creatine phosphokinase increased	-0.037 [-0.046—0.029]	EORTC QLQ C30 mapped to EQ-5D-3L.	UK	ALTA-1L HRQL analysis. The impact of a Grade 3/4 AE on HRQoL is captured within the HRQoL analysis – a decrement of -0.037 was multiplied by the probability of a Grade 3/4 AE per cycle. It was assumed that each AE would last 28 days. TA670(6)
Neutropenia, Peripheral neuropathy, Cognitive effects, Mood effects	-0.090 [NR]	EQ-5D	UK	Neutropenia disutility was identified in Nafees et al.(41) Peripheral neuropathy, cognitive effects, and mood effects was assumed the same as neutropenia to reflect the relative severity of these events in the absence of identified literature.
CNS-progression intercurrent event	Utility multiplier of 75.36%	EQ-5D	Not reported	Used to estimate the effect of CNS-progression on utility. Roughley et al. 2014 (59)

Table 40 Adverse event duration estimatation

Adverse event	Duration (days)	Source

Hypertriglyceridemia	714	CROWN
Weight increased	778	CROWN
Hypercholesterolemia	770.5	CROWN
Neutropenia	30	Nafees et al. (41)
Increased lipase, Aspartate aminotransferase increased, Gamma-glutamyl transferase increased, Hypertension, Anaemia, Amylase increased, Blood creatine phosphokinase increased, and Neutrophil count decreased	30	Assumed same as neutropenia
Peripheral neuropathy	380	CROWN
Cognitive effects	221	CROWN
Mood effects	218	CROWN

Table 41 Overview of health state utility values used in the model base case

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
PFS (on treatment) – lorlatinib	[redacted]	EQ-5D-5L	DK	Estimated based on the regression presented in section 10.2.1.
PFS (off treatment) – lorlatinib	[redacted]			
Progression-free – alectinib and brigatinib (on and off treatment)	0.793 [0.774-0.812]	EORTC QLQ C30 mapped to EQ-5D-3L.	UK	Derived from EORTC QLQ C30 completed by patients in ALTA-1L clinical trial - TA670 (6)
Progressed disease	0.624 [0.582-0.665]			
Adverse event disutilities		See Table 39		
CNS-progression disutilities		See Table 39		

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Drug costs were sourced from medicinpriser.dk. The available packages for lorlatinib, alectinib and brigatinib are presented in Table 42.

Table 42 Drug packages with AIP prices

Treatment	Form	Unit	Pack size	Pack price (AIP)
Lorlatinib	Tablets	25 mg	90	DKK 35,970.68
	Tablets	100 mg	30	DKK 35,970.68
Alectinib	Capsules	150 mg	224	DKK 33,269.72
Brigatinib	Tablets	Starter pack	28	DKK 35,210.29
	Tablets	30 mg	28	DKK 8,731.74
	Tablets	90 mg	28	DKK 25,913.06
	Tablets	180 mg	28	DKK 34,461.26

In the cases where more packages of the medicine are available, the pack size with the lowest cost per mg was selected. Drug costs are incurred at the beginning of each cycle so differences between pack size (drug cycle) and model cycle length produce drug 'wastage' which is included in modelling. For lorlatinib the pack size aligns with cycle length but for alectinib and brigatinib the pack size is equivalent to 28 days and so any pill wastage is costed. The dosing of medicines is presented in Table 43.

Table 43 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Lorlatinib	100 mg	[redacted]	Once daily	N/a
Alectinib	600 mg	95.6% (44)	Twice daily	
Brigatinib (cycle 1)	Starter pack	85.5% (6)	Once daily	
Brigatinib (cycle 2+)	180 mg			

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

As both lorlatinib, alectinib, and brigatinib was administered orally, no administration costs were incurred for either of the comparators in 1st line treatment. Some of the subsequent treatment regimens are administrated intravenously, a unit cost for these administrations were estimated based on the DRG-tariff system (Table 44).

Table 44 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference

Oral administration	Daily / twice daily	0	N/a	Assumption
Intravenously administration	Every three weeks	1,311	04MA98	DRG 2024. A: DC349M Procedure: BWAA60

11.4 Disease management costs

The unit costs for disease management and frequencies are presented in Table 45. The frequency of each resource use was divided into progression-free and progressed patients. Resource use for disease management was based on the TA670 (6) for brigatinib, excluding additional general practitioner visits and cancer nurse visits. This was found to align broadly with the brigatinib DMC assessment for 1st line treatment of advanced ALK-positive NSCLC patients (60).

As mentioned in section 8.4.1, CNS-progression was modelled as an intercurrent event separately. Therefore, a one-off cost is applied for the additional costs associated with CNS progression for each intercurrent evet, The CNS progression resource use was sourced from the unpublished Le et al. 2023 (45). Use of the Le et al. 2023 (45) resource use is discussed in section J.1.3. Details on resource use and DRG 2024 tariffs applied to calculate the CNS progression one-off cost are presented separately in Appendix L. The intercurrent event one-off CNS progression cost amounted to DKK 146,186.

Table 45 Disease management costs used in the model

Activity	Frequency	Unit cost	DRG code	Reference
Oncology	PF: Once per months PD: Once per months	DKK 1,311	04MA98	DRG 2024
CT scan	PF: Every two months PD: Every six weeks	DKK 2,582	30PR06	DRG 2024
X-ray	PF: Every three months PD: Every two months	DKK 1,697	30PR18	DRG 2024
MRI	PF: Every five months PD: Every two months	DKK 2,511	30PR03	DRG 2024
ECG	PF: Once per months PD: N/a	DKK 2,026	05PR04	DRG 2024
CNS progression	Based on event rates	DKK 146,186	See Appendix L	

Abbreviations: PD, progressed disease; PF, progression free.

11.5 Costs associated with management of adverse events

To account for costs related to management of AEs, unit costs were applied to the yearly AE rate to calculate annual AE costs, before these were combined with life years in each

cycle of the model. This was preferred over applying AE management costs as a one-off, which could lead to bias in favour of treatments with a shorter trial follow-up. The frequencies of the adverse events included as model input was presented in section 9, while the unit costs are presented in Table 46.

Table 46 Cost associated with management of adverse events

	DRG code	Unit cost/ DRG tariff
Hypertriglyceridemia	10MA98 MDC10 1-dagsgruppe, pat. Mindst 7 år, A: (DE780C) Hyperlipidæmi Gruppe A	DKK 1,847
Weight increased	10MA98 MDC10 1-dagsgruppe, pat. Mindst 7 år, A: (DR635) Abnorm Vægtstigning,	DKK 1,847
Increased lipase level	07MA98 MDC07 1-dagsgruppe, pat. Mindst 7 år, A: (DR748D) Abnorm Serumlipase	DKK 1,947
Hypercholesterolemia	10MA98 MDC10 1-dagsgruppe, pat. Mindst 7 år, A: (DE780C) Hyperlipidæmi Gruppe A	DKK 1,847
Aspartate amino-transferase increased	07MA98 MDC07 1-dagsgruppe, pat. Mindst 7 år, A: (DK769) Leversygdom UNS	DKK 1,947
Gamma glutamyl-transferase increased	07MA98 MDC07 1-dagsgruppe, pat. Mindst 7 år, A: (DK769) Leversygdom UNS	DKK 1,847
Hypertension	05MA98 MDC05 1-dagsgruppe, pat. Mindst 7 år, A: (DI158) Anden form for sekundær hypertension	DKK 1,183
Anaemia	16MA98 MDC16 1-dagsgruppe, pat. Mindst 7 år, A: (DD611) Aplastisk anæmi forårsaget af lægemiddel	DKK 2,111
Amylase increased	07MA98 MDC07 1-dagsgruppe, pat. Mindst 7 år, A: (DR748A) Abnorm Serumamylase	DKK 1,947
Neutropenia	16MA98 MDC16 1-dagsgruppe, pat. Mindst 7 år, A: (DD709) Neutropeni UNS	DKK 2,111
Blood creatine phos-phokinase increased	10MA98 MDC10 1-dagsgruppe, pat. Mindst 7 år, A: (DE883) Forstyrrelser I fosforomsætningen og fosfataser	DKK 1,847
Neutrophil count decreased	16MA98 MDC16 1-dagsgruppe, pat. Mindst 7 år, A: (DD709) Neutropeni UNS	DKK 2,111
Peripheral neuropathy	01MA98 MDC01 1-dagsgruppe, pat. Mindst 7 år, A: (DG620) Polyneuropati forårsaget af lægemiddel	DKK 1,947
Cognitive effects	21MA98 MDC21 1-dagsgruppe, pat. Mindst 7 år, A: (DT983D8) Følgetilstand m. kognitiv forstyrrelse efter kræftbehandling	DKK 1,684
Mood effects	19MA98 MDC19 1-dagsgruppe, pat mindst 7 år, A: (DF339) Periodisk depression UNS	DKK 2,555

11.6 Subsequent treatment costs

Subsequent treatments are included in the model to capture the cost related to treatment post progression. In the model, costs of subsequent treatments following progression and cessation of initial treatment are applied as a one-off cost at the point of progression as a simplifying assumption. The proportion of patients incurring the cost of subsequent treatments in each cycle was estimated as the proportion of patients who transitioned out of the on-treatment health state in each model cycle without dying. This was estimated using the proportion of INV assessed PFS events that were deaths from the October 2023 data cut-off of the CROWN trial for lorlatinib (16.36%) and crizotinib (4.35%), and assuming the same proportion as crizotinib for alectinib and brigatinib (17). The proportion of INV assessed PFS events that were deaths was assumed to be constant over time. The inverse of this proportion was applied to the proportion of patients leaving the on-treatment health state in each cycle to estimate the proportion of patients whose ToT events were discontinuation.

Chemotherapy (pemetrexed + cisplatin) was dosed as per SmPC recommended dosing (61). An IV administration cost of DKK 1,311 (DRG: 04MA98) was added for chemotherapy administrations. Vial sharing was assumed to be allowed for the chemotherapy agents, pemetrexed and cisplatin. Alectinib, brigatinib and lorlatinib was dosed in the same manner as for 1st line treatment found in section 11.1. As second-line RDI data was not identified for all relevant subsequent treatments, 100% RDI was applied for all subsequent treatments as a conservative assumption. Duration of treatment was based on data from the CROWN clinical study report stratified by ALK-TKIs [redacted] and non-ALK-TKIs [redacted].

Subsequent treatment distributions for lorlatinib were applied based on CROWN trial data(35). Patients treated with lorlatinib who continued on lorlatinib in second-line following progression was excluded. Patients that were treated with immunotherapy and VEGF-R was also excluded, as this was not found relevant Danish clinical practice. Subsequent treatment distributions following first-line treatment with alectinib or brigatinib estimation is based on the current recommendation of lorlatinib as second-line treatment. Consequently, 95% of the patients eligible for second-line were expected to be treated with lorlatinib. The distributions are presented in Table 48. Distribution solely relying on clinical data was explored in scenario analysis.

Table 47 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Alectinib	100 mg	100%	Once daily	N/a
Crizotinib	250 mg	100%	Twice daily	N/a
Ceritinib	450 mg	100%	Once daily	N/a
Brigatinib	600 mg	100%	Twice daily	N/a
Lorlatinib	Starter pack	100%	Once daily	N/a

Pemetrexed	500 mg/m^2	100%		Once every 21 days	Yes
Cisplatin	75 mg/m^2	100%		Once every 21 days	Yes

Table 48 Distribution of subsequent treatment following lorlatinib, alectinib or brigatinib

	First-line treatments		
Subsequent treatment	Lorlatinib	Alectinib	Brigatinib
Alectinib	[redacted]	0.00%	0.00%
Crizotinib	[redacted]	0.00%	0.00%
Ceritinib	[redacted]	0.00%	0.00%
Brigatinib	[redacted]	0.00%	0.00%
Lorlatinib	[redacted]	95.00%	95.00%
Chemotherapy	[redacted]	53.85%	53.85%

11.7 Patient costs

Hospital visits were estimated to last 3 hours, presented in Table 49. This was assumed to account for all activities during visits including blood tests and disease monitoring. Based on the unit cost catalogue, each patient hour was costed by DKK 203. In line with the estimated resource use, patients had one visit in the first model cycle (62). For the remaining cycles, patients were estimated to have 1.35 visits per model cycle pre-progression, while patients were estimated to have 2.95 visits per model cycle post progression. For each hospital visit, a transport cost of DKK 149.20 was applied based on the unit cost catalogue (DKK 3.73 per km for 40 km per visit) (62).

Table 49 Patient costs used in the model

Activity	Time spent
Hospital visit	3 hours

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

An overview of the base case including the central aspects are presented in Table 50.

Table 50 Base case overview

Feature	Description		
Comparators	Alectinib and brigatinib		
Type of model	Partitioned survival model with pseudo-transition state modelling for comparators.		
Time horizon	30 years (lifetime)		
Treatment line	1st line. Subsequent treatment costs included.		
Measurement and valuation of health effects	CROWN HRQoL was measured with EQ-5D-5L and Danish population weights were used to estimate health-state utility values. Crown health state utility values were only used for the lorlatinib progression-free health states. Remaining health state utility values were derived from literature.		
Costs included	Medicine costs, hospital costs, costs of adverse events, and patient costs.		
Dosage of medicine	Fixed doses informed by the SmPCs. RDI applied.		
Average time on treatment	Lorlatinib: 7.06 years, alectinib: 4.50 years, brigatinib: 4.25 years		
Parametric function for PFS	Lorlatinib: 36-months piecewise Weibull Crizotinib: Log-logistic		
Parametric function for OS	Lorlatinib: Weibull Crizotinib: Weibull		
Inclusion of waste	Only in 1st line treatment		
Average time in model health state		PFS (years)	OS (years)
	Lorlatinib	8.84	10.13
	Alectinib	4.50	7.58
	Brigatinib	4.25	7.38

12.1.1 Base case results

Base case results for the comparison of lorlatinib and alectinib is presented in Table 51 and lorlatinib versus brigatinib in Table 51. It should be noted that the majority of the lorlatinib QALY-gain comes from the progression-free health state.

Table 51 Base case results, lorlatinib vs. alectinib, discounted estimates

	Lorlatinib	Alectinib	Difference
Medicine costs	[redacted]	DKK 1,412,667	[redacted]
Medicine costs – co-administration	NA	NA	NA

Administration	DKK 0	DKK 0	DKK 0
Disease management costs	DKK 544,506	DKK 451,363	DKK 93,143
Costs associated with management of adverse events	DKK 2,827	DKK 448	DKK 2,379
Subsequent treatment costs	[redacted]	DKK 670,441	[redacted]
Patient costs	DKK 72,958	DKK 61,798	DKK 11,160
Palliative care costs	DKK 0	DKK 0	DKK 0
Total costs	[redacted]	[redacted]	[redacted]
Life years gained PFS	7.00	3.64	3.36
Life years gained OS	0.81	2.52	-1.71
Total life years	**7.82**	**6.16**	**1.65**
QALYs PFS*	[redacted]	[redacted]	[redacted]
QALYs PD*	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Incremental costs per life year gained	**DKK 494,185.88**
Incremental cost per QALY gained (ICER)	**DKK 355,645.07**

*QALY decrements included in health states

Table 52 Base case results, lorlatinib vs. brigatinib, discounted estimates

	Lorlatinib	Brigatinib	Difference
Medicine costs	[redacted]	DKK 1,368,621	[redacted]
Medicine costs – co-administration	NA	NA	NA
Administration	DKK 0	DKK 0	DKK 0
Disease management costs	DKK 544,506	DKK 473,879	DKK 70,626
Costs associated with management of adverse events	DKK 2,827	DKK 4,143	-DKK 1,316
Subsequent treatment costs	[redacted]	DKK 674,206	[redacted]
Patient costs	DKK 72,958	DKK 61,052	DKK 11,906
Palliative care costs	NA	NA	NA

Total costs	[redacted]	[redacted]	[redacted]
Life years gained PFS	7.00	3.52	3.48
Life years gained OS	0.81	2.55	-1.74
Total life years	**7.82**	**6.07**	**1.74**
QALYs PFS*	[redacted]	[redacted]	[redacted]
QALYs PD*	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Incremental costs per life year gained	**DKK 477,621.45**
Incremental cost per QALY gained (ICER)	**DKK 339,688.96**

*QALY decrements included in health states

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The results of deterministic one-way sensitivity analyses for the 10 most influential parameters are presented in Table 53 and Table 54. The results are also presented as tornado diagrams in Figure 40 and Figure 41. It is seen that the most influential parameters are related to the efficacy, which seems logical given the relatively few PFS and OS events despite the long follow-up time in the modelled data. It is seen that especially the OS shape creates an extreme scenario with very small QALY-decrements. Generally, most parameters seem to confirm the base case robustness. The robustness is confirmed by the scenario analyses presented in Table 55.

Table 53 One-way sensitivity analyses results versus alectinib

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA	Base case	[redacted]	[redacted]	355,645
OS: Lorlatinib - Weibull: shape	[redacted]	Explore most influential parameter uncertainty	[redacted]	[redacted]	[redacted]
PFS: Lorlatinib - Weibull: shape	[redacted]		[redacted]	[redacted]	[redacted]
OS: Lorlatinib - Weibull: scale	[redacted]		[redacted]	[redacted]	[redacted]

PFS: Lorlatinib - Weibull: scale	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR: Crizotinib vs. Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib – subs. treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - subs. treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS: Crizotinib - Log-logistic: shape	[redacted]	[redacted]	[redacted]	[redacted]
OS: Crizotinib - Weibull: shape	[redacted]	[redacted]	[redacted]	[redacted]
PFS: Crizotinib - Log-logistic: scale	[redacted]	[redacted]	[redacted]	[redacted]

Table 54 One-way sensitivity analyses results versus brigatinib

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA	Base case	[redacted]	[redacted]	339,689
OS: Lorlatinib - Weibull: shape	[redacted]	Explore most influential parameter uncertainty	[redacted]	[redacted]	[redacted]
PFS: Lorlatinib - Weibull: shape	[redacted]		[redacted]	[redacted]	[redacted]
OS: Lorlatinib - Weibull: scale	[redacted]		[redacted]	[redacted]	[redacted]
PFS: Lorlatinib - Weibull: scale	[redacted]		[redacted]	[redacted]	[redacted]
PFS HR: Crizotinib vs. Brigatinib	[redacted]		[redacted]	[redacted]	[redacted]
Lorlatinib - subsequent treatment duration (months)	[redacted]		[redacted]	[redacted]	[redacted]
Brigatinib - subsequent treatment % - Lorlatinib	[redacted]		[redacted]	[redacted]	[redacted]

PFS: Crizotinib - Log-logistic: shape	[redacted]	[redacted]	[redacted]	[redacted]
OS: Crizotinib - Weibull: shape	[redacted]	[redacted]	[redacted]	[redacted]
PFS: Crizotinib - Log-logistic: scale	[redacted]	[redacted]	[redacted]	[redacted]

Figure 40

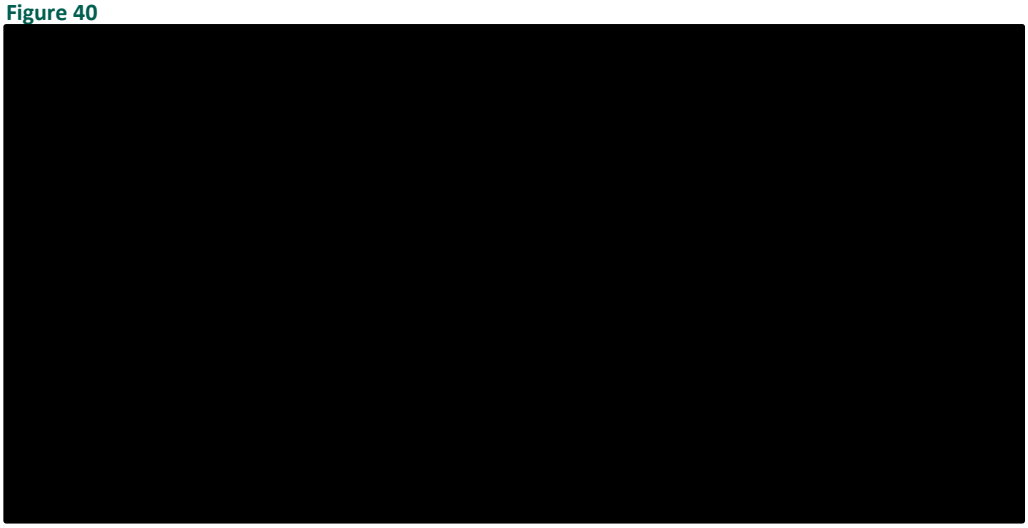


Figure 41

Table 55 Scenario analyses

	Incr. cost (DKK)	Incr. QALY	ICER vs. (DKK/QALY)	Incr. cost (DKK)	Incr. QALY	ICER vs. (DKK/QALY)
	Versus alectinib			Versus brigatinib		
Base case	[redacted]	[redacted]	355,645	[redacted]	[redacted]	339,689
Discounting set to 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

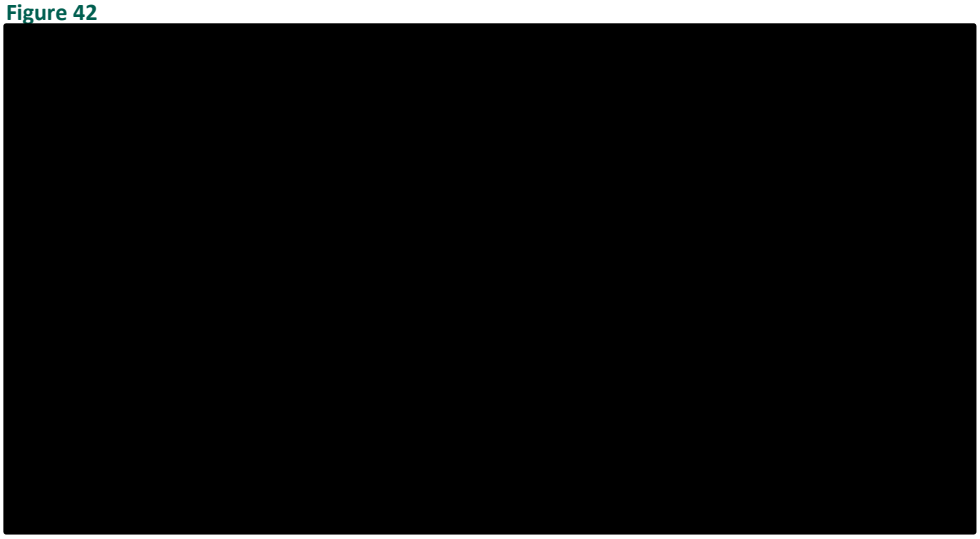
Discounting set to 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon set to 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon set to 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon set to 39 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS Separate models - Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS trial data: CROWN only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CNS-progression effects excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib PFS - Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib PFS - Log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib PFS - 36-months piecewise Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - Pseudo transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib ToT - Parametric exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities: all values from TA670	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities: all values based on CROWN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No adverse event disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subs. treatment distribution: trial data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.2.2 Probabilistic sensitivity analyses

To assess the overall parameter uncertainty for the variables in the model, a probabilistic sensitivity analyses (PSA) was performed with 5,000 iterations, which was deemed reasonable based on convergence testing (see Figure 92 in Appendix G). As such, the performed PSA evaluated the impact on the model results when multiple parameters included in the model were varied simultaneously. Cost-effectiveness acceptability curve (CEAC) and cost-effectiveness planes are presented in Figure 42, Figure 43, and Figure 44. An overview of included parameters can be found in the “Model parameters” sheet

of the cost-effectiveness model. An overview of the PSA data along with the convergence test is presented in Appendix G.

Figure 42



The CEAC indicated that lorlatinib has the highest likelihood of cost-effectiveness at a WTP threshold of [redacted] compared to alectinib and brigatinib. Most PSA iterations are within the [redacted] The PSA estimated a mean ICER of [redacted] compared to alectinib and [redacted].

Figure 43

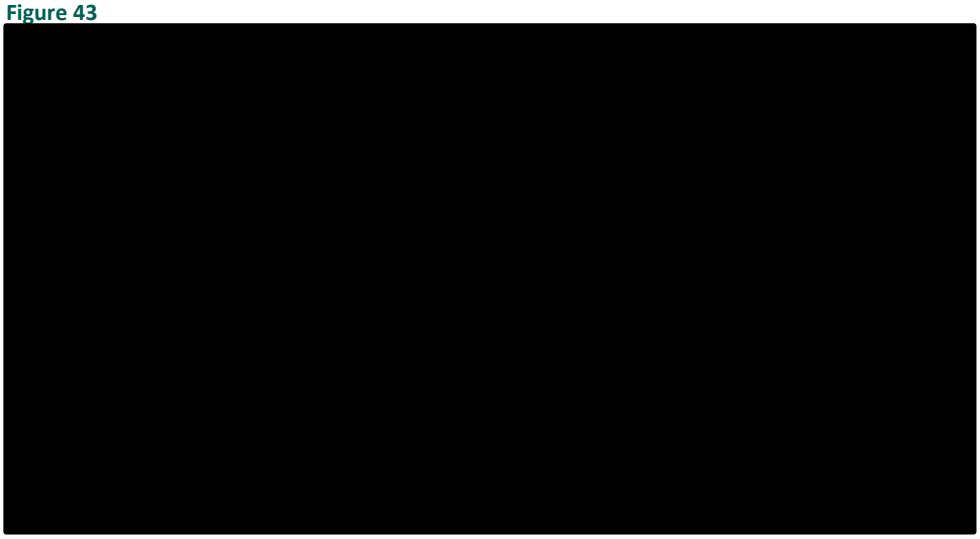


Figure 44 Cost-effectiveness plane versus brigatinib

13. Budget impact analysis

The budget impact model is developed to estimate the expected budgetary consequences of recommending lorlatinib for the 1st line treatment of adult ALK-positive NSCLC patients in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and any changes in the settings of the cost-effectiveness model affects the results of the budget impact model. The budget impact analysis is based on undiscounted cost, and patient cost and transportation cost have not been included as per DMC guidelines.

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where lorlatinib is recommended as the SoC with a scenario where lorlatinib is not recommended as SoC. The total budget impact per year is the difference between the two scenarios

Number of patients (including assumptions of market share)
As described in section 3.2, it was estimated that 35 incident patients per year are candidates for 1st line treatment. In the scenario where lorlatinib is recommended, it is expected that lorlatinib will have a market share of 95% of patients per year, while the remaining patients will be treated with brigatinib. In the scenario where lorlatinib is not recommended, brigatinib is expected to keep 95% the patients based on the current DMC NSCLC treatment recommendation (7), while the remaining patients are treated with alectinib.

Table 56 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Lorlatinib	33	33	33	33	33

Alectinib	0	0	0	0	0
Brigatinib	2	2	2	2	2
			Non-recommendation		
Lorlatinib	2	2	2	2	2
Alectinib	0	0	0	0	0
Brigatinib	33	33	33	33	33

Budget impact

The budget impact results are presented in Table 57. It is seen that a negative budget impact is estimated the initial two years.

Table 57 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Lorlatinib is recommended	DKK 20,283,487	DKK 13,848,258	DKK 11,478,398	DKK 9,677,632	DKK 9,388,624
Lorlatinib is NOT recommended	DKK 24,023,072	DKK 15,172,616	DKK 9,988,918	DKK 7,421,705	DKK 5,962,580
Budget impact of the recommendation	DKK -3,739,585	DKK -1,324,358	DKK 1,489,480	DKK 2,255,927	DKK 3,426,044

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 58 Main characteristic of studies included

Trial name: CROWN (26)	NCT number: 03052608
Objective	To demonstrate that lorlatinib as a single agent is superior to crizotinib alone) in prolonging progression-free survival (PFS) in advanced ALK-positive NSCLC patients who are treatment naïve.
Publications – title, author, journal, year	First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. Shaw, A. T., Bauer, T.M.. de Marinis, F., Felip, E., Goto, Y. Liu, G. et al. N Engl J Med 2020, Vol 383(21): 2018-2029. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. Solomon, J.S., Bauer, T.M., Mok, T.S.K., Liu, G, Mazieres, J. de Marinis, F. et al. Lancet Respir Med 2022, 11(4):354-366. Post Hoc Analysis of Lorlatinib Intracranial Efficacy and Safety in Patients With ALK-Positive Advanced Non-Small-Cell Lung Cancer From the Phase III CROWN Study. Solomon, B.J., Bauer, T.M., Ou, SH.I., Liu, G., Hayashi, H., Bearz, A. et al. J Clin Oncol 2022; 40:3593-3602 Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. Solomon, J.S., Liu, G., Felip, E., Mok, T.S.K., Soo, R.A., Mazieres, J. et al. J Clin Oncol. 2024 Oct 10;42(29):3400-3409
Study type and design	Phase 3, multinational, multicenter, randomized, open-label, parallel 2-arm study in which previously untreated patients with advanced ALK-positive NSCLC was randomized 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy. Patients are stratified according to: Presence of brain metastases (Yes vs No and Ethnic origin (Asian vs non-Asian). Crossover was not allowed. Study still ongoing but not recruiting.
Sample size (n)	296
Main inclusion criteria	Patients should meet all the following inclusion criteria to be eligible for enrollment into the study: 1. Diagnosis: a. 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;

	b. Tumor Requirements: At least 1 extracranial measurable target lesion per RECIST v. 1.1 that has not been previously irradiated. CNS metastases are allowed if: i. Asymptomatic: either not currently requiring corticosteroid treatment, or on a stable or decreasing dose of ≤ 10 mg QD prednisone or equivalent; or ii. Previously diagnosed and treatment has been completed with full recovery from the acute effects of radiation therapy or surgery prior to randomization, and if corticosteroid treatment for these metastases has been withdrawn for at least 4 weeks with neurological stability; or iii. Leptomeningeal disease (LMD) or carcinomatous meningitis (CM) if visualized on MRI (magnetic resonance imaging), or if baseline CSF positive cytology is available c. Tissue Requirements: All patients must have an archival formalin fixed, paraffin embedded (FFPE) tissue specimen available and collected prior to randomization. If archived tissue is unavailable, then a mandatory de novo biopsy must be performed. 2. 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 randomization. 3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1, or 2. 4. Age ≥18 years (or ≥20 years as required by local regulation). 5. Adequate Bone Marrow Function, Pancreatic Function, Renal Function, Liver Function. 9. Acute effects of prior radiotherapy resolved to baseline severity or to CTCAE Grade ≤1 except for AEs that in the investigator's judgment do not constitute a safety risk for the patient. 10. Serum pregnancy test (for females of childbearing potential) negative at screening. 11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study. 12. Willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures
Main exclusion criteria	Patients with any of the following characteristics/conditions will not be included in the study: 1. Spinal cord compression unless the patient has good pain control attained through therapy, and there is stabilization or recovery of neurological function for the 4 weeks prior to randomization. 2. Major surgery within 4 weeks prior to randomization. Minor surgical procedures (eg, port insertion) are not excluded, but sufficient time should have passed for adequate wound healing.

3. Radiation therapy within 2 weeks prior to randomization, including stereotactic or partial brain irradiation. Patients who complete whole brain irradiation within 4 weeks prior to randomization or palliative radiation therapy outside of the CNS within 48 hours prior to randomization will also not be included in the study.

4. 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 6 months; malabsorption syndromes.

5. Known prior or suspected severe hypersensitivity to study drugs or any component in their formulations.

6. Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV) or hepatitis C virus (HCV) (e.g., in case of known HBsAg or HCV antibody positivity), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.

7. Clinically significant cardiovascular disease, that is, active or within 3 months prior to enrolment.

8. Patients with predisposing characteristics for acute pancreatitis according to investigator judgement (eg, uncontrolled hyperglycaemia, current gallstone disease) in the last month prior to randomization.

9. History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis.

10. Evidence of active malignancy (other than NSCLC, non-melanoma skin cancer, in situ cervical cancer, papillary thyroid cancer, lobular carcinoma in situ/ductal carcinoma in situ (LCIS/DCIS) of the breast or localized prostate cancer) within the last 3 years prior to randomization.

11. Concurrent use of any of the following food or drugs (consult the sponsor if in doubt whether a food or a drug fall into any of the above categories) within 12 days prior to the first dose of lorlatinib or crizotinib.

a. known strong CYP3A inhibitors

b. known strong CYP3A inducers

c. known P-gp substrates with a narrow therapeutic index (eg, digoxin).

12. Concurrent use of CYP3A substrates with narrow therapeutic index within 12 days prior to the first dose of lorlatinib or crizotinib.

13. Other severe acute or chronic medical or psychiatric condition

14. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.

	15. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 90 days after the last dose of investigational product.
Intervention	Lorlatinib 100 mg once daily (4 x25 mg oral tablets), 149 patients assigned and treated. Treatment will continue until confirmation of disease progression, patient refusal, or unacceptable toxicity, whichever occurs first. If according to the Investigator's clinical judgment and after discussion between the Investigator and Pfizer, a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the assigned drug.
Comparator(s)	Crizotinib 250 mg capsule twice daily, 147 patients assigned and 142 treated. Treatment will continue until confirmation of disease progression, patient refusal, or unacceptable toxicity, whichever occurs first. If according to the Investigator's clinical judgment and after discussion between the Investigator and Pfizer, a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the assigned drug.
Follow-up time	Median follow-up time for PFS was 60,2 months (95% CI, 57.4 to 61.6) for lorlatinib and 55.1 months (95% CI, 36.8 to 62.5) for crizotinib (17)
Is the study used in the health economic model?	Yes. CROWN is the main evidence to model lorlatinib.
Primary, secondary and exploratory endpoints	Endpoints included in this application: The primary endpoint was PFS based on Blinded Independent Central Review (BICR) assessment (RECIST v.1.1). Secondary endpoint: OS PFS based on Investigator's assessment (RECIST v1.1) Objective Response rates (ORR) based on BICR and on Investigator's assessment; Duration of Response (DOR) by BIRC an INV Intracranial OR (IC-OR) by BIRC and INV, IC-time to progression (IC-TTP) by BIRC and INV, IC-DOR, Time to Tumor Response (TTR), and IC-TTR all by BICR (RECIST v. 1.1), and PFS2; Safety: Adverse Events (AEs), as graded by NCI CTCAE (National cancer Institute Common Terminology Criteria for Adverse Events) v.4.03; laboratory abnormalities (as graded by NCI CTCAE v.4.03). Treatment discontinuation due to AEs, death, Serious Adverse events and AEs of special interest.

	HRQoL as assessed by EORTC (European Organisation for Research and Treatment of Cancer) QLC-C30, EORTC QLQ-LC13, EQ-5D-5L Other endpoints: Tumor tissue biomarkers including, but not limited to, ALK gene rearrangement and/or mutations as measured by next-generation sequencing (NGS) and/or immunohistochemistry (IHC); Peripheral blood cfDNA biomarkers including, but not limited to, ALK gene rearrangement and/or ALK kinase domain mutations. Additional peripheral blood-based and tumor tissue-based biomarkers consisting of the levels of cells, DNA, RNA (Ribonucleic acid), metabolites or proteins; Potential results from exploratory analyses of banked biospecimen (these results may or may not be generated in the context of the present study); Plasma concentrations of lorlatinib and its metabolite(s) if appropriate
Method of analysis	Efficacy end points were measured in the intention-to-treat population, which included all the patients, who had undergone randomization. The Kaplan–Meier method was used to estimate time-to-event end points. One-sided log rank tests, stratified according to baseline factors, were used for between-group comparison of PFS and OS; stratified Cox regression models were applied to estimate hazard ratios. A one-sided stratified Cochran-Mantel-Haenszel test was used to compare the between-group difference in response. Safety evaluations were performed in all patients who had received at least one dose of study drug. Safety results were not adjusted for shorter duration of treatment in the crizotinib group(32) . At the unplanned 3 years analysis, no formal analysis was done, and no p value were provided, and no significance level was set. (33) At the post hoc analysis conducted after 5 years of follow-up to present efficacy by investigator, safety and biomarker analysis (17). A longitudinal random-intercept, random-slope, mixed-effect model was used to assess EORTC QLQ-C30 score change from baseline up to, but not including end of treatment. The model had an intercept term, treatment, time (continuous variable), treatment by time, baseline, and randomization stratification factors as covariates. A ≥ 10-point minimally important difference from baseline in EORTC QLQ-C30 has been established as correlative with clinically meaningful change in disease symptoms and functioning.(24) P values were two-sided without adjustment for multiple comparisons. PRO changes from baseline included all postbaseline assessments; the results were presented up to cycle 18 to ensure a meaningful sample size(34).
Subgroup analyses	Following subgroups analysis were performed for PFS and ORR by BIRC assessment: Randomisation stratification factors: Presence of brain metastases (yes,no) and Ethnic origrin (Asian, non-Asian).

	Baseline characteristics: Age, Gender, Smoking status, ECOG PS (0/1 vs 2) extent of disease and histology. To assess the impact of brain metastases and prior brain radiotherapy on efficacy, post hoc exploratory PFS analyses were conducted. The probability of the first event being CNS progression, non-CNS progression, or death was evaluated with a competing risk approach by estimating cumulative incidence functions. To assess the effect of lorlatinib dose modifications on efficacy, measured as relative dose intensity (RDI) or dose reduction, a post hoc PFS landmark analysis was performed. The landmark point of 16 weeks was chosen to allow for early assessment while providing sufficient time for potential dose modifications. P values were one-sided without adjustment for multiple comparisons.
Other relevant information	

Trial name: ALEX (48)	**NCT number: 02075840**
Objective	To evaluate and compare the efficacy of alectinib compared to crizotinib in patients with treatment-naïve ALK-positive advanced NSCLC
Publications – title, author, journal, year	Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. Peters, S., Camidge, D.R., Shaw, A.T., Gadgeel, S. Ahn, J.S., Kim, D.-W. et al. N Engl J Med 2017; 377:829-38 Updated Efficacy and Safety Data and Impact of the EMLA4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-Positive Advanced Non-Small Cell Lung Cancer in the Global Phase III ALEX Study. Camidge, D.R., Dziadziuszko, R., Peters, S., Mok, T., Noe, J., Nowicka, M. et al. J Thor Oncol. 2019;14: 1233-1243 Patient-reported outcomes from the randomized phase III ALEX study of alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer. Pérol, M., Pavlakis, N., Levchenko, E., Platania, M., Oliveira, J., Novello, S. et al. Lung Cancer 2019;138:79-87 Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in ALEX study. Mok, T., Camidge, D.R., Gadgeel, S.M., Rosell, R., Dziadziuszko, R., Kim, D.-W. et al. Ann Oncol 2020; 31 (8): 1056-1064

Study type and design	A randomized, active controlled, multicenter Phase III open-label study in patients with treatment-naïve ALK-positive advanced NSCLC. All patients are required to provide pretreatment tumor tissue to confirm the presence of ALK rearrangement (by immunohistochemistry [IHC] test). Patients will be randomized 1:1 into one of the two treatment arms to receive either alectinib or crizotinib. Study did not allow crossover and is active, not recruiting. Central randomization was performed via an interactive voice or web-based response system (IxRS) using the following stratification factors: Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0/1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes vs. no).
Sample size (n)	303 patients
Main inclusion criteria	• Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive as assessed by the Ventana IHC test. Sufficient tumor tissue to perform ALK IHC and ALK FISH is required. Both tests will be performed at designated central laboratories. • Age ≥ 18 years old. • Life expectancy of at least 12 weeks. • ECOG PS of 0-2. • Patients had no prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC. • Adequate hematologic and renal function • Patients must have recovered from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment. • Measurable disease (by RECIST v1.1) prior to the administration of study treatment. • Prior brain or leptomeningeal metastases allowed if asymptomatic and diagnosed incidentally at study baseline. If patients have neurological symptoms or signs due to CNS metastasis, patients need to complete whole brain radiation or gamma knife irradiation treatment at least 14 days before enrollment and be clinically stable. • For all females of childbearing potential, a negative pregnancy test must be obtained within 3 days before starting study treatment. • For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of study drug.

	Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate < 1% per year. Barrier methods must always be supplemented with the use of a spermicide. For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. • Able and willing to provide written informed consent prior to performing any study related procedures and to comply with the study protocol, including patients must be willing and able to use the electronic patient-reported outcome device.
Main exclusion criteria	Patients who meet any of the following criteria was excluded from study entry: Patients with a previous malignancy within the past 3 years are excluded (other than curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have no impact in PFS and OS for the current NSCLC). Any GI disorder that may affect absorption of oral medications, such as mal-absorption syndrome or status post-major bowel resection. Liver disease characterized by: ALT or AST >3×ULN (≥ 5×ULN for patients with concurrent liver metastasis) confirmed on two consecutive measurements OR Impaired excretory function (e.g., hyperbilirubinemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices OR Acute viral or active autoimmune, alcoholic, or other types of hepatitis. National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) Grade 3 or higher toxicities due to any prior therapy (e.g., radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication. History of organ transplant. Co-administration of anti-cancer therapies other than those administered in this study.

	Patients with baseline QTc> 470 ms or patients with symptomatic bradycardia <45 beats per minute. Administration of strong/potent cytochrome P4503A inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib or crizotinib except for oral corticosteroids up to 20 mg of prednisolone equivalent per day Administration of agents with potential QT interval prolonging effects within 14 days prior to the first administration of study drug and while on treatment. History of hypersensitivity to any of the additives in the alectinib drug formulation (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose, sodium lauryl sulfate [SLS], magnesium stearate). History of hypersensitivity to any of the additives in the crizotinib drug formulation (silica, colloidal anhydrous cellulose, microcrystalline calcium hydrogen phosphate, anhydrous sodium starch glycolate, magnesium stearate). Pregnant or lactating women. Known HIV positivity or AIDS-related illness Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial entry.
Intervention	Alectinib 600 mg (4 capsules) administered orally BID with food (within 30 minutes after a meal in the morning and evening. After progression (as per RECIST v1.1), patients should discontinue the study medication. After disease progression, patients will be treated at the discretion of the investigator according to local practice. Information regarding the nature and the duration of subsequent therapies will be collected. 152 patients received alectinib
Comparator(s)	Crizotinib 250 mg capsules administered orally BID. 151 patients received crizotinib.
Follow-up time	Longest follow-up was for OS: Median follow-up was 48.2 months (range 0.5–62.7) for alectinib and 23.3 months (range 0.3-60.6) for crizotinib.

Is the study used in the health economic model?	Yes. ALEX was included in the NMA. The NMA results are applied in the model.
Primary, secondary and exploratory endpoints	Primary outcome: PFS, which is defined as the time from randomization to the first documented disease progression, as determined by the investigators or IRC (secondary endpoint) using RECIST v1.1 or death from any cause, whichever occurs first. Patients without an event will be censored at the last tumor assessment either during follow-up or during study treatment. Patients with no post-baseline assessments will be censored at the date of randomization. Secondary outcomes: ORR, which is defined as the percentage of patients who attain complete response (CR) or partial response (PR); response, as determined by the investigators using RECIST v1.1. Patients without any assessments will be regarded as non-responders. Time to CNS progression, which is defined as the time from randomization to the first occurrence of disease progression in the CNS as determined by IRC using RECIST v1.1 and RANO (separate assessments and analyses), as well as C-ORR in patients with CNS metastases who have measurable disease in the CNS at baseline, C-DOR in patients who have a CNS Objective Response, and C-PR at 6, 12, 18, and 24 months. DOR, which is defined as the time from when response (CR or PR) was first documented to first documented disease progression or death (whichever occurs first). This will only be calculated for patients who have a best overall response of CR or PR. Patients who do not progress or die after they have had a response are censored at the date of their last tumor measurement. OS, which is defined as the time from randomization to death from any cause. Patients without an event will be censored at the last date known to be alive. Patients without any follow-up information will be censored at the date of randomization. Safety Outcome Measures: Serious and non-serious adverse events, Safety laboratory tests values, Vital signs (blood pressure, heart rate), ECG, Physical examination Pharmacokinetic Outcome Measures: Sparse (pre-dose) PK samples for measurement of alectinib and its major metabolite(s) will be collected in all study patients receiving alectinib treatment , Serial/intensive PK sampling will be collected in a subset of consenting patients enrolled to receive alectinib treatment (approximately 10%−15%, at least approximately n = 20), PK parameters will be determined as appropriate and where data allow: The pharmacokinetics of alectinib (and metabolite[s], if appropriate) will be described, and the between-patient variability will be estimated using a population PK approach. Patient-Reported Outcome Measures: The PRO measures for this study are as follows: EORTC QLQ-C30 and the EORTC QLQ-LC13 to determine the impact of alectinib compared with crizotinib as measured by TTD in patient-reported lung cancer symptoms (e.g., cough, dyspnea [single item and multi-item scales], pain in chest, pain in arm/shoulder, fatigue). The EORTC QLQ-C30 and EORTC QLQ-LC13 to measure PROs of

	HRQoL, patient functioning, and side effects of therapy compared between patients treated with alectinib and those treated with crizotinib. The potential influence of covariates that contribute significantly to the between-patient differences in PK parameters of alectinib will also be explored and quantified. Non-compartmental analysis may be conducted in patients undergoing serial/intensive PK sample collection, as appropriate and where data allow. Exploratory Outcome Measures: EQ-5D-3L to generate utility scores for use in economic models for reimbursement. • Total testosterone, albumin and SHBG to calculate free testosterone level, FSH, and LH, in blood to measure an onset of hypogonadism in adult men. • The FISH Vysis® ALK Break Apart FISH Probe Kit (Abbott) to evaluate and compare efficacy and safety in patients with treatment-naïve NSCLC that is ALK-positive by FISH test. • Post progression tumor mutation status to study molecular mechanisms of resistance to ALK inhibitors. • ALK mutation status in plasma DNA to monitor efficacy and disease progression. • ALK fusion status in circulating tumor cells in blood. Other endpoints: E.g.: Time-to-next-treatment and objective response rate were included as secondary endpoints in the study, but results are not included in this application.
Method of analysis	The comparison between the treatment groups with respect to progression-free survival was based on a stratified log-rank test at a 5% level of significance (two-sided). The Kaplan–Meier method was used to estimate the median progression-free survival for each treatment group with 95% confidence intervals. A stratified Cox proportional-hazards regression model was used to estimate the treatment effect, expressed as a hazard ratio with a 95% confidence interval. Secondary end points were analysed with the use of a hierarchical testing strategy to account for multiplicity. If the difference between the treatment groups with respect to the primary end point of investigator-assessed progression-free survival was significant, secondary end points were each tested (at a two-sided 5% significance level) in the following sequence: independent review committee–assessed progression-free survival, time to independent review committee–assessed CNS progression according to RECIST criteria, investigator-assessed response rate, and overall survival. Efficacy end points were evaluated in the intention-to-treat population, comprising all randomly assigned patients. The safety population included all the patients who received at least one dose of trial medication. All the patients in the intention-to-treat

	population were included in the analysis of time to CNS progression, regardless of status with regard to baseline CNS metastases. To account for the competing risks inherent in the comparison of CNS progression between the alectinib and crizotinib groups, a stratified two-sided log rank test was computed based on a cause specific hazard function. The probability of CNS progression, non-CNS progression, and death were estimated with the use of cumulative-incidence functions.(47).
Subgroup analyses	An exploratory analysis of efficacy by EML4-ALK fusion variant. Biomarker-evaluable population (BEP) subgroup: patients with evaluable plasma or tissue samples that passed NGS quality control. PFS between the EML4-ALK variant groups within each of the treatment arms was compared by using a two-sided log rank test at a 5% significance level. ORR between EML4-ALK variants was compared by using the Pearson chi-square test. (36)
Other relevant information	

Trial name: ALTA-1L (28)	**NCT number: 02737501**
Objective	The objective of the study is to compare the efficacy of brigatinib to that of crizotinib in ALK+ locally advanced or metastatic NSCLC patients naive to ALK inhibitors
Publications – title, author, journal, year	Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. Camidge, D.R., Kim, H.R., Ahn, M.-J., Yang, J.C.-H., Han, J.-Y., Lee, J.-S., et al. N Engl J Med 2018; 379:2027-2039 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. Camidge, D.R., Kim, H.R., Ahn, M.-J., Yang, J.C.H., Han, J.-Y., Hochmair, M.J. et al. J Clin Oncol 2020; 38: 3592-3603 Brigatinib Versus Criziotinib in ALK inhibitor-Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. Camidge, D.R., Kim, H.R., Ahn, M.-J., Yang, J.C.H., Han, J.-Y., Hochmiar, J., et al. J Thora Oncol 2021; 16(12): 2091-2108
Study type and design	A phase 3, randomized, open-label, comparative, multicenter, international study in which ALK+ NSCLC patients who have not previously received an ALK-targeted TKI will be randomized in a 1:1 fashion to receive brigatinib or crizotinib. Patients will be stratified by the presence of intracranial CNS metastases at baseline (Yes versus No) and prior chemotherapy use for locally advanced or metastatic disease (Yes versus No). For the purposes of stratification, prior chemotherapy

	is defined as completion of ≥1 full cycle of chemotherapy in the locally advanced or metastatic setting. Crossover from crizotinib to brigatinib was also permitted, at the investigator's discretion with the sponsor's medical monitor approval, for patients who have experienced objective progression confirmed by the blinded Independent Review Committee (BIRC). Study is completed.
Sample size (n)	275 patients
Main inclusion criteria	All patients must meet all the following eligibility criteria for study entry: 1. Have histologically or cytologically confirmed stage IIIB (and not a candidate for definitive multimodality therapy) or stage IV NSCLC. 2. Must meet one of the following two criteria (a or b): a. Have documentation of ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or the Ventana ALK (D5F3) CDx Assay. The test must have been performed according to the product's instructions for use (IFU). b. Have documented ALK rearrangement by a different test and adequate tissue available for central laboratory testing by an FDA-approved test. Confirmation of central test positivity is not required prior to randomization. 3. Have sufficient tumor tissue available for central analysis (see the Study Reference Manual for minimum requirements) 4. Have at least 1 measurable (i.e., target) lesion per RECIST v1.1 (see Appendix C). 5. Recovered from toxicities related to prior anticancer therapy to NCI CTCAE v 4.0 grade ≤1. 6. Are a male or female patient ≥18 years old. 7. Have adequate organ function, as determined by : a. ALT/AST ≤2.5 × upper limit of normal (ULN); ≤5 × ULN is acceptable if liver metastases are present b. Total serum bilirubin ≤1.5 × ULN (<3.0×ULN for patients with Gilbert syndrome) c. Serum creatinine ≤1.5 × ULN d. Serum lipase/amylase ≤1.5 × ULN e. Absolute neutrophil count (ANC) ≥1.5 × 109/L f. Platelet count ≥75 × 109/L g. Hemoglobin ≥10 g/dL 8. Have Eastern Cooperative Oncology Group (ECOG) performance status <2

	9. Have normal QT interval on screening ECG evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤450 milliseconds (msec) in males or ≤470 msec in females. 10. For female patients of childbearing potential, have a negative pregnancy test documented prior to randomization. 11. For female and male patients who are fertile, agree to use a highly effective form of contraception with their sexual partners throughout study participation (Section 14.3.1). 12. Provide signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study, including the potential risks, and is willingly participating. 13. Have the willingness and ability to comply with scheduled visit and study procedures
Main exclusion criteria	Patients meeting any of the criteria below are ineligible for the study: 1. Previously received an investigational antineoplastic agent for NSCLC. 2. Previously received any prior TKI, including ALK-targeted TKIs. 3. Previously received more than 1 regimen of systemic anticancer therapy for locally advanced or metastatic disease. Note: a systemic anticancer therapy regimen will be counted if it is administered over at least 1 cycle. A new antineoplastic agent used as maintenance therapy will be counted as a new regimen. Neo-adjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if completion of (neo) adjuvant therapy occurred <12 months prior to randomization. 4. Received chemotherapy or radiation within 14 days of first dose of study drug, except stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT). 5. Received anti-neoplastic monoclonal antibodies within 30 days of the first dose of study drug. 6. Had major surgery within 30 days of the first dose of study drug, minor surgical procedures such as catheter placement or minimally invasive biopsies are allowed. 7. Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy. 8. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days prior to randomization. Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for 7 days prior to randomization.

	9. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed. 10. Be pregnant, planning a pregnancy, or breastfeeding 11. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug, b. Unstable angina within 6 months prior to first dose of study drug, c. Congestive heart failure (CHF) within 6 months prior to first dose of study drug, d. History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician, e. Any history of ventricular arrhythmia, f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug 12. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure. 13. Have a history or the presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis. 14. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous (IV) antibiotics. 15. Have a known history of human immunodeficiency virus (HIV) infection. Testing is not required in the absence of history. 16. Have a known or suspected hypersensitivity to brigatinib or its excipients. 17. Have a known or suspected hypersensitivity to crizotinib or its excipients. 18. Have malabsorption syndrome or other gastrointestinal (GI) illness or condition that could affect oral absorption of the study drug. 19. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the study drug
Intervention	Brigatinib 180 mg once daily, with a 7 day lead-in period at 90 mg until progression or intolerable toxicity. Treatment with brigatinib could be continued after progression, at the discretion of the investigator, if there was still evidence of clinical benefit. 137 patients were assigned to brigatinib.
Comparator(s)	Crizotinib 250 mg twice daily until progression or intolerable toxicity. At the discretion of the investigator with the sponsors approval, patients who experienced disease progression confirmed by the BIRC while on crizotinib therapy could crossover to treatment with brigatinib. All patients who crossover to brigatinib from crizotinib must have a washout period of at least 10 days between treatments.

Follow-up time	At study end the median follow-up was 40.4 months (range 0-52.4) in brigatinib arm and 15.2 (range 0.1-51.7) in crizotinib arm. (9)
Is the study used in the health economic model?	Yes. ALTA-1L was included in the NMA. The NMA results are applied in the model.
Primary, secondary and exploratory endpoints	Primary Endpoint: PFS, as assessed by the BIRC, per RECIST v1.1 Secondary Endpoints: 1. Confirmed ORR, as assessed by the BIRC, per RECIST v1.1 2. Confirmed intracranial ORR as assessed by the BIRC 3. Intracranial PFS, as assessed by the BIRC 4. OS 5. Duration of response, as assessed by the BIRC 6. Time to response, as assessed by the BIRC 7. Disease control rate, as assessed by the BIRC 8. Safety and tolerability of brigatinib 9. Patient-reported symptoms and HRQoL scores, assessed with the EORTC QLQ-C30 (v3.0) and time to deterioration in dyspnea assessed with QLQ-LC13 (v3.0) Exploratory Endpoints: 1. Confirmed ORR for brigatinib, as assessed by the BIRC, per RECIST v1.1, in patients who crossover from Arm B (crizotinib) 2. PFS from the first dose of brigatinib, as assessed by the BIRC, per RECIST v1.1, in patients who crossover from Arm B (crizotinib) 3. Correlation of brigatinib plasma pharmacokinetics with both efficacy and safety 4. Molecular determinants of efficacy and safety with brigatinib and crizotinib
Method of analysis	The primary analysis was based on the ITT population. The primary analysis of the primary endpoint (PFS) and the secondary endpoint OS were performed using a 2-sided stratified log-rank test (stratification factors: presence of iCNS metastases at baseline [Yes versus No], and prior chemotherapy for locally advanced or metastatic disease [Yes versus No]) to compare the BIRC-assessed PFS of subjects randomized to brigatinib with the BIRC-assessed PFS of subjects randomized to crizotinib. The overall (2-sided) Type I error rate were controlled at 0.05. Median PFS and OS and their associated 95% confidence intervals were estimated for each treatment arm using the Kaplan-Meier method. Additionally, hazard ratios were estimated using the Cox regression model with the stratification factors as covariates.

	Confirmed ORR and Confirmed intracranial ORR were analysed with the Mantel-Haenszel test (using the stratification factors) on 1) the ITT population (confirmed ORR), 2) the measurable iCNS disease population (confirmed intracranial ORR), 3) the non-measurable iCNS disease population (confirmed intracranial ORR), and 4) the all iCNS disease population (confirmed intracranial ORR). Analysis will differ in that the iCNS ORR will be analysed with the Mantel-Haenszel test using only the stratification factor of prior chemotherapy. The analysis of response duration will only include ITT subjects with confirmed CR or PR. An additional analysis of duration of response will be performed using disease assessment performed by the investigator. Median values and 2-sided 95% confidence intervals will be estimated using Kaplan-Meier (KM) method in the ITT population. The KM-estimated PFS rates and OS rates at 12 and 24 months and the associated 2-sided 95% confidence intervals will be computed. Duration of response will also be summarized with descriptive statistics for subjects with confirmed CR or PR and the Kaplan-Meier method in which follow-up for subjects without PFS events will be censored. Disease control rate, as assessed by the BIRC and will be analysed with the Mantel-Hanzel test (using the stratification factors) on the ITT population to compare the proportion of subjects achieving disease control. Intracranial PFS, as assessed by the BIRC, will be defined and analyzed in the same manner as for PFS used in the primary endpoint with the exceptions that the progression events used will come from the iCNS BIRC and the analysis will be restricted to subjects identified as having brain metastases at baseline in the randomization. The primary evaluation of iCNS PFS will be performed in all the iCNS disease population, with a sensitivity analysis in the active iCNS disease population. Additional analyses will be performed in the no iCNS disease population, in which case PFS events would consist of either the appearance of new brain metastases or death. iCNS PFS will also be analysed in the measurable iCNS disease population with a sensitivity analysis in the active measurable iCNS disease population. The treated population for each regimen includes all subjects receiving at least one dose of study drug. Safety was analysed using the treated population.(28) (54)
Subgroup analyses	All iCNS Disease Population: All iCNS disease population will consist of those subjects in the ITT population who were determined by the iCNS BIRC to have iCNS metastases at baseline regardless of whether they had at least one lesion that qualified as a target lesion in their baseline assessment. No iCNS Disease Population: The no iCNS disease population will consist of those subjects in the ITT population who were not determined by the iCNS BIRC to have iCNS metastases at baseline. Measurable iCNS Disease Population: Measurability of lesions is a core component definition of a potential target lesion in the RECIST v1.1

process and is retained in the modified RECIST used for iCNS disease assessment (Section 3.4.1.2). Therefore, the measurable iCNS disease population will consist of those subjects in all the iCNS Disease population who were determined by the iCNS BIRC to have had at least one target lesion in their baseline assessment.

Non-Measurable iCNS Disease Population: The non-measurable iCNS disease population is intended to characterize subjects who were determined to have iCNS disease at baseline but did not have measurable lesions. This means that subjects with both measurable and non-measurable lesions at baseline will not be included in this population. Therefore, the non-measurable iCNS disease population will consist of all subjects in the all iCNS disease population who are not included in the measurable iCNS disease population.

Other relevant information	

Trial name: Study 1001 Phase II part (26)	**NCT number: 01970865**
Objective	To evaluate overall (intra- and extracranial) and intracranial anti-tumor activity of single-agent lorlatinib at RP2D in patients with advanced ALK+ NSCLC or advanced ROS1+ NSCLC.
Publications – title, author, journal, year	Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Solomon, BJ, Besse, B, Bauer, TM, Felip, E, Soo, RA, Camidge, DR, Chiari, R, Bearz, A, Lin, C-C, Gadgeel, SM, Riely, GJ, Tan, EH, Seto, T, James, LP, Clancy, JS, Abbattista, A, Martini, J-F, Chen, J, Peltz, G, Thurm, H, Ignatius Ou, S-H, et Shaw, AT. Lancet Oncol 2018; 19: 1654–67 Intracranial and extracranial efficacy of lorlatinib in patients with *ALK*-positive non-small-cell lung cancer previously treated with second-generation ALK TKI. Felip, E, Shaw, AT, Bearz, A, Camidge, DR, Solomon, BJ, Bauman, JR, Bauer, TM, Peters, S, Toffalorio, F, Abbattista, A, Thurm, H, Peltz, G, Wiltshire, R and Besse, B. Ann Oncol 2021;32:620-630 Brief Report: Final overall survival and long-term safety of lorlatinib in patients with ALK-positive non-small cell lung cancer from the pivotal phase 2 study. Ignatius Ou S-H, Solomon BJ, Besse B, Bearz A, Lin C-C, Chiari R, Camidge DR, Lin JJ, Abbattista A, Toffalorio F, et Soo RA. J of Thorac Oncol 2024, https://doi.org/10.1016/j.jtho.2024.11.021
Study type and design	Phase 2, multinational, multicenter, open-label, single- arm study in naive and previously treated patients with advanced ALK-positive NSCLC to receive lorlatinib monotherapy.

Sample size (n)	276
Main inclusion criteria	Patients with asymptomatic CNS metastases (including patients controlled with stable or decreasing steroid use within the last 2 weeks before study entry) will be eligible. The brain metastases may be newly diagnosed or be present as progressive disease after surgery, whole-brain radiotherapy, or stereotactic radiosurgery. Patients who have leptomeningeal disease (LM) or carcinomatous meningitis (CM) will be eligible if the LM/CM is visualized on MRI or if documented baseline cerebral spinal fluid positive cytology is available Adequate bone marrow function, adequate pancreatic function, adequate renal function, adequate liver function. Acute effects of any prior therapy resolved to baseline severity or to CTCAE grade ≤1 except for AEs that do not constitute a safety risk for the patient in the investigator's judgment Serum pregnancy test (for females of childbearing potential) negative at screening (before the patient may receive the investigational product). A patient is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception from the time of the first negative pregnancy test at screening, throughout the study, and for 90 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active
Main exclusion criteria	Spinal cord compression is excluded unless the patient demonstrates good pain control attained through therapy and there is stabilisation or recovery of neurological function for the 4 weeks before study entry. Major surgery within 4 weeks of study entry. Minor surgical procedures (eg, port insertion) are not excluded, but sufficient time (eg, up to 2 weeks) should have passed for wound healing Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤10 fractions) must have been completed at least 48 hours before study entry. Stereotactic or small-field brain irradiation must have been completed at least 2 weeks before study entry. Whole-brain radiation must have completed at least 4 weeks before study entry. Systemic anticancer therapy completed within a minimum of five half-lives of study entry (unless clinically meaningful

tumour flare per discretion of the investigator, in which discussion with the sponsor is warranted)

Prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including, but not limited to, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) antibody.

Previous high-dose chemotherapy requiring stem cell rescue.

Prior irradiation to >25% of the bone marrow.

Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus, hepatitis C virus, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.

Clinically significant cardiovascular disease (that is, active or <3 months before enrolment): cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure (New York Heart Association functional class ≥II), second- or third-degree AV block (unless paced) or any AV block with PR >220 msec

Ongoing cardiac dysrhythmias of National Cancer Institute CTCAE grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless patient is otherwise healthy such as long-distance runners, etc.), machine-read electrocardiogram with QTc >470 msec, or congenital long QT syndrome

Patients with predisposing characteristics for acute pancreatitis according to investigator judgment (eg, uncontrolled hyperglycaemia, current gallstone disease, alcoholism.

History of extensive, disseminated, bilateral, or presence of grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis.

Patients with history of prior radiation pneumonitis are not excluded

Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behaviour, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

Evidence of active malignancy (other than current NSCLC, non-melanoma skin cancer, in situ cervical cancer, papillary

thyroid cancer, DCIS of the breast, or localized and presumed cured prostate cancer) within the last 3 years

Active inflammatory gastrointestinal disease, chronic diarrhoea, symptomatic diverticular disease, or previous gastric resection or lap band

Current use or anticipated need for food or drugs that are known strong or moderate CYP3A4 inhibitors, including their administration within 10 days before the first lorlatinib dose. Moderate CYP3A4 inhibitors. Concomitant medication with a suspected CYP3A4 inhibitory effect must be approved by the sponsor

Current use or anticipated need for drugs that are known strong CYP3A4 inducers, including their administration within 12 days before the first lorlatinib dose (ie, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, clevidipine, and St. John's wort). Concomitant medication with a suspected CYP3A4 inductive effect must be approved by the sponsor. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices is not permitted or caution is warranted. Concomitant medication suspected of being a CYP3A4 substrate with a narrow therapeutic index must be approved by the sponsor

Concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices, such as warfarin, phenytoin or a sensitive substrate such as celecoxib is not permitted or caution is warranted. Concomitant medication suspected of being a CYP2C9 substrate with a narrow therapeutic index must be approved by the sponsor

Concurrent use of drugs that are sensitive CYP2B6 substrates, such as bupropion or efavirenz, is not permitted or caution is warranted.

Concomitant medication suspected of being a CYP2B6 substrate with a narrow therapeutic index must be approved by the sponsor

Current use or anticipated need for drugs that are known strong CYP2C19 inhibitors, including their administration within 12 days before study entry (ie, fluconazole, fluvoxamine, and ticlopidine). Concomitant medication with a suspected CYP2C19 inhibitory effect must be approved by the sponsor

Current use or anticipated need for drugs that are known strong CYP2C8 inhibitors, including their administration within 12 days before study entry (ie, gemfibrozil). Concomitant medication with a suspected CYP2C8 inhibitory effect must be approved by the sponsor

Current use or anticipated need for drugs that are known P-gp substrates with a narrow therapeutic index, including their administration within 12 days before study entry (ie,

	digoxin). Concomitant medication with suspected P-gp substrates with a narrow therapeutic index must be approved by the sponsor Patients presenting with abnormal left ventricular ejection fraction by echocardiogram or multi-gated acquisition scan according to institutional lower limits Breastfeeding female patients (including patients who intend to interrupt breastfeeding)
Intervention	Lorlatinib 100 mg once daily, 276 patients assigned and treated. Treatment will continue until confirmation of disease progression, patient refusal, or unacceptable toxicity, whichever occurs first. If according to the Investigator's clinical judgment and after discussion between the Investigator and Pfizer, a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the assigned drug.
Comparator(s)	NA
Follow-up time	The median follow-up for OS was 72.7 months (95% CI, 69.3-76.3) for EXP1 and the median follow-up for OS was 66.7 months (95% CI, 63.0-67.7) for EXP3B-5. (40)
Is the study used in the health economic model?	[redacted]
Primary, secondary and exploratory endpoints	Primary Endpoints Phase II part: The primary endpoint was objective tumor response (defined as a confirmed complete response or partial response) and intracranial tumor response according to modified RECIST version 1.1, which allowed for up to five CNS target lesions, as assessed by independent central radiology review (ICR) and assessed in pooled subgroups of ALK-positive patients (ie, EXP1, EXP2–3A, EXP3B, EXP4–5 and EXP2–5). Secondary endpoints: Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), seriousness and relationship to study therapy. Laboratory abnormalities as characterized by type, frequency, and severity (as graded by NCI CTCAE v.4.03). Left Ventricular Ejection Fraction (LVEF). QTc interval. Vital Signs (heart rate, blood pressure). Mood assessment, Cognitive Function assessment, Suicidal Ideation and Behavior assessment [Phase 2 only].

	Patient reported functioning and impact on disease/treatment-related symptoms of lung cancer and global QOL. Disease Control Rate (DCR) at 12 weeks defined as the percent of patients with a confirmed complete response (CR), partial response (PR) or stable disease (SD) according to RECIST 1.1 at 12 weeks. Objective tumor response, as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 (Appendix 3) [Phase 1 only – primary endpoint in Phase 2]. In patients with asymptomatic CNS metastases, up to 5 intracranial target lesions in addition to the 5 extracranial target lesions will be assessed. Time-to-event endpoints: Progression-Free Survival (PFS), Overall Survival (OS) at 1 year and 18 months, Duration of Response (DR), and Time to Tumor Response (TTR). Probability of first event being a central nervous system (CNS) progression, non CNS progression, or death. Time to Progression (TTP).
Method of analysis	The proportions of patients with objective response and objective intracranial response were defined as those who achieved a confirmed complete response or partial response according to RECIST version 1.1 in the safety analysis as their best overall or intracranial response, respectively. The corresponding 95% Cis were calculated using the exact method based on the binomial distribution. For time-to-event endpoints, such as duration of response and progression-free survival, we estimated median values and two-sided 95% CIs using Kaplan-Meier methods. Time to first tumour response and PROs were summarised with descriptive statistics. All analyses were done using SAS version 9.4. The data cutoff for the first analysis of the primary endpoints (ORR and IC-ORR) was March 15, 2017. Analyses of activity and safety in this report were based on the safety analysis set (ie, all patients who received at least one dose of lorlatinib, as assessed by ICR). Patients with measurable CNS metastases at baseline by ICR were included in the intracranial activity analyses. The PRO-evaluable analysis set was defined as all enrolled patients who received at least one dose of lorlatinib and completed a baseline and at least one post-baseline PRO assessment.
Subgroup analyses	Overall responses and efficacy results in the following EXP groups: EXP1 (*ALK* positive and treatment naïve), EXP2-3A (*ALK* positive with disease progression following crizotinib ± chemotherapy), EXP3B (*ALK* positive with disease progression following one second generation ALK TKI ± chemotherapy), EXP4-5 (*ALK* positive with disease

	progression following ≥2 ALK TKIs ± chemotherapy), and EXP3B-5. Safety data for all treated patients (EXP1-6).
Other relevant information	

Appendix B. Efficacy results per study

Results per study

Table 59 Results per study

Results of CROWN (NCT03052608) (33)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS by BIRC: 18.3 months follow-up	lorlatinib	149	NR (NR,NR) months	NR			0.28	0.19-0.41	p<0.001	For this interim analysis the primary endpoint of PFS was tested at a one-sided alpha level of 0.0081 based on an updated boundary corresponding to the 72% information fraction observed at the interim analysis. 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 Kaplan-Meier method was used to estimate time to event endpoint. The HR and corresponding 95%CI are based on a stratified Cox proportional hazards model.	(32)
	crizotinib	147	9.3 (7.6-11.1) months								
Median PFS by BIRC: 36.7 months follow-up	lorlatinib	149	NR (NR–NR) months	NR			HR: 0.27	0.18–0.39		Primary endpoint met at interim analysis, no further formal analysis of PFS planned per protocol and is presented descriptively. 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 Kaplan-Meier	(33)
	crizotinib	147	9.3 (7.6–11.1) months								

							method was used to estimate time to event endpoint. The HR and corresponding 95%CI are based on a stratified Cox proportional hazards model.	
Median PFS by INV: 60.2-month follow-up	lorlatinib	149	NR (64.3–NR) months	NR	HR: 0.19	0.13–0.27	Post hoc analysis. No formal statistical testing performed	(17)
	crizotinib	147	9.1 (7.5–10.9) months					
Overall survival: follow-up: 18.3 months	lorlatinib	149	NE (NE-NE)		HR: 0.72	0.41-1.25	Overall survival hierarchically tested for significance at the interim analysis of PFS. Overall survival (OS) data has not reached maturity at the 5-year data cut-off. OS times associated with each treatment arm were summarised using the Kaplan–Meier method. The Cox proportional hazards model was fitted to compute the treatment HRs and the corresponding 95% CIs for OS.	(32)
	crizotinib	147	NE (NE-NE)					
Confirmed objective response rate, ORR: 60.2 months follow-up	lorlatinib	149	81 (73-87) %	18%			A one-sided stratified Cohran-Mantel-Haenszel test was used to compare differences in response.	(17)
	crizotinib	147	63 (54-70) %					
Duration of response, median DOR: 60.2-months follow-up	lorlatinib	149	NR (NR–NR) months				DOR times associated with each treatment arm were summarised using the Kaplan–Meier method. The Cox proportional hazards model was fitted to compute the treatment HRs. For DOR, the median and 95% CI for the median were also calculated.	(17)
	crizotinib	147	9.2 (7.5-11.1)					

Median time to Intercranial progression, IC-TTP: 60.2-months follow-up	lorlatinib	149	NR (NR-NR)	NR	HR: 0.06	0.03-0.12	IC-TTP times associated with each treatment arm were summarised using the Kaplan–Meier method. The Cox proportional hazards model was fitted to compute the treatment HRs and the corresponding 95% CIs for IC-TTP.	(17)
	crizotinib	147	16.4 (12.7-21.7) months					
Drug Discontinua-tion rate, treatment related: n (%) 60.2-months follow-up	Lorlatinib	149	8 (5%)	1%			Median duration of treatment was 57.0 months for lorlatinib (IQR, 13.9-63.3) and 9.6 months (IQR, 4.7-17.1) with crizotinib	(17)
	Crizotinb	147	8 (6%)					
Adverse events, Grade 3-4, n (%), all causality 60.2-months follow-up	Lorlatinib	149	115 (77%)	20%			Safety evaluation were performed in as treated population, which included all patients who received at least one dose. Safety results were not adjusted for shorter duration of crizotinib.	(17)
	Crizotinib	142	81 (57%)					
	Lorlatinib	149	64.6 ±1.82					(32)

HRQoL: 18 months follow-up Change in Global Quality of llfe score: Mean (±SE) from baseline to cycle 18:	Crizotinib	147	59.8±1.90 4.65 (95% CI (1.14-8.16)	PROs were evaluated in all treated patients who completed a baseline assessment and at least one post-baseline assessment. Longitudinal random intercept random slope mixed-effect model was performed to compare treatment arms based on change from baseline of the EORTC QLQ-C30 global health status/QoL scale. A change in score from baseline of ≥10 points was considered to be clinically meaningful. Estimated means are based on longitudinal mixed-effects regression analysis for change from baseline in global QoL.	
Median time to deterioration: EORTC QLQ-C30: 36.7 months follow-up	lorlatinib	149	24.7 months 95%CI: 6.5-NR)		(33)
	crizotinib	147	12.0 months, 95%CI: 6.5-NR)		

Results of ALEX (NCT02075840)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS by INV: Follow-up 37.8 months	alectinib	152	34.8 (17.7-NE) months	23.9 months			HR: 0.43	0.32–0.58	<0.0001	PFS according to RECIST 1.1. Comparison between treatment groups with respect to PFS was based on a stratified log-rank test at a 5% level of significance (two-sided). The Kaplan-Meier method was used to estimate PFS for each group with 95% CI. The stratified Cox proportional hazard regression model used to estimate effect, expressed as an HR with a 95% CI.	(36)
	crizotinib	151	10.9 (9.1–12.9) months								
Median PFS by IRC: 18.6 months follow-up	alectinib	152	25.7 (19.9-NE) months	15.3 months			HR: 0.50	0.36-0.70	p<0.001	Comparison of PFS was based on a stratified log-rank test at a 5% level of significance (two sided). The Kaplan-Meier method was used to estimate PFS for each group with 95% CI. The stratified Cox proportional hazard regression model used to estimate effect, expressed as an HR with a 95% CI.	(24, 47)
	crizotinib	151	10.4 (7.7-14.6) months								

Median OS: 48.2 months follow-up	alectinib	152	NR (64.3–NR) month	NR	HR: 0.67	0.46–0.98	0.0376	The Kaplan-Meier method was used to estimate OS for each group with 95% CI. The stratified Cox proportional hazard regression model used to estimate effect, expressed as an HR with a 95% CI. Secondary endpoints analysed with use of hierarchical testing to account for multiplicity.	(16)
	crizotinib	151	57.4 (34.6–NR)						
Objective response rate: median follow-up 27.8 months	alectinib	152	82.9% (75.95-88.51)	7.4%			P=0.09	Investigator assessed ITT population. Calculated by using the Clopper-Pearson method, with treatment groups compared by using stratified Mantel-Haenszel test for differences in response.	(36)
	crizotinib	151	75.5% (67.84-82.12						
Duration of response, DOR: median follow-up 27.8 months	alectinib	126	33.1 (31.3, NE) months	22.0 months				DOR times associated with each treatment arm were summarised using the Kaplan–Meier method. For DOR, the median and 95% CI for the median were also calculated.	(24, 36)
	crizotinib	114	11.1 months (7.9-13.0)						
Time to CNS progression:	alectinib	152	NF		HR: 0.16	0.10-0.28	<0.0001	The Cox proportional hazards model was fitted to compute the	(24, 47)

18.6 month follow-up	crizotinib	151	NF				treatment HRs and the corresponding 95% CIs for IC-TTP.	
Adverse events: Grade 3-5, all-causality: 48.2 months follow-up	alectinib	152	79 pt (52.0%)	4.3%			The safety population included patients who received at least one dose of study drug. NCI-CTC-for AEs version 4.03 used.	(16)
	crizotinib	151	85 pt (56.3%)					
Drug Discontinua-tion, % due to AEs: 48.2 months follow-up	alectinib	152	22 (14.5%)	0.1%				(16)
	crizotinib	151	22 (14.6%)					
HRQoL: TTD, Time to deterioration in Global Health status	alectinib	152	NR		HR: 0.72	0.38–1.39	TTD scores were summarized using Kaplan-Meier methods and a stratified log-rank test was used to compare TTD between arms. If a baseline or post-baseline PRO evaluation was not available, TTD was censored at the date of randomization. If they had not deteriorated, patients were censored at the time when they last completed a PRO assessment.	(37)
	crizotinib	151	NR					

Results of ALTA-1L (NCT02737501)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median PFS by BIRC: Follow-up 40.4 months	brigatinib	137	24.0 (18.5-43.2) months	13 months			HR: 0.48	0.35–0.66	<0.0001	Evaluated in ITT population according to RECIST 1.1.death or use of radiotherapy to the brain, whichever occurred first. PFS was compared between arms using a 2-sided stratified log-rank test. The Kaplan-Meier method was used to estimate PFS for each group with 95% CI. The stratified Cox proportional hazard regression model used to estimate effect, expressed as an HR with a 95% CI.	(19)
	crizotinib	138	11.0 (9.1–13.0) months								
Median PFS by INV: Follow-up 40.4 months	brigatinib	137	30.8 months (21.3-40.6)				HR: 0.43	0.31-0.58	<0.0001	Evaluated in ITT population. PFS was compared between arms using a 2-sided stratified log-rank test. The Kaplan-Meier method was used to estimate PFS for each group with 95% CI. The stratified Cox proportional hazard regression model used to estimate effect, expressed as an HR with a 95% CI.	(19)
	crizotinib	136	9.2 months (7.4-12.7)								

Median OS: 40.4 months follow-up	brigatinib	137	NE	NE	HR: 0.81	0.53–1.22	0.3311	Evaluated in ITT population. Analysis of OS was performed using 2-sided stratified log rank test. Time to event analysis estimated median values and 2-sided CI using Kaplan-Meier method. Stratified for presence of iCNS metastases at baseline and prior chemotherapy.	(19, 25)
	crizotinib	138	NR						
Objective response rate, BIRC: % (95%CI)	brigatinib	137	74.5% (66-82)	12.2%			0.0330	Confirmation of response occurred ≥ 4 weeks after initial response. Stratified by presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran Mantel-Haenszel test, respectively.	(19)
40.4-month follow-up	crizotinib	138	62.3% (54-70)						
Duration of response, DOR: median (95% CI) 40.4 months follow-up	brigatinib	102	33.2 months (22.1-NR)	19.4 months				DOR times associated with each treatment arm were summarised using the Kaplan–Meier method. The Cox proportional hazards model was fitted to compute the treatment HRs. For DOR, the median and 95% CI for the median were also calculated.	(19, 25)
	crizotinib	86	13.8 months (10.4-22.1)						
IC-TTP, median (95% CI) BIRC 11.0 months follow-up	brigatinib	137			HR: 0.30	0.15-0.60	<0.0001	A competing risk analysis of intracranial progression, where the time to cause-specific event is defined as time from randomization to the first cause-specific event. Patients with other prior competing events were no longer at risk for the cause-specific event and were censored at the time of these competing events. Patients without any events were censored at the last assessment timepoint.	(38)
	crizotinib	138							

Adverse events: Grade 3-4, all-causality 40.4 month follow-up	brigatinib	136	95 pt (70%)	14%				The safety population included patients who received at least one dose of study drug. NCI-CTC-for AEs version 4.03 was used. All adverse events (AEs) starting/worsening on or after the first dose of study treatment and no later than 30 days after the last dose date were considered as treatment emergent. Adverse Events captures all events experienced during the study. There is therefore no causality assessment associated with AEs. AEs were coded in MedDRA. Worsening of signs and symptoms associated with progression of the underlying disease was considered Adverse Events.	(19)
	crizotinib	137	77 pt (56%)						
Drug Discontinuation, %: 40.4-month follow-up	brigatinib	136	18 (13%)	4%					(19)
	crizotinib	137	12 (9%)						
HRQoL: Median time to deterioration in GHS	brigatinib	137	26.7 months (8.3-NE)	18.4 months	HR:0.69	0.49-0.98	p=0.047	The time to worsening in EORTC QLQ-C30 GHS/QoL and other functioning and symptom scores (defined as a ≥ 10-point decrease from baseline) in patients with baseline and any postbaseline EORTC assessment were compared between treatment arms using a two-sided stratified log-rank test. Kaplan-Meier plot of time to worsening in EORTC QLQ-C30 GHS score.	(19)
	crizotinib	138	8.3 months (5.7-13.5)						

Results of B7461001 (NCT01970865)									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Overall survival: Month (95%CI) (72.7 month follow up)	EXP1 lorlatinib	30	NR (NR-NR) months	NA			NA			For time to event timepoints such as OS median values and two-sided 95 % CI were estimated using Kaplan-Meier methods.	(40)
	EXP2-3A	59	NR (51.5-NR)								
	EXP3B	28	37.4 (12.3-NR)								
	EXP4-5	111	19.2 (15.4-30.2)								
	EXP3B-5	139	20.7 (16.1-30.3)								
Progression-free survival: Month (95%CI)	EXP1 lorlatinib	30	17.7 (12.5-40.5)	NA			NA			For time to event timepoints such as PFS median values and two-sided 95 % CI were estimated using Kaplan-Meier methods.	(40)
	EXP2-3A	59	12.5 (8.2-22.2)								
	EXP3B	28	5.5 (3.2-9.0)								
	EXP4-5	111	7.1 (5.5-11.0)								
	EXP3B-5	139	6.9 (5.5-8.4)								
Confirmed objective response rate, ORR: % (95% CI)	EXP1 lorlatinib	30	90 % (73.5-97.9)	NA			NA			Objective response according to RECIST version 1.1. Corresponding 95 % CI s were calculated using the exact method based on binomial distribution. Cut off March 15, 2017.	(5)
	EXP2-3A	59	69.5 % (56.1-80.8)								
	EXP3B	28	32.1 % (15.9-52.4)								
	EXP4-5	111	38.7 % (29.6-48.5)								

	EXP2-5	198	47 % (39.9-54.2)				
Intracranial responses: % (95% CI)	EXP1 lorlatinib	3	66.7 % (9.4-99.2)	NA	NA		(5)
	EXP2-3A	23	87.0 % (66.4-97.2)				
	EXP3B	9	55.6 % (21.2-86.3)				
	EXP4-5	49	53.1 % (38.3-67.5)				
	EXP2-5	81	63 % (51.5-73.4)				
HRQoL: Change in Global Quality of Life score:	EXP2–5:	184		NA	NA	PROs were assessed using the EORTC QLQ-C30 global health status scale and its corresponding Lung Cancer Module (QLQ-LC13) and were summarised with descriptive statistics.	(5)
	≥10-point improvement from baseline:		72 pat. (39.1 %)				
	Stable (less than 10 % change):		78 pat. (42.4%)				
	≥10-point decrease from baseline		34 pat. (18.5%)				

Appendix C. Comparative analysis of efficacy

To facilitate a comparison of lorlatinib versus brigatinib and alectinib, an indirect treatment comparison was carried out. As all trials shared a common comparator (crizotinib), and trials were considered sufficiently similar to allow for indirect treatment comparison without population adjustment, a frequentist NMA was chosen as the appropriate method for indirect comparison.

This application includes three studies reporting efficacy data for either lorlatinib, brigatinib, or alectinib for the treatment of NSCLC in ALK-positive patients: the CROWN, ALTA-1, and ALEX trials. A description of the trial design and methods is provided in section 6. The data, and sources for data, included in the NMA is presented in C.1.

C.1 Overview of included data and studies

The efficacy data included for each of the three included trials (CROWN, ALTA-1, and ALEX) as well as the sources for the data are shown in Table 60. Safety data and sources are shown in Table 61. Baseline characteristics and treatment are detailed in Table 62 and Table 63.

Table 60 Efficacy data included in the NMA of lorlatinib versus brigatinib and alectinib

Outcome	CROWN Lorlatinib (n = 149) versus crizotinib (n= 147)	ALTA-1 Brigatinib (n = 137) versus crizotinib (n = 138)	ALEX Alectinib (n = 152) versus crizotinib (n = 151)
OS	HR: 0.72 (95% CI: 0.41 to 1.25)(32)	HR: 0.92 (95% CI: 0.57 to 1.47)(19)	HR: 0.67 (0.46 to 0.98)(16)
PFS (by investigator)	HR: 0.19 (95% CI: 0.13 to 0.27)(17)	HR: 0.43 (95% CI: 0.31 to 0.58)(19)	HR: 0.43 (95% CI: 0.32 to 0.58)(16)
PFS (by BICR)	HR: 0.27 (95% CI: 0.18 to 0.39)(33)	HR: 0.48 (0.35 to 0.66)(19)	HR: 0.50 (95% CI: 0.36 to 0.70)(47)
IC-TTP	HR: 0.06 (95% CI: 0.03 to 0.12)(17)	HR: 0.30 (0.15 to 0.60)(38)	HR: 0.16 (95% CI: 0.10 to 0.28)(47)

Abbreviations: CI: confidence interval; HR: hazard ratio; IC-TTP: Intra-cranial time to progression; OS: overall survival; PFS: progression-free survival

Table 61 Safety data included in the NMA of lorlatinib versus brigatinib and alectinib

Outcome	CROWN(17)		ALTA-1(19)		ALEX(16)	
	Lorlatinib (n = 149)	Crizotinib (n = 142)	Brigatinib (n = 136)	Crizotinib (n = 137)	Alectinib (n = 152)	Crizotinib (n = 151)
Grade 3-4 adverse events	115	81	95	77	72	78
Adverse events leading to discontinuation	16	15	18	12	22	22

Note: Patient numbers are for the safety populations in the respective studies.

Table 62 Baseline characteristics of patients included for in the NMA (32, 38)

	CROWN		ALEX		ALTA-1L	
	Lorlatinib (n=149)	Crizotinib (n=147)	Alectinib (n=152)	Crizotinib (n=151)	Brigatinib (n=137)	Crizotinib (n=138)
Age, years mean+/- SD	59.1 ± 13.1	55.6 ±13.5	56.3 ± 12.0	53.8 ± 13.5	58 (27-86)	60 (29-89)
Male, n (%)	65 (44)	56 (38)	68 (45)	64 (42)	68 (50)	57 (41)
Ethnic group, n (%)						
Non-Asian	72 (48)	73 (50)	83 (55)	82 (54)	78 (57)	89 (64)
Asian	65 (44)	65 (44)	69 (45)	69 (46)	59 (43)	49 (36)
Missing	12 (8)	9 (6)	0	0	0	0
ECOG PS, n (%)						

0/1	146 (98)	138 (94)	142 (93)	141 (93)	131(96)	132 (96)
2	3 (2)	9(6)	10 (7)	10 (7)	6 (4)	6 (4)
Smoking status, n (%)						
Never	81 (54)	94 (64)	92 (61)	98 (65)	84 (61)	75 (54)
Previous	55 (37)	43 (29)	48 (32)	48 (32)	49 (36)	56 (41)
Current	13 (9)	9(6)	12 (8)	5 (3)	4 (3)	7 (5)
Stage of disease, n (%)						
IIIA	1 (1)	0				
IIIB	12 (8)	8 (5)	4 (3)	6(4)	8 (6)	12(9)
IV	135 (91)	139 (95)	148 (97)	145 (96)	129 (94)	126 (91)
Other*	1 (1)	0	0	0	0	0
Histological type, n (%)						
Adenocarcinoma	140 (94)	140 (95)	137 (90)	142 (94)	126 (92)	137 (99)
Other**	9 (6)	7 (5)	15 (10)	9 (6)	11 (8)	1 (1)
Brain metastases at baseline, n (%)***	38 (26)	40 (27)	64 (42)	58 (38)	40 (29)	41 (30)
Previous brain radiotherapy, n (%)	9 (6)	10 (7)	26 (17)	21 (14)	18 (13)	19 (14)

Table 63 Summary of treatment and their respective subsequent treatments for the studies included in the NMA

Study name	Study drug	Patients (ITT)	Dose	Route of admin	Cross-over	Lorlatinib subsequent therapy	Alectinib subsequent therapy	Brigatinib subsequent therapy	Crizotinib subsequent therapy	Ceritinib subsequent therapy
CROWN(17, 63)	Lorlatinib	149	100 mg QD	Oral	No	3/46 (6.5%); 3/149 (2.0%)[a,b]	12/46 (26.1%); 12/149 (8.1%)[a,b]	1/46 (2.2%); 1/149 (0.7%)[a,b]	4/46 (8.7%); 4/149 (2.75)[a,b]	3/46 (6.5%); 3/149 (2.0%)[a,b]
	Crizotinib	147	250 mg BID	Oral	No	4/110 (3.6%); 4/147 (2.7%)[a]	68/110 (61.8%); 68/147 (46.3%)[a]	21/110 (19.1%); 21/147 (14.3%)[a]	5/110 (4.5%); 5/147 (3.4%)[a]	3/110 (2.7%); 3/147 (2.0%)[a]
ALEX[a](16, 27, 36, 64)	Alectinib	152	600 mg BID	Oral	No	11/84 (13.1%); 11/152 (7.3%)[a]	2/84 (2.4%); 2/152 (1.3%)[a]	8/84 (9.5%); 8/152 (5.3%)[a]	11/84 (13.1%); 11/152 (7.3%)[a]	7/84 (8.3%); 7/152; (4.6%)[a]
	Crizotinib	151	250 mg BID	Oral	No	10/114 (8.8%); 10/151 (6.6%)[a]	24/114 (21.1%); 24/151 (15.8%)[a]	11/114 (9.6%); 11/151(72%)[a]	9/114 (7.9%); 9/151 (5.9%)[a]	24/114 (21.1%); 24/151 (15.8%)[a]
ALTA-1L(52, 65)	Brigatinib	137	180 mg QD	Oral	Yes	22/74 (29.7%); 22/137 (16.2%)[a]	16/74 (21.6%); 16/137 (11.8%)[a]	2/74 (2.7%); 2/137 (1.5%)[a]	11/74 (14.9%); 11/137 (8.1%)[a]	4/74 (5.4%); 4/137 (2.9%)[a]
	Crizotinib	138	250 mg BID	Oral	Yes	21/101 (20.8%); 21/138 (15.3%)[a]	28/101 (27.7%); 28/138 (20.4%)[a]	80/101 (79.2%); 80/138 (58.4%)[a]	6/101 (5.9%); 6/138 (4.4%)[a]	5/101 (5.0%); 5/138 (3.6%)[a]

Key: BID, twice daily; ITT, intention-to-treat; QD, once a day.

Notes: [a] n/N (% over PD); n/N (% over total patients); b, only includes second-line treatments

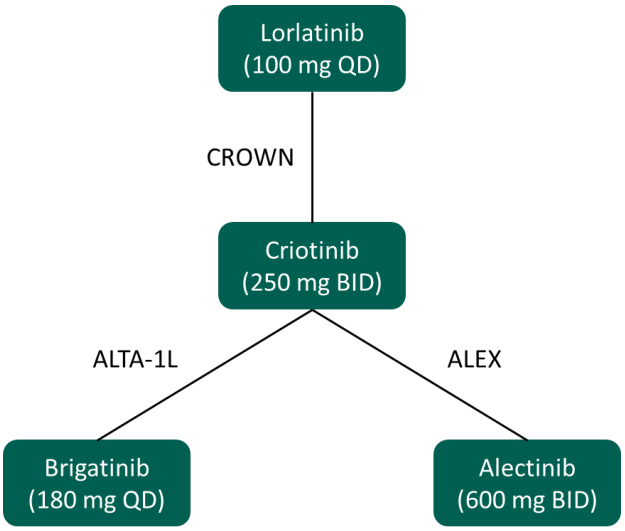
C.2 Method of synthesis

The included studies were combined using frequentist NMA methodology as implemented in the *netmeta* package for R(50). The detailed methods of the frequentist NMA are described in the paper accompanying the R package (Balduzzi et al. 2023) and will not be described in detail here.

The *netmeta* package adopts the approach proposed by Rücker, which relies on graph-theoretical methods(49). All efficacy outcomes included in the NMA were time-to-event outcomes, and thus random- and fixed effect models were fitted with the *netmeta* function, using HRs as the summary measure. As all safety outcomes were binary, random- and fixed effect models were fitted with the *netmetabin* function, using risk ratios (RR) as the summary measure. The pooling of study-specific estimates was done using the inverse-variance method, where more weight is given to studies with larger sample sizes and more precise estimates. For the random-effects model, the direct treatment estimates are based on the common between-study variance τ^2 from the network meta-analysis. The default estimator for τ^2 in the *netmeta* package, is a special case of the generalised DerSimonian-Laird estimate(50).

Within-design heterogeneity (i.e., heterogeneity between studies examining the same treatments, e.g., nirsevimab versus placebo) can be assessed using τ^2. Between-design heterogeneity can only be assessed when "closed loops" exist in the treatment network, i.e., when at least one comparison is informed by both direct and indirect evidence. As the treatment network employed here (shown in Figure 45) only contains one trial for each comparison and no closed loops, neither within- or between-design heterogeneity was assessed. Therefore, only fixed-effects results were presented.

Figure 45 Network graph for NMA of lorlatinib versus brigatinib and alectinib



Abbreviations: BID: Twice a day; NMA: Network meta-analysis; QD: Once a day

C.3 Results of NMA

C.3.1 Overall survival

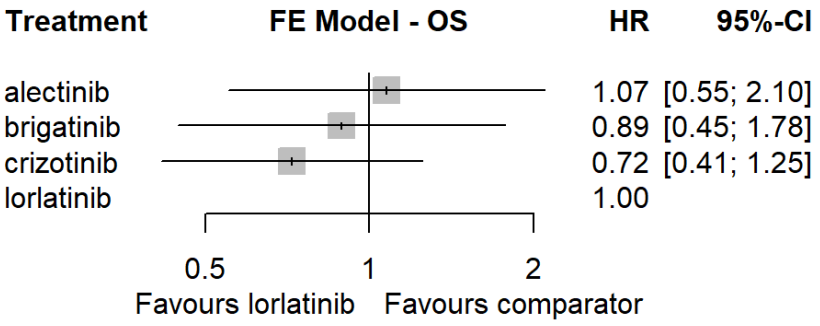
The results of the frequentist NMA for overall survival are shown in Table 64 and Figure 46. As random- and fixed effect models produced the same results (due to the structure of the network), only results from the fixed effect model are presented.

Table 64 Results of NMA for overall survival

	Lorlatinib	Brigatinib	Alectinib	Crizotinib
Lorlatinib	N/A	HR: 0.89 95% CI: 0.45 - 1.78	HR: 1.07 95% CI: 0.38 - 1.62	HR: 0.72 95% CI: 0.38 - 1.62
Brigatinib	HR: 1.12 95% CI: 0.56 – 2.25	N/A	HR: 1.21 95% CI: 0.69 – 2.12	HR: 0.81 95% CI: 0.53 – 1.23
Alectinib	HR: 0.93 95% CI: 0.48 – 1.82	HR: 0.83 95% CI: 0.47 – 1.45	N/A	HR: 0.67 95% CI: 0.46 – 0.98
Crizotinib	HR: 1.39 95% CI: 0.80 – 2.41	HR: 1.23 95% CI: 0.81 – 1.87	HR: 1.49 95% CI: 1.02 – 2.18	N/A

Notes: The risk-ratios presented above can be interpreted in the following way: The treatment in the row is the reference treatment and the treatment in the column is the comparator, i.e., lorlatinib versus brigatinib results in a HR of 0.89, whereas brigatinib versus lorlatinib results in a HR of 1.12.

Figure 46 Forest plot of NMA for overall survival - lorlatinib versus comparators



C.3.2 PFS (by investigator)

The results of the frequentist NMA for progression-free survival by investigator are shown in Table 65 and Figure 47. As random- and fixed effect models produced the same

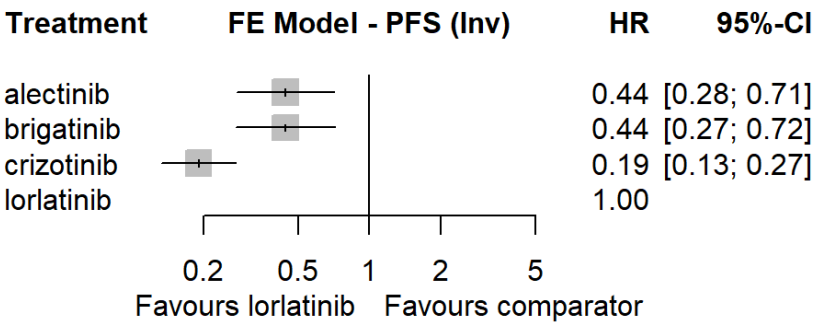
results (due to the structure of the network), only results from the fixed effect model are presented.

Table 65 Results of NMA for progression-free survival (by investigator)

	Lorlatinib	Brigatinib	Alectinib	Crizotinib
Lorlatinib	N/A	HR: 0.44 95% CI: 0.28 - 0.71	HR: 0.44 95% CI: 0.27 – 0.72	HR: 0.19 95% CI: 0.13 – 0.27
Brigatinib	HR: 2.26 95% CI: 1.40 – 3.66	N/A	HR: 1.00 95% CI: 0.65 – 1.54	HR: 0.43 95% CI: 0.32 – 0.58
Alectinib	HR: 2.26 95% CI: 1.41 – 3.63	HR: 1.00 95% CI: 0.65 – 1.54	N/A	HR: 0.43 95% CI: 0.32 – 0.58
Crizotinib	HR: 5.26 95% CI: 3.65 – 7.58	HR: 2.33 95% CI: 1.70 – 3.18	HR: 2.33 95% CI: 1.73 – 3.13	N/A

Notes: The risk-ratios presented above can be interpreted in the following way: The treatment in the row is the reference treatment and the treatment in the column is the comparator, i.e., lorlatinib versus brigatinib results in a HR of 0.44, whereas brigatinib versus lorlatinib results in a HR of 2.26

Figure 47 Forest plot of NMA for progression-free survival (by investigator) - lorlatinib versus comparators



C.3.3 PFS (by BICR)

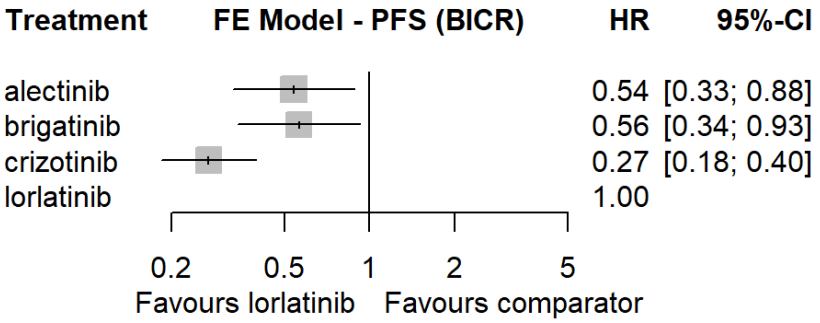
The results of the frequentist NMA for progression-free survival by BICR are shown in Table 66 and Figure 48. As random- and fixed effect models produced the same results (due to the structure of the network), only results from the fixed effect model are presented.

Table 66 Results of NMA for progression-free survival (by BICR)

	Lorlatinib	Brigatinib	Alectinib	Crizotinib
Lorlatinib	N/A	HR: 0.56 95% CI: 0.34 - 0.93	HR: 0.54 95% CI: 0.33 – 0.88	HR: 0.27 95% CI: 0.18 – 0.40
Brigatinib	HR: 1.78 95% CI: 1.08 – 2.93	N/A	HR: 0.96 95% CI: 0.62 – 1.49	HR: 0.48 95% CI: 0.35 – 0.66
Alectinib	HR: 1.85 95% CI: 1.13 – 3.03	HR: 1.04 95% CI: 0.67 – 1.62	N/A	HR: 0.50 95% CI: 0.37 – 0.68
Crizotinib	HR: 3.70 95% CI: 2.52 – 5.45	HR: 2.08 95% CI: 1.52 – 2.86	HR: 2.00 95% CI: 1.48 – 2.71	N/A

Notes: The risk-ratios presented above can be interpreted in the following way: The treatment in the row is the reference treatment and the treatment in the column is the comparator, i.e., lorlatinib versus brigatinib results in a HR of 0.56, whereas brigatinib versus lorlatinib results in a HR of 1.78.

Figure 48 Forest plot of NMA for progression-free survival (by BICR) - lorlatinib versus comparators



C.3.4 IC-TTP

The results of the frequentist NMA for intracranial time-to-progression are shown in Table 67 and Figure 49. As random- and fixed effect models produced the same results (due to the structure of the network), only results from the fixed effect model are presented.

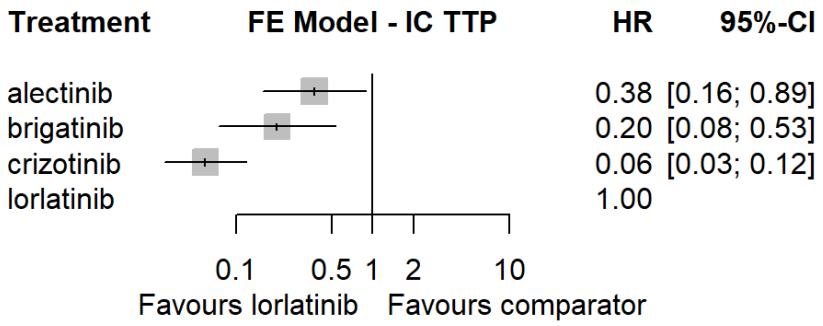
Table 67 Results of NMA for IC-TTP

	Lorlatinib	Brigatinib	Alectinib	Crizotinib

Lorlatinib	N/A	HR: 0.20 95% CI: 0.08 - 0.53	HR: 0.38 95% CI: 0.16 – 0.89	HR: 0.06 95% CI: 0.03 – 0.12
Brigatinib	HR: 5.00 95% CI: 1.88 – 13.33	N/A	HR: 1.88 95% CI: 0.79 – 4.45	HR: 0.30 95% CI: 0.15 – 0.60
Alectinib	HR: 2.67 95% CI: 1.12 – 6.32	HR: 0.53 95% CI: 0.22 – 1.26	N/A	HR: 0.16 95% CI: 0.10 – 0.27
Crizotinib	HR: 16.67 95% CI: 8.33 – 33.33	HR: 3.33 95% CI: 1.67 – 6.67	HR: 6.25 95% CI: 3.74 – 10.46	N/A

Notes: The risk-ratios presented above can be interpreted in the following way: The treatment in the row is the reference treatment and the treatment in the column is the comparator, i.e., lorlatinib versus brigatinib results in a HR of 0.20, whereas brigatinib versus lorlatinib results in a HR of 5.00

Figure 49 Forest plot of NMA for IC-TTP - lorlatinib versus comparators



C.3.5 Grade 3/4 adverse events

The results of the frequentist NMA for intracranial time-to-progression are shown in Table 68 and Figure 50. As random- and fixed effect models produced the same results (due to the structure of the network), only results from the fixed effect model are presented.

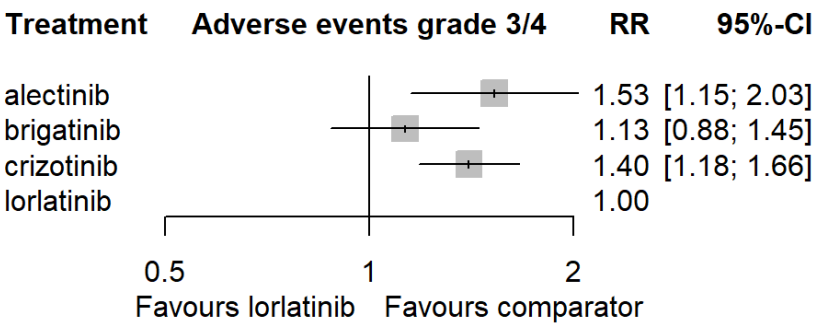
Table 68 Results of NMA for grade 3 and 4 adverse events

	Lorlatinib	**Brigatinib**	**Alectinib**	**Crizotinib**
Lorlatinib	N/A	RR: 1.13 95% CI: 0.88 – 1.45	RR: 1.53 95% CI: 1.15 – 2.03	RR: 1.40 95% CI: 1.18 – 1.66

Brigatinib	RR: 0.89 95% CI: 0.69 – 1.14	N/A	RR: 1.36 95% CI: 1.01 – 1.82	RR: 1.24 95% CI: 1.03 – 1.49
Alectinib	RR: 0.65 95% CI: 0.49 – 0.87	RR: 0.74 95% CI: 0.55 – 0.99	N/A	RR: 0.92 95% CI: 0.73 – 1.15
Crizotinib	RR: 0.71 95% CI: 0.60 – 0.85	RR: 0.80 95% CI: 0.67 – 0.97	RR: 1.09 95% CI: 0.87 – 1.37	N/A

Notes: The risk-ratios presented above can be interpreted in the following way: The treatment in the row is the reference treatment and the treatment in the column is the comparator, i.e., lorlatinib versus brigatinib results in a RR of 1.13, whereas brigatinib versus lorlatinib results in a RR of 0.89

Figure 50 Forest plot of NMA for grade 3 and 4 adverse events - lorlatinib versus comparators



C.3.6 Discontinuation due to adverse events

The results of the frequentist NMA for intracranial time-to-progression are shown in Table 69 and Figure 51. As random- and fixed effect models produced the same results (due to the structure of the network), only results from the fixed effect model are presented.

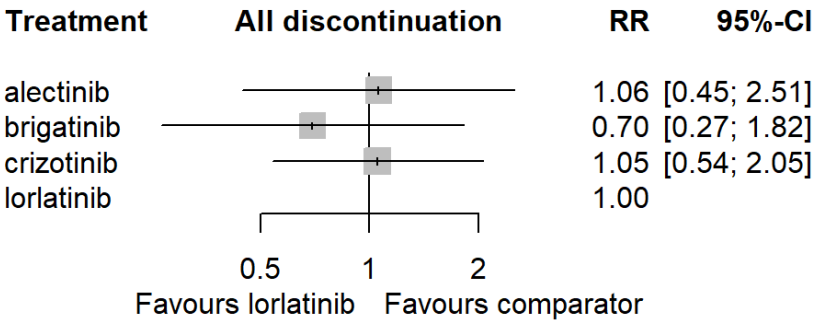
Table 69 Results of NMA for discontinuation due to adverse events

	Lorlatinib	Brigatinib	Alectinib	Crizotinib
Lorlatinib	N/A	RR: 0.70 95% CI: 0.27 – 1.82	RR: 1.06 95% CI: 0.45 – 2.51	RR: 1.05 95% CI: 0.54 – 2.05
Brigatinib	RR: 1.44 95% CI: 0.55 – 3.75	N/A	RR: 1.52 95% CI: 0.63 – 3.67	RR: 1.51 95% CI: 0.76 – 3.02

Alectinib	RR: 0.94 95% CI: 0.40 – 2.23	RR: 0.66 95% CI: 0.27 – 1.59	N/A	RR: 0.99 95% CI: 0.58 – 1.72
Crizotinib	RR: 0.95 95% CI: 0.49 – 1.85	RR: 0.66 95% CI: 0.33 – 1.32	RR: 1.01 95% CI: 0.58 – 1.74	N/A

Notes: The risk-ratios presented above can be interpreted in the following way: The treatment in the row is the reference treatment and the treatment in the column is the comparator, i.e., lorlatinib versus brigatinib results in a RR of 0.70, whereas brigatinib versus lorlatinib results in a RR of 1.44

Figure 51 Forest plot of NMA for discontinuation due to adverse events - lorlatinib versus comparators



Per instructions in the DMC application template, Table 70 was not filled out as the application did not include a meta-analysis. Please see the tables above for results of the NMA.

Table 70 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
NA. Please see the results of the NMA in the tables above		NA	NA	NA	NA	NA	NA		NA

C.4 Assessment of proportional hazards

As PFS, OS, IC-PFS, and IC-TTP are time-to-event endpoints, the relative effect estimates are expressed as HRs, which are assumed constant over time (i.e. the HR is assumed to remain constant beyond the period observed in clinical trials). As such, the HR relies on the assumption of proportional hazards (PH), which has been tested in exploratory analyses by visual assessment of Kaplan–Meier, log-cumulative hazard curves, and Schoenfeld residual plots, and statistically through the Schoenfeld individual test. These are presented further below.

Where Kaplan–Meier curves were reported for OS, PFS (both INV and BICR assessed), and IC-TTP in the ITT population, the PH assumption has been assessed – this is outlined in Table 71. Across all endpoints, there is evidence against the PH assumption for most studies, particularly for the CROWN study.

Using standard NMA methods is likely to introduce bias to results and could underestimate the treatment effect of lorlatinib, particularly at the end of the study. Therefore, a standard NMA may be a more conservative approach for analysis and ultimately underestimate the relative treatment effect between lorlatinib and comparator treatments.

Table 71 Overview of assessment of proportional hazards assumption

Trial name	Treatments	OS PH assessment	PFS (investigator) PH assessment	PFS (BICR) PH assessment	IC-TTP PH assessment
CROWN	Lorlatinib Crizotinib	Potential evidence against the PH assumption: ▪ LCH are not parallel; overlap at the start and end of the time period ▪ Schoenfeld residual plot approximately horizontal (p > 0.05)	Evidence against the PH assumption: ▪ LCH are not parallel; overlap at the start of the time period and then diverge ▪ Schoenfeld residual plot not horizontal **(p < 0.05)**	Evidence against the PH assumption: ▪ LCH are not parallel; overlap at the start of the time period and then diverge ▪ Schoenfeld residual plot not horizontal **(p < 0.05)**	Potential evidence against the PH assumption: ▪ LCH are not parallel; diverge throughout the time period ▪ Schoenfeld residual plot mostly horizontal
ALEX	Alectinib Crizotinib	Potential evidence against the PH assumption: ▪ Log-cumulative hazard curves overlap and are not parallel ▪ Schoenfeld residual plot approximately horizontal (p > 0.05)	Evidence against the PH assumption: ▪ Log-cumulative hazard curves are not parallel; overlap at ~5 months and then diverge ▪ Schoenfeld residual plot not horizontal **(p < 0.05)**	Evidence against the PH assumption: ▪ Log-cumulative hazard curves are not parallel; overlap at the start of the time period and then diverge ▪ Schoenfeld residual plot not horizontal **(p < 0.05)**	Evidence against the PH assumption: ▪ Log-cumulative hazard curves are not parallel; overlap at the start of the time period and then diverge ▪ Schoenfeld residual plot not horizontal (p > 0.05)
ALTA-1	Brigatinib	Potential evidence against the PH assumption:	No clear evidence against the PH assumption:	No clear evidence against the PH assumption:	Kaplan–Meier NR

	Crizotinib	▪ Log-cumulative hazard curves overlap throughout time period ▪ Schoenfeld residual plot approximately horizontal (p > 0.05)	▪ Log-cumulative hazard curves overlap at the start of the time period (this is acceptable) ▪ Schoenfeld residual plot approximately horizontal (p > 0.05)	▪ Log-cumulative hazard curves overlap at the start of the time period (this is acceptable) ▪ Schoenfeld residual plot approximately horizontal (p > 0.05)

Figure 52 PH assessments plots for CROWN OS

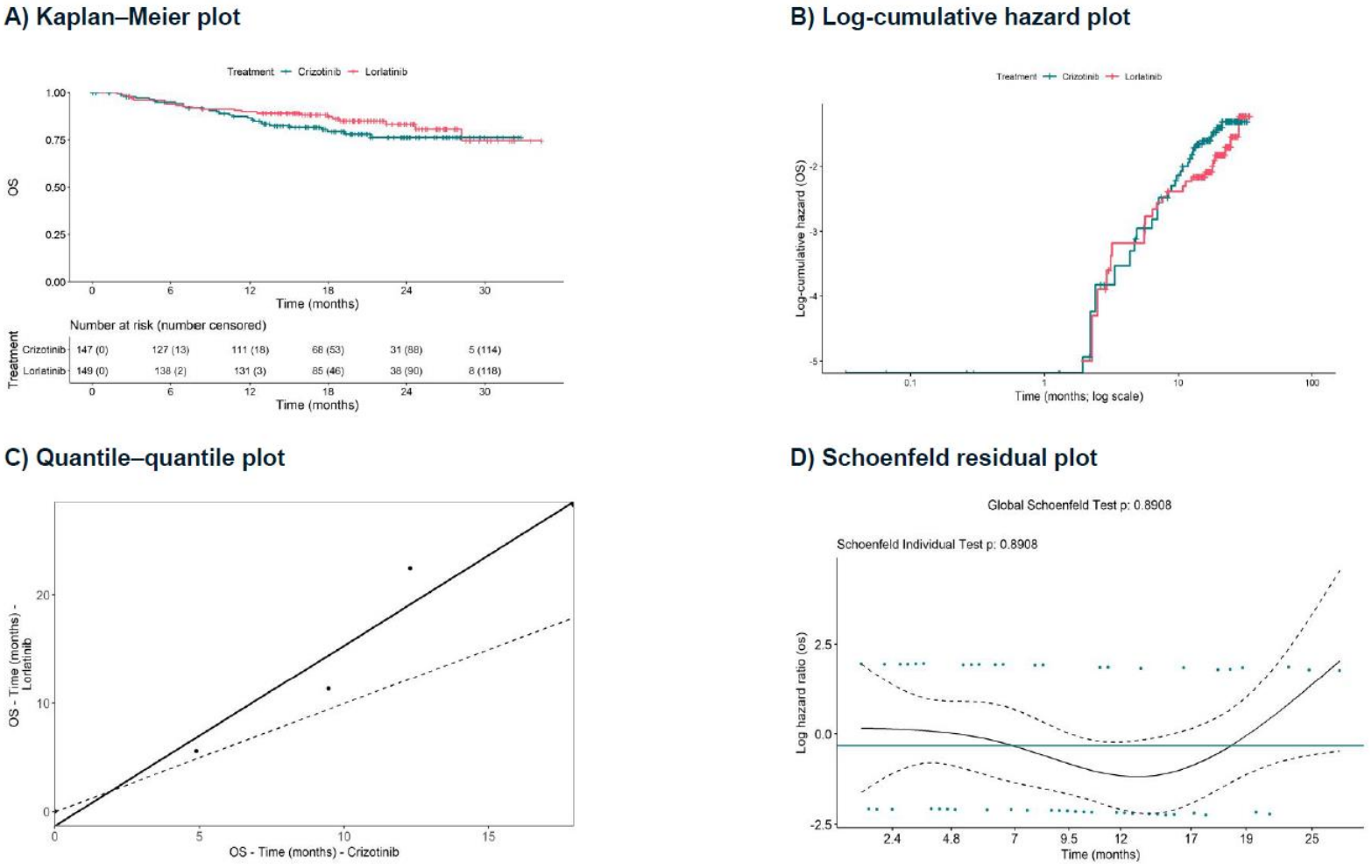


Figure 53 PH assessments plots for ALEX OS

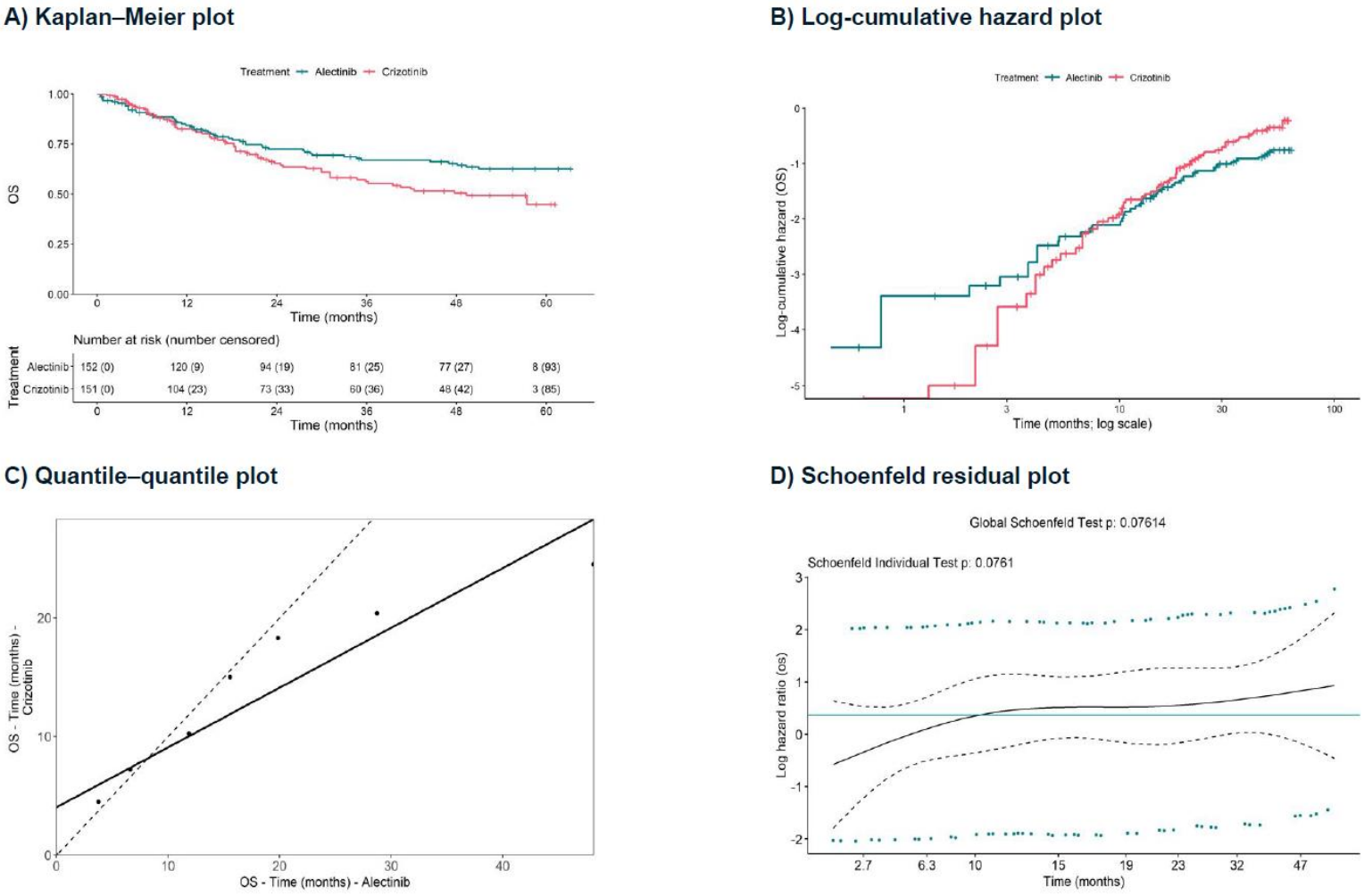


Figure 54 PH assessments plots for ALTA-1L OS

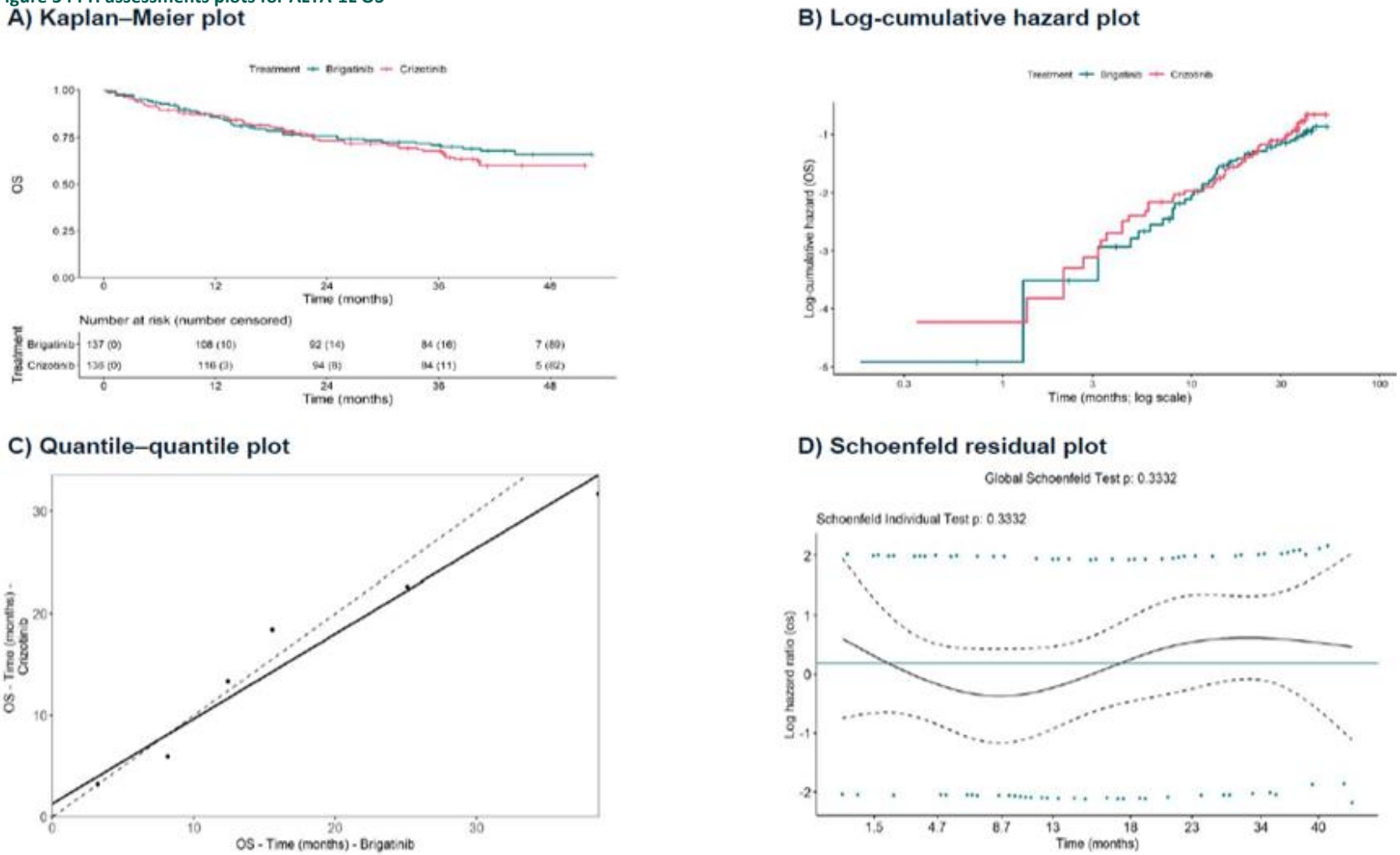


Figure 55 PH assessments plots for CROWN PFS BICR

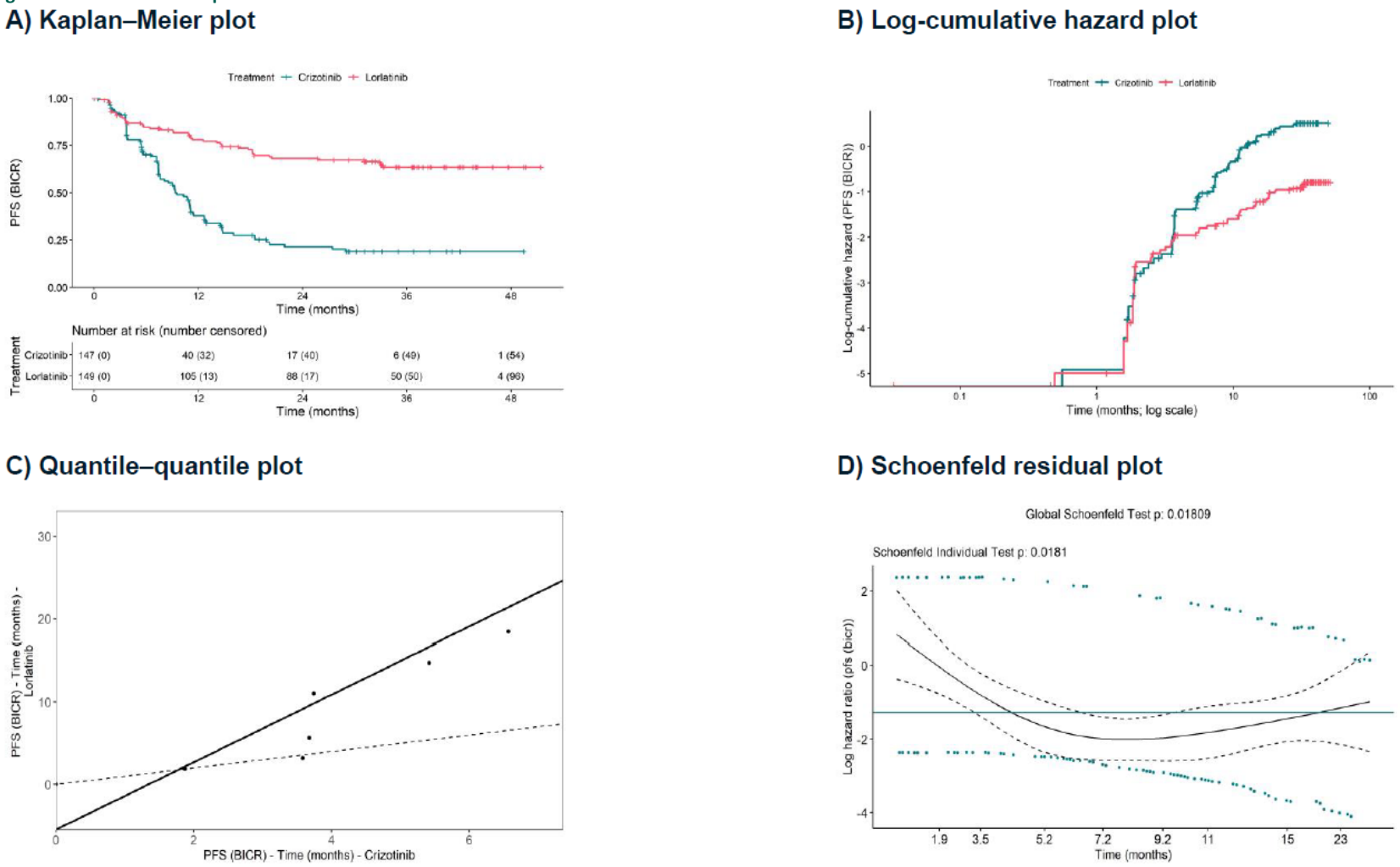


Figure 56 PH assessments plots for ALEX PFS IRC

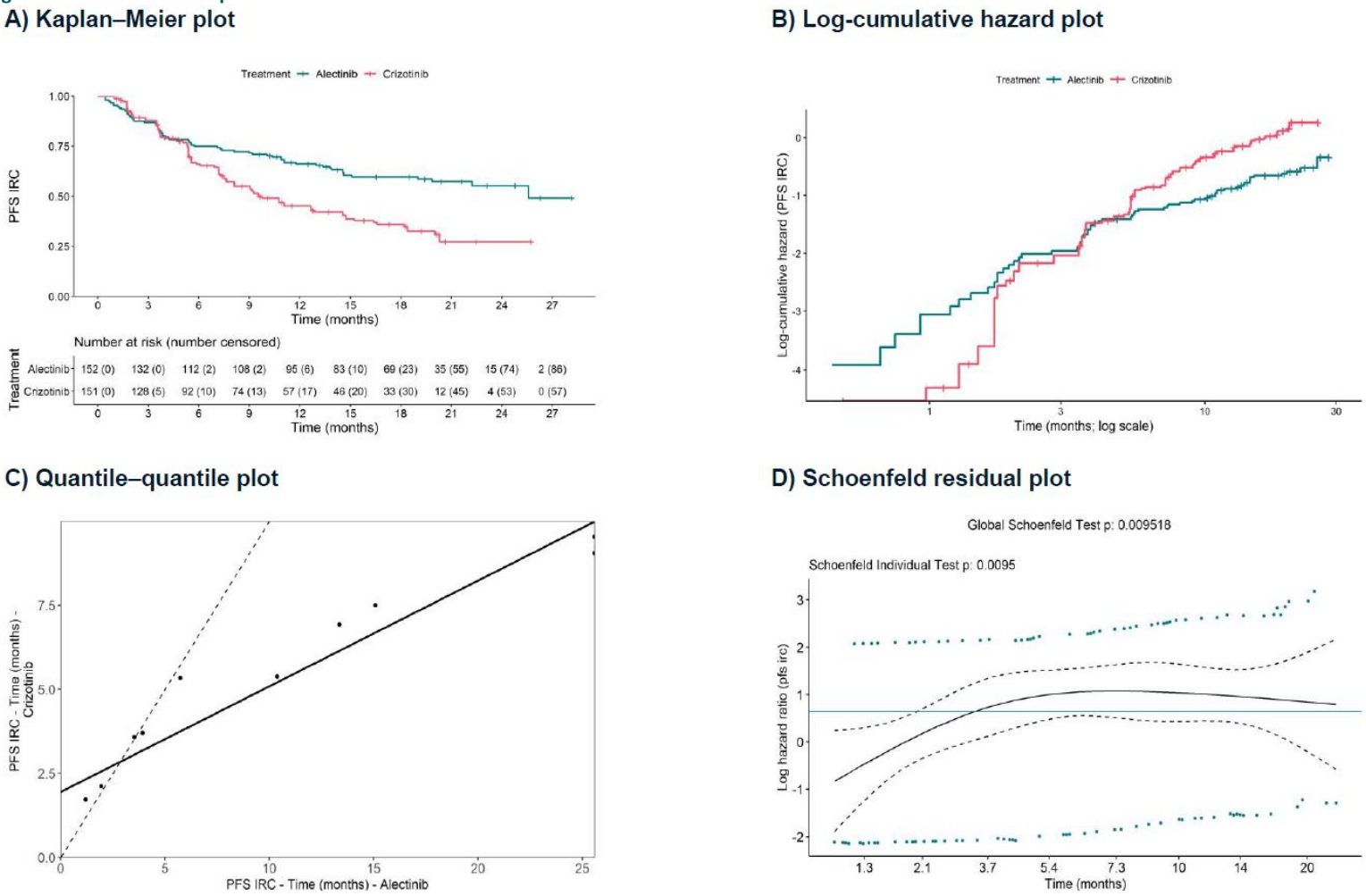


Figure 57 PH assessments plots for ALTA-1L PFS BICR

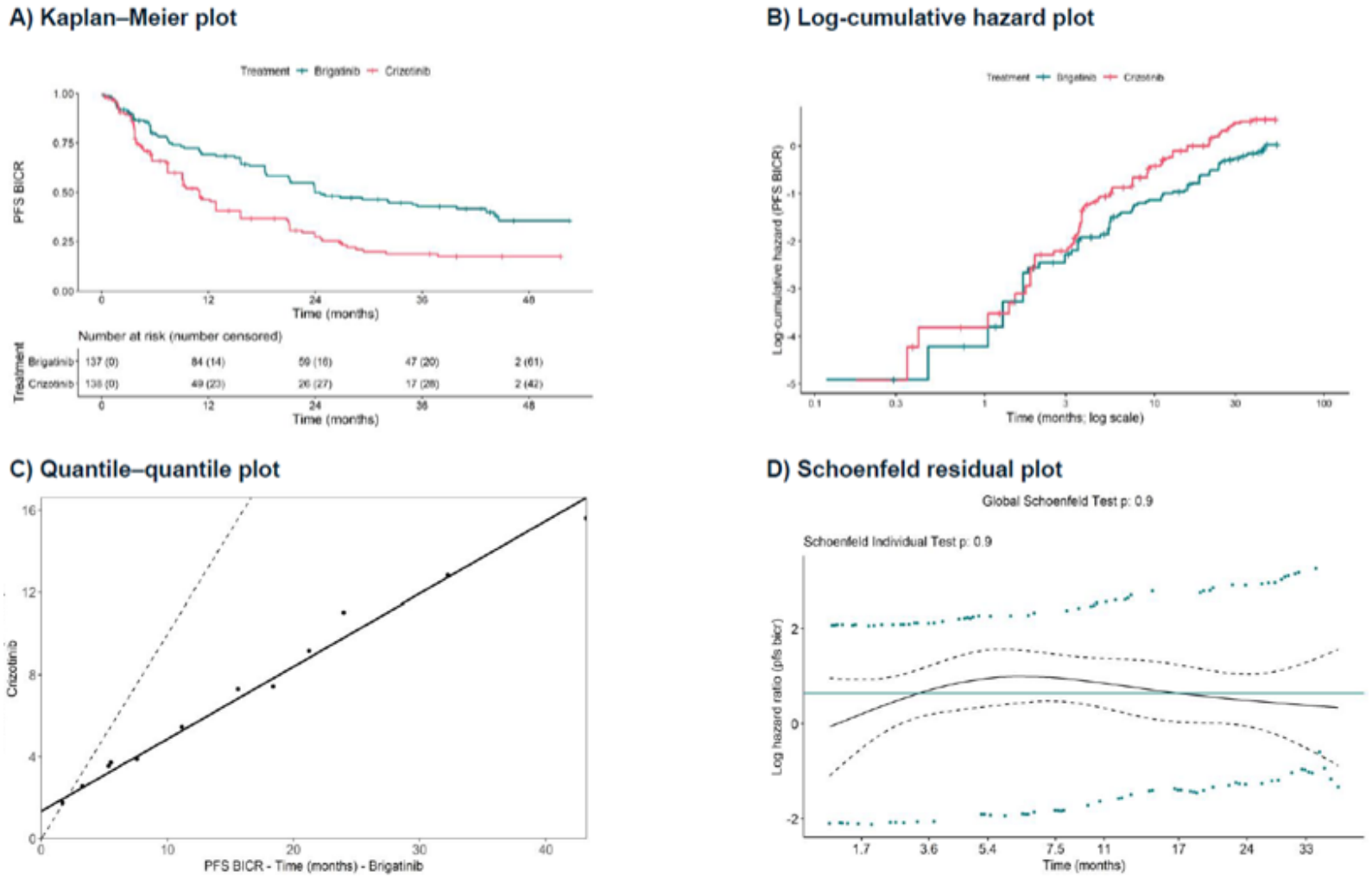


Figure 58 PH assessments plots for CROWN PFS INV

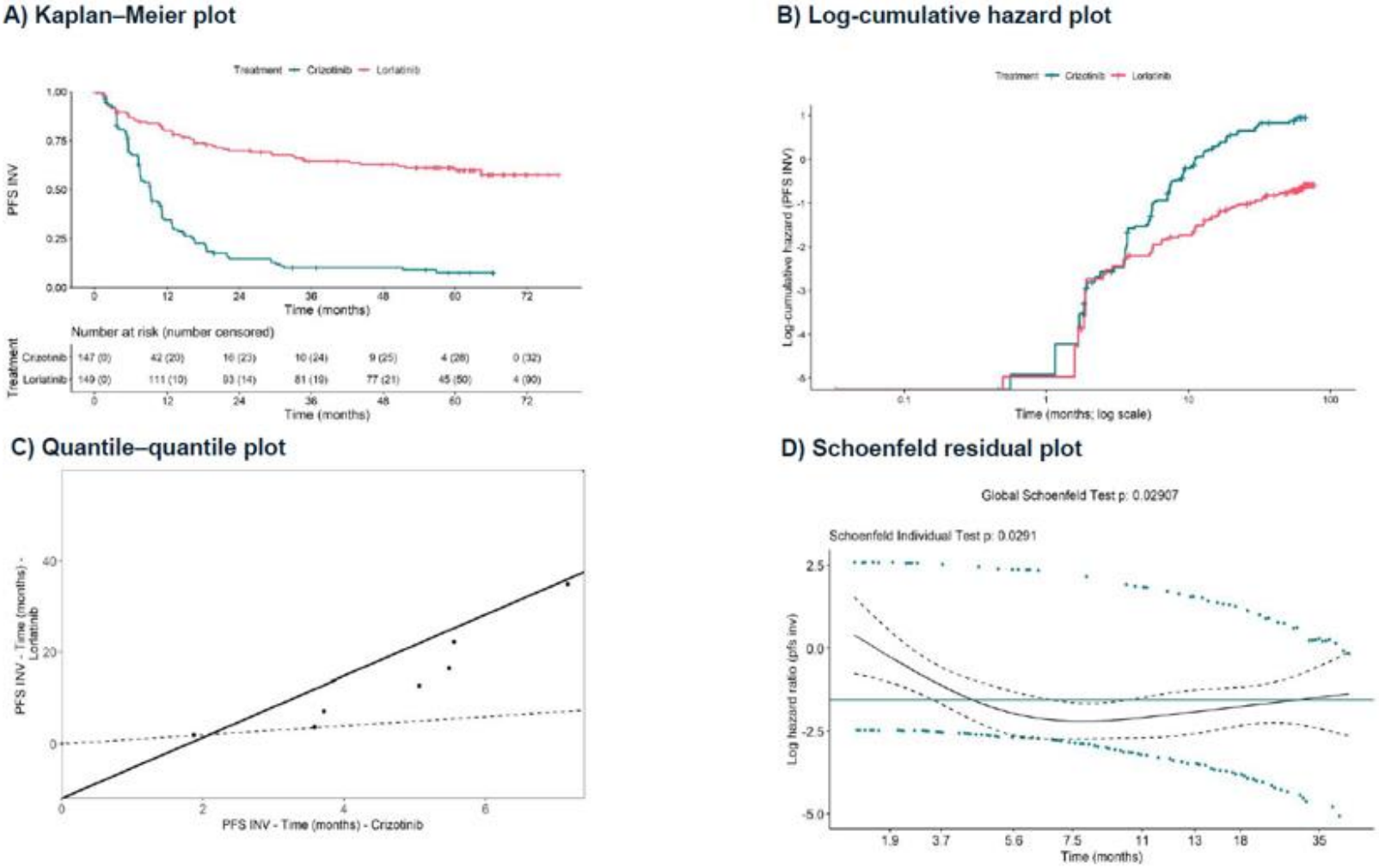


Figure 59 PH assessments plots for ALEX PFS INV

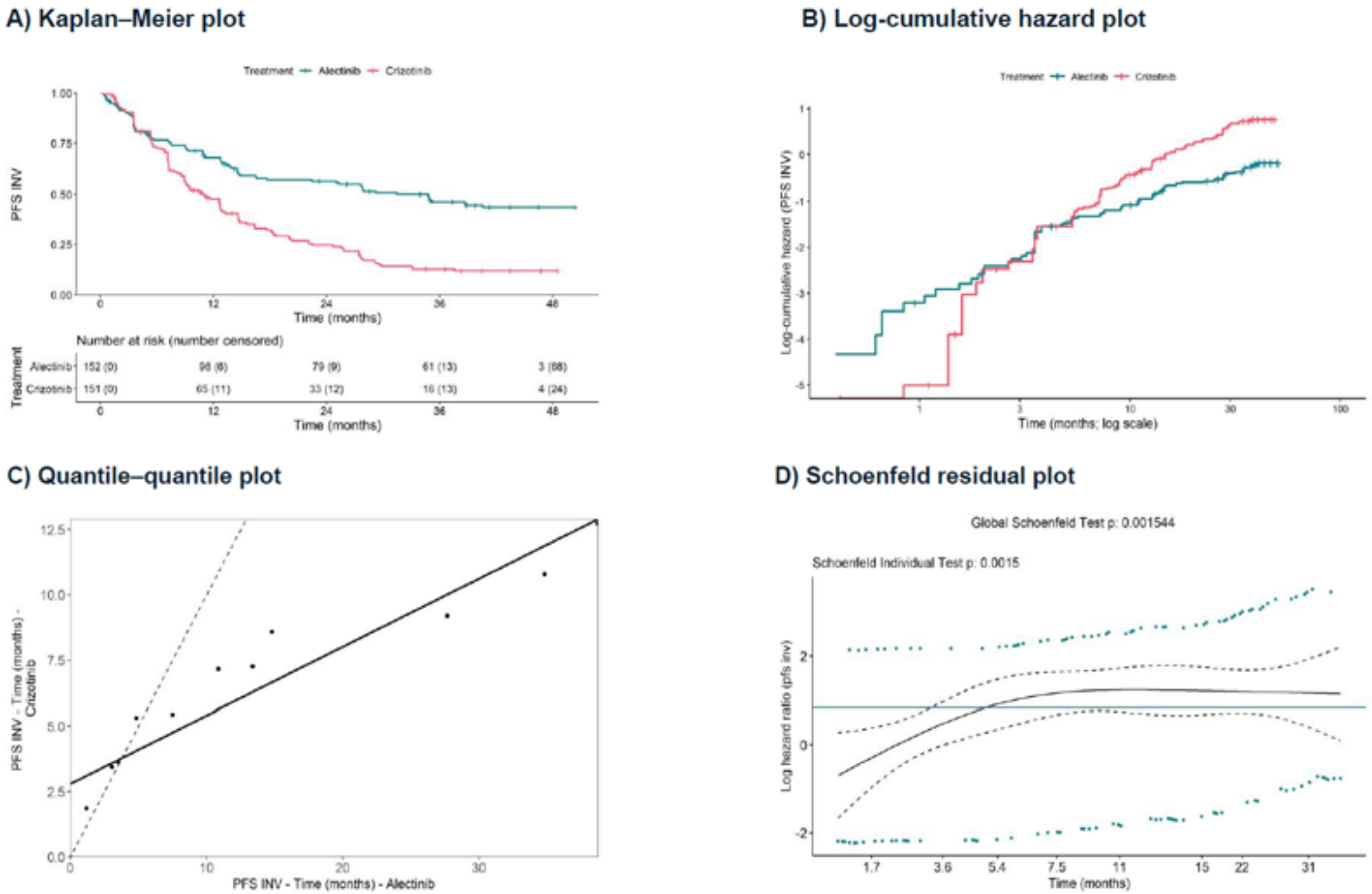


Figure 60 PH assessments plots for ALTA-1L PFS INV

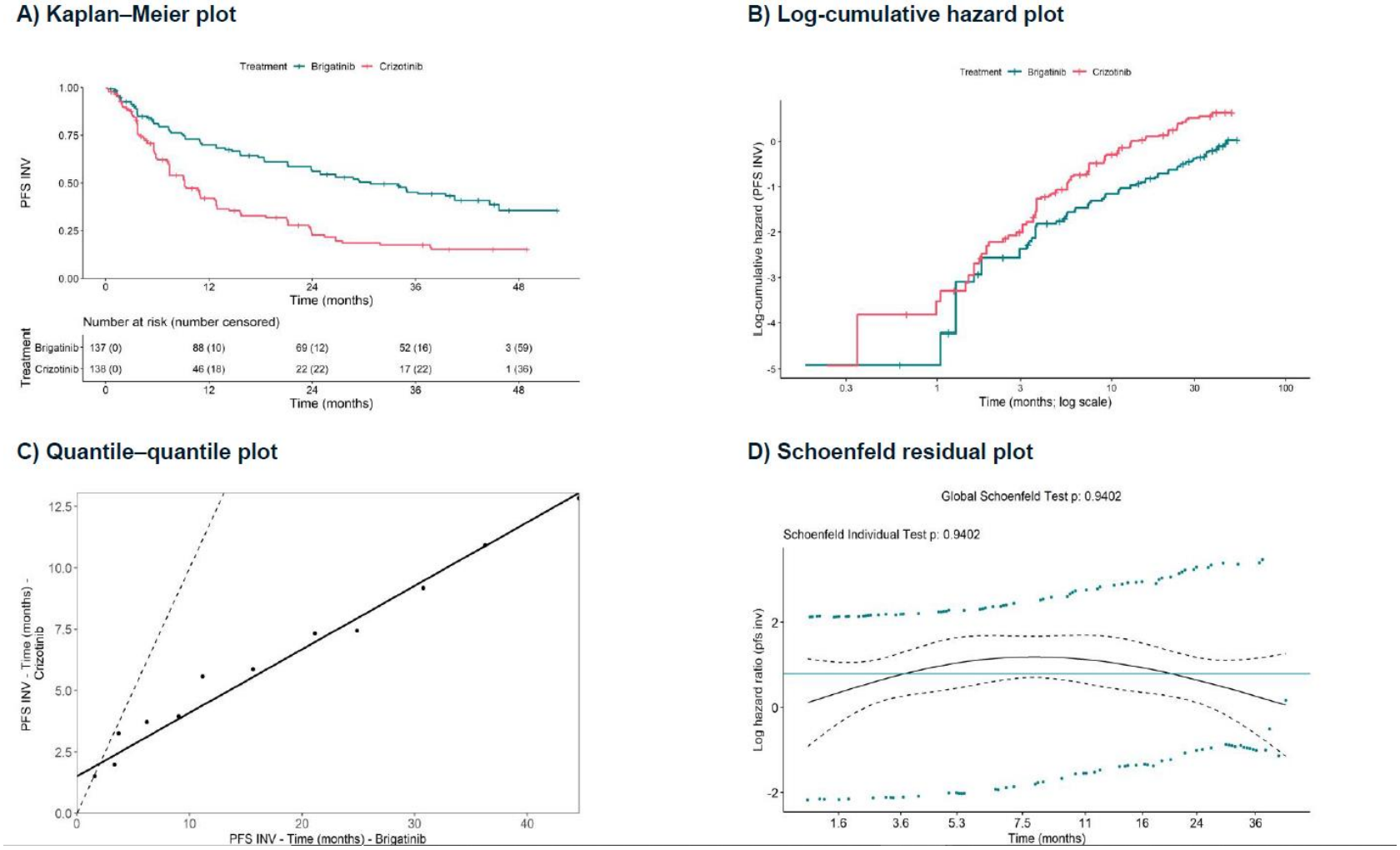


Figure 61 PH assessments plots for CROWN IC-TTP

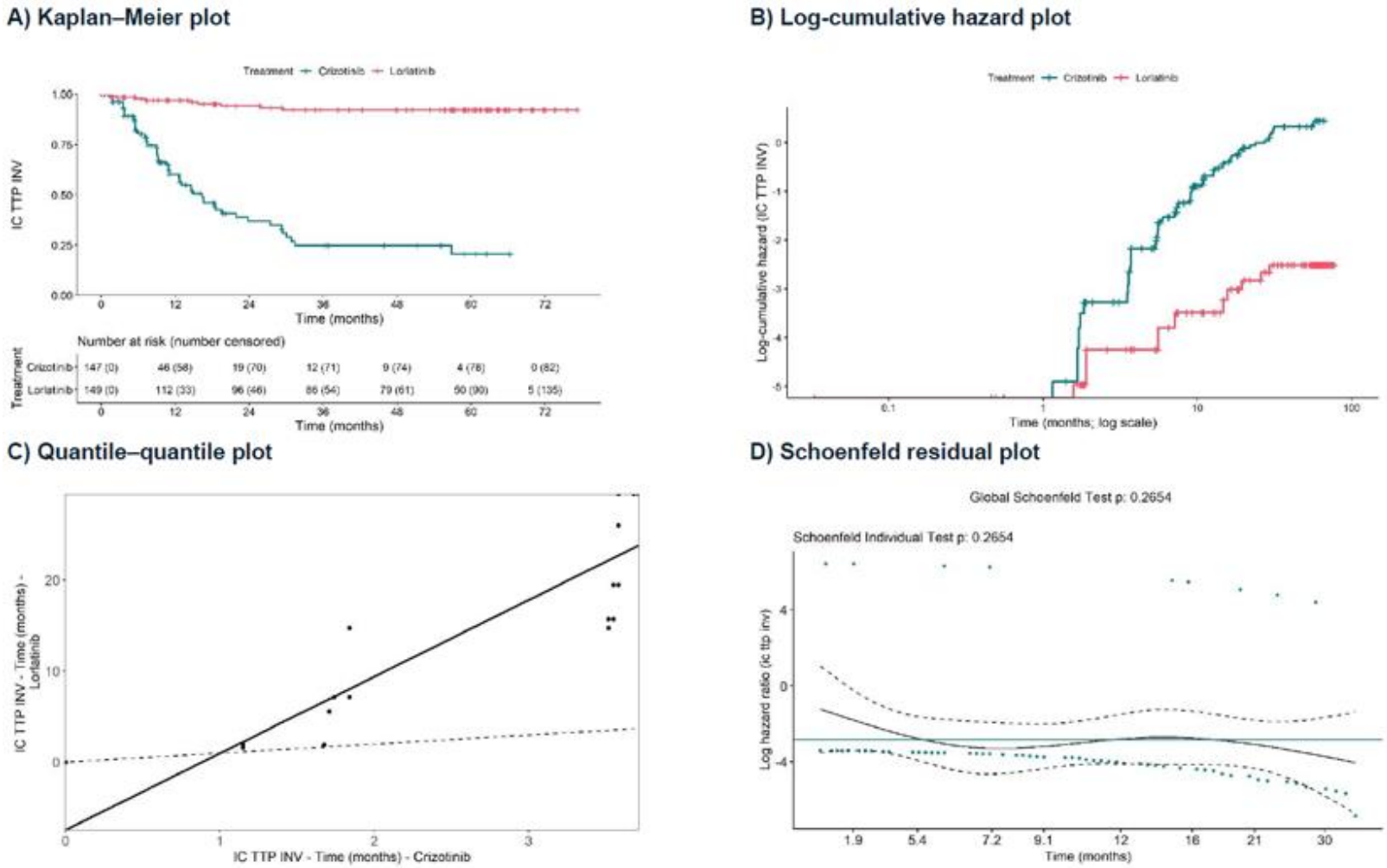
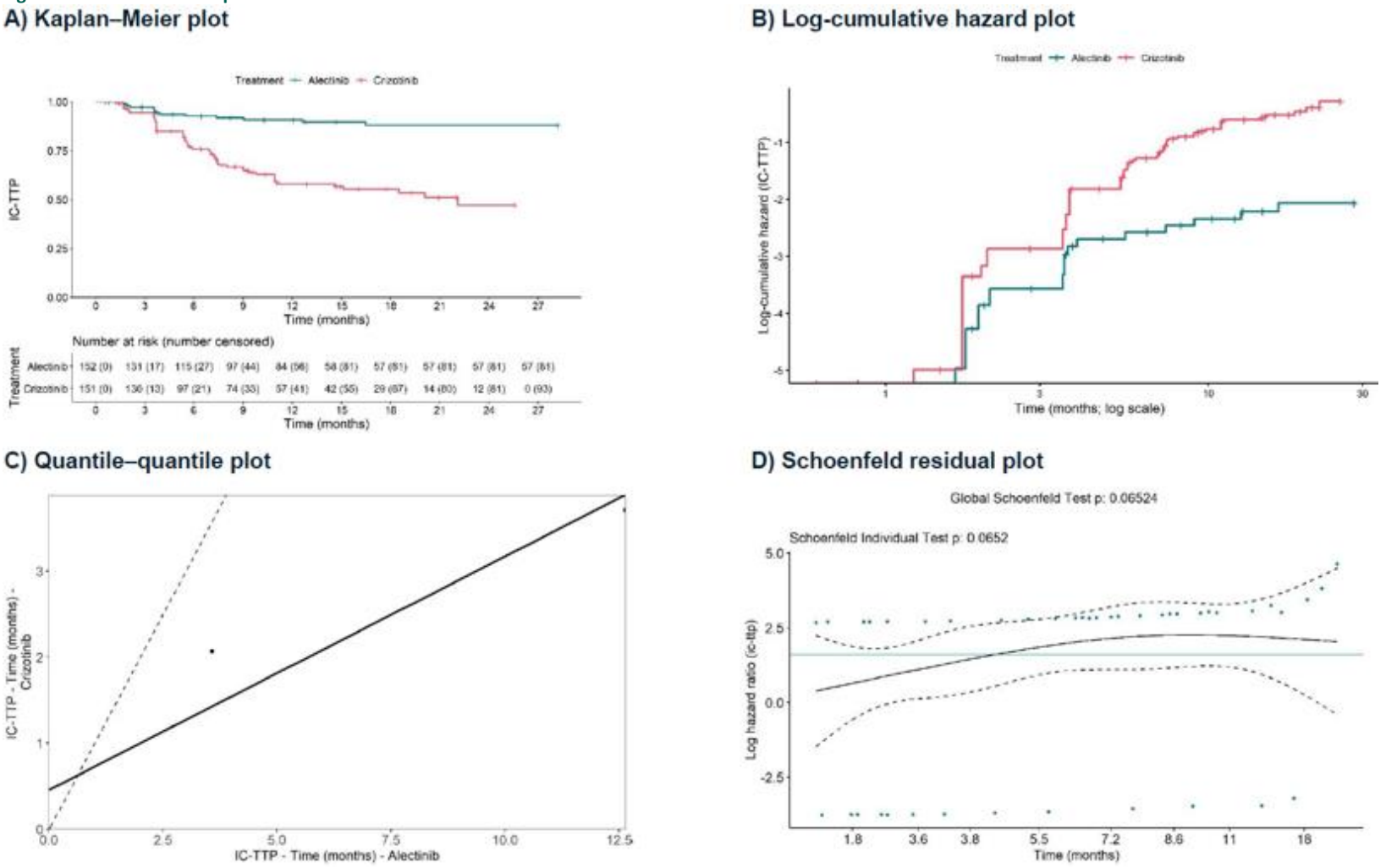


Figure 62 PH assessments plots for ALEX IC-TTP



Plots were not available for IC-TTP for ALTA-1L, as the initial report did not find it relevant to compare the IC-TTP of ALTA-1L with IC-TTP of CROWN and ALEX, as the IC-TTP of ALTA-1L was an exploratory endpoint. We choose to include ALTA-1L IC-TTP in the NMA in order to compare efficacy.

Appendix D. Extrapolation

D.1 Extrapolation of progression-free survival

D.1.1 Data input

The model includes the functionality to model either PFS assessed by BICR or PFS assessed by an investigator (INV). However, the October 2023 data cut does not include PFS BICR. Therefore, PFS based on INV (October 2023 data cut) was selected as the base case analysis.

D.1.2 Model

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

D.1.3 Proportional hazards

The log-cumulative hazard plot of PFS (INV) in CROWN from the 5-year data cut-off is presented in Figure 63. The curves cross several times early in the plot, suggesting that the proportional hazards assumption is violated for PFS (INV). The Schoenfeld residual plot presented in Figure 64 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 65 do not appear to be evenly scattered around the straight line, suggesting that there is evidence that the accelerated failure time assumption is violated. 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 63 Log-cumulative hazard plot for progression-free survival (INV) in CROWN

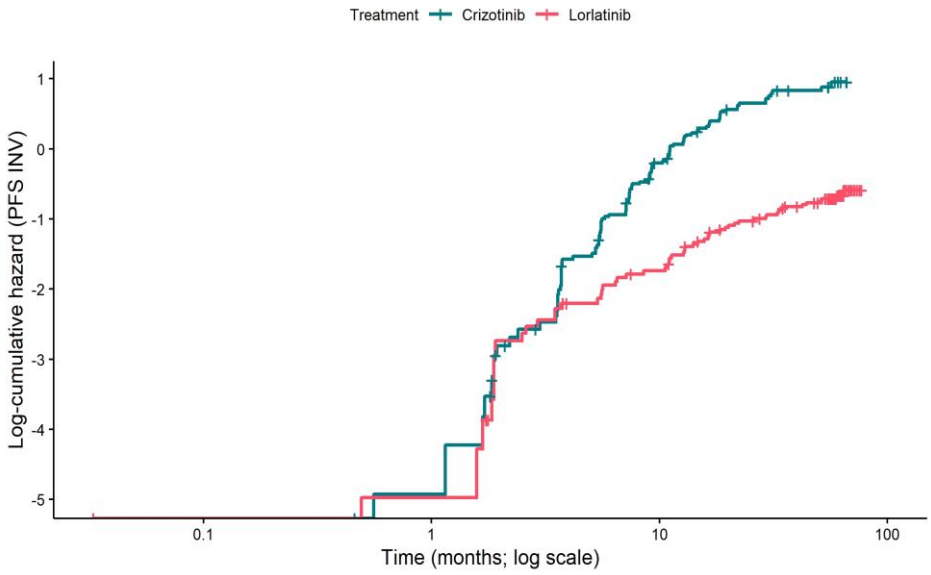


Figure 64 Schoenfeld residual plot for progression-free survival (INV) in CROWN

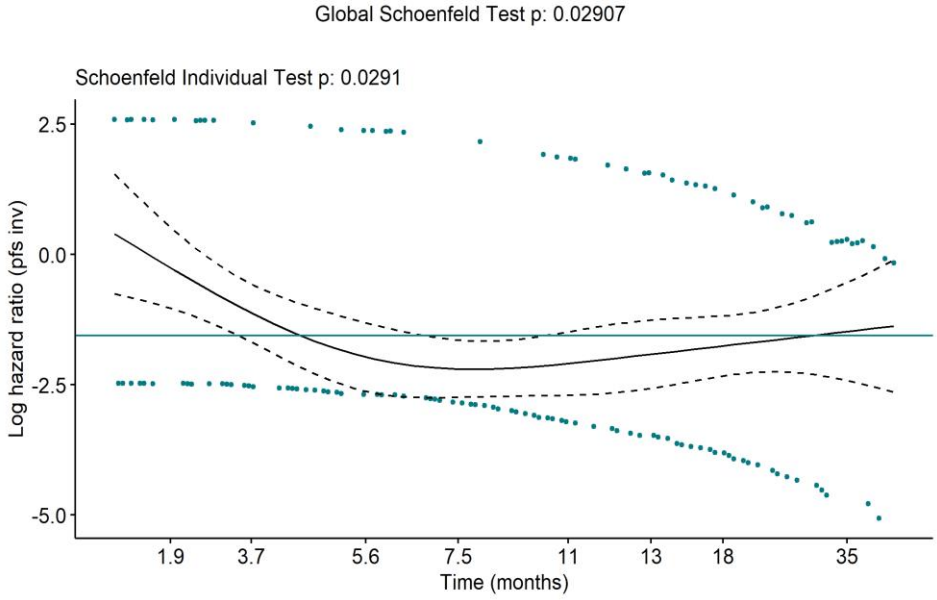
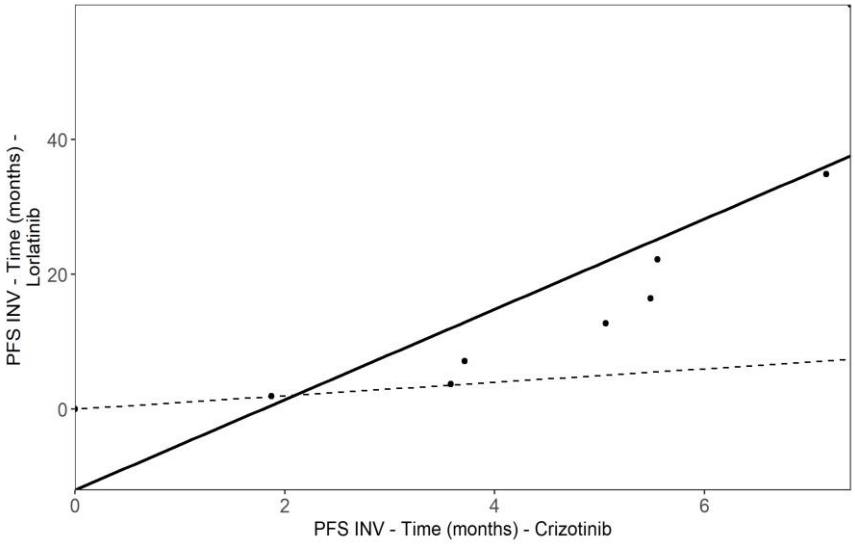


Figure 65 Quantile–quantile plot for progression-free survival (INV) in CROWN



D.1.4 Evaluation of statistical fit (AIC and BIC)

The statistical fits of PFS extrapolations based on INV assessment of PFS are presented here. To ensure the consistency with the observed 60% PFS at 60 months (5 years), the 36-month piecewise was prioritized for the base case with statical fit presented in Table 72. The statistical fits of PFS lorlatinib standard parametric curves, and lorlatinib 23-month piecewise, and crizotinib standard parametric curves in Table 73, Table 74, and Table 75.

It is seen in Table 72 and Table 73, the exponential and Weibull models provide the best statistical fit for the piecewise models for lorlatinib, while Gompertz and gamma models have the worst statical fit in the piecewise models for lorlatinib. For the standard parametric models, the generalized gamma and Gompertz curves have the best statistical fit, while the exponential, gamma, and Weibull models provide worse fits.

For the crizotinib standard parametric curves, generalized gamma, log-logistic, and log-normal provided the best statical fits, while the exponential, gamma, and Weibull models provide worse fits.

Table 72 Fit statistics of INV assessed PFS extrapolation – lorlatinib 36 months piecewise

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	83.86	1	86.26	1
Generalized gamma	84.78	5	89.57	5
Gompertz	85.61	7	92.79	7
Log-logistic	84.72	3	89.51	3
Log-normal	84.74	4	89.53	4
Weibull	84.42	2	89.21	2
Gamma	85.31	6	90.10	6

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

Table 73 Fit statistics of INV assessed PFS extrapolation – lorlatinib standard parametric curves

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	623.98	7	626.98	7
Generalized gamma	600.00	1	609.02	2
Gompertz	602.60	2	608.61	1
Log-logistic	607.92	4	613.93	4
Log-normal	603.58	3	609.59	3
Weibull	610.96	5	616.97	5
Gamma	612.75	6	618.76	6

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

Table 74 Fit statistics of INV assessed PFS extrapolation – lorlatinib 23 months piecewise

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	170.93	1	173.46	1
Generalized gamma	172.92	7	177.98	6
Gompertz	172.78	4	180.38	7
Log-logistic	172.90	6	177.97	5
Log-normal	172.76	3	177.82	3
Weibull	171.88	2	176.95	2
Gamma	172.80	5	177.87	4

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

Table 75 Fit statistics of INV assessed PFS extrapolation – crizotinib

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

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

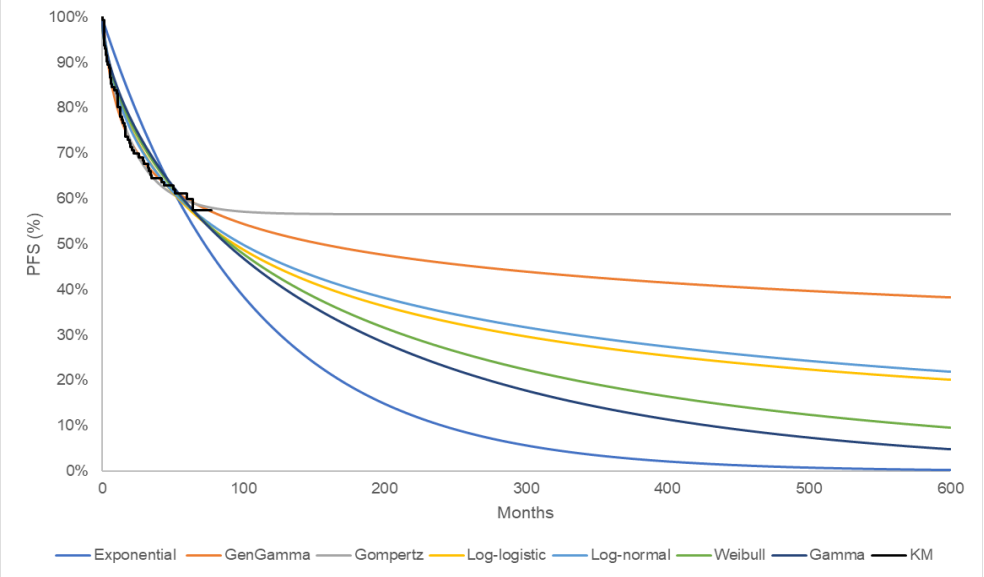
D.1.5 Evaluation of visual fit

The resulting PFS extrapolations based on INV assessment of PFS are presented for lorlatinib standard parametric curves, and lorlatinib 23-month piecewise, lorlatinib 36-month piecewise and crizotinib standard parametric curves in Figure 66, Figure 67, Figure 68 and Figure 69, respectively. The fit statistics are presented in Table 72, Table 73, Table 74, and Table 75.

For lorlatinib, it is seen that the standard parametric models are not fitting well to the KM data, therefore, the piecewise models were prioritized. For the 36-months piecewise models, it is seen that generalized gamma and Gompertz produce some extreme results compared to the remaining options. Exponential and log-normal models seem to produce longer tails, compared to log-logistic, gamma and Weibull 36-months piecewise models, which all looks like producing 'middle of the bunch' extrapolations.

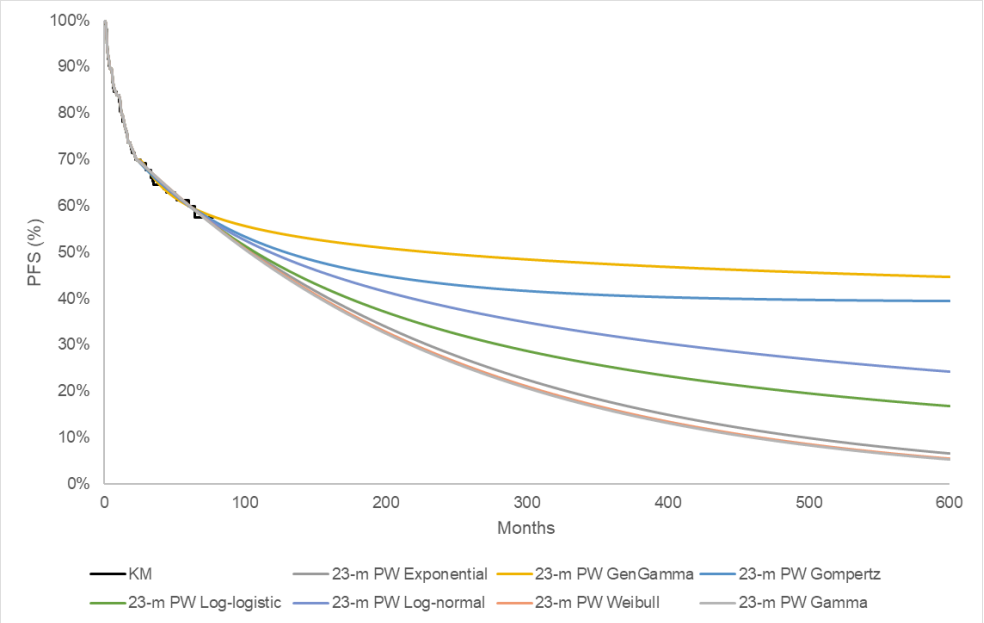
For crizotinib, it seen that most of the standard parametric models are fitting the KM data well. The Gompertz extrapolation does seem to estimate a long tail, which could overestimate the PFS for a small fraction of the patients.

Figure 66 INV assessed PFS for lorlatinib – standard parametric curves



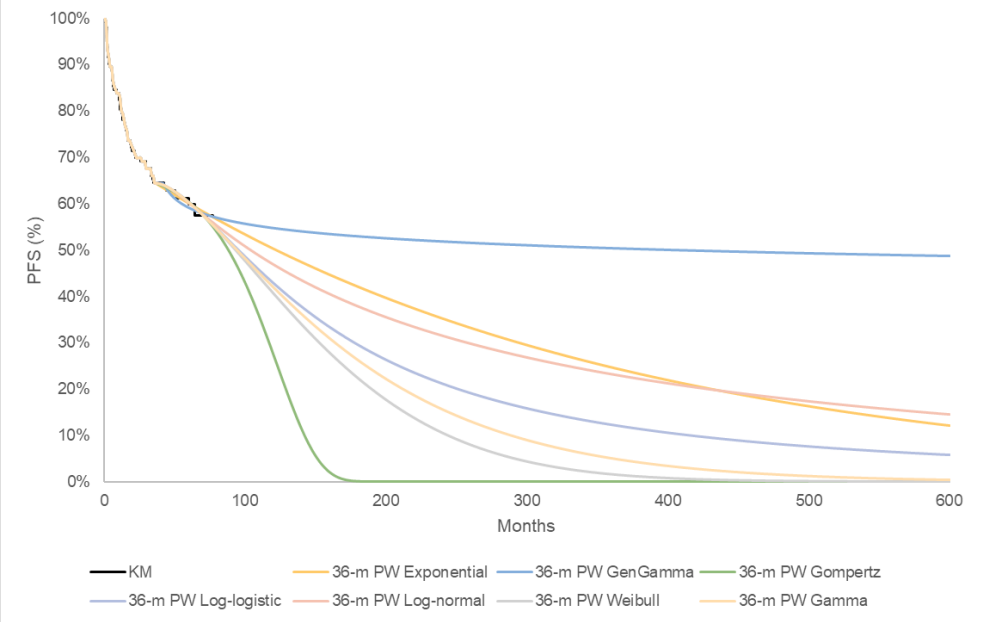
Abbreviations: BICR, blinded independent central review; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.

Figure 67 INV assessed PFS for lorlatinib – 23 months piecewise



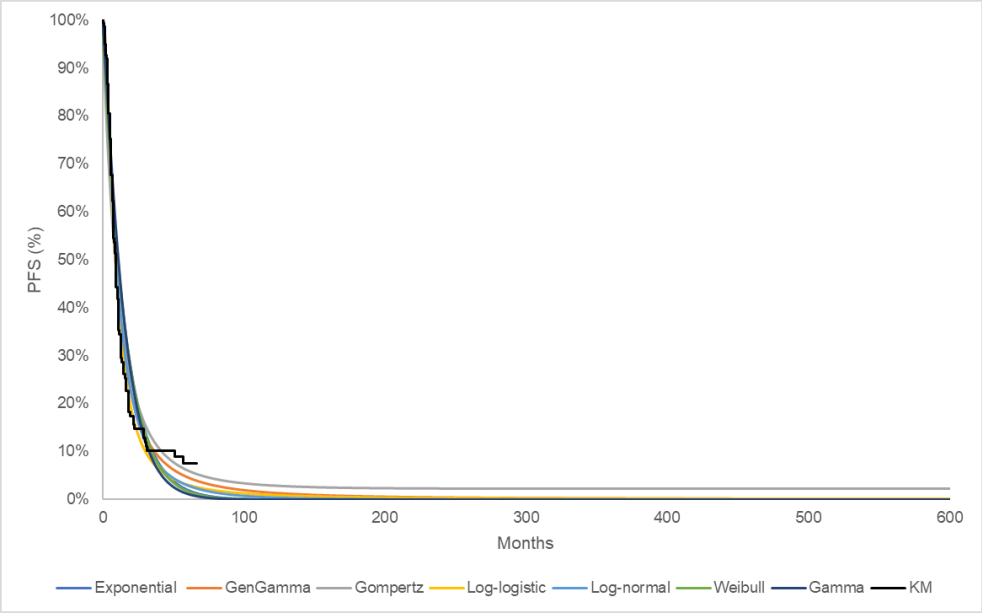
Abbreviations: BICR, blinded independent central review; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival.

Figure 68 INV assessed PFS for lorlatinib – 36 months piecewise



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

Figure 69 INV assessed PFS for crizotinib



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

D.1.6 Evaluation of hazard functions

The smoothed hazard was estimated using the bshazard package in R, and the smoothed hazard function was plotted to identify any changes in the hazard over the time period of available data (Figure 70). Prior to 24 months, the shape of the hazard function is almost linear. At 24 months we begin to see a slowing in the rate of change of the hazard

function and more slowing beginning at 36 months. This aligns with the observed KM, where we begin to see a flattening of the KM around 2 years. Based on this, more flexible modelling approaches were explored, ultimately leading to the choice of using piecewise models for the base case.

To maintain a consistent approach for survival modelling across both treatments, piecewise modelling for crizotinib was explored. The smoothed hazard for crizotinib is presented in Figure 71. The hazard is increasing until just after 12 months when it begins decreasing. We selected an initial cut time of 12 months. However, there are only 42 patients remaining risk for PFS at 12 months in the crizotinib arm (28.8% of the original sample). Therefore, we chose a secondary cut time of 3 months to allow for a greater number at risk at the cut time. At 3 months, 122 patients in the crizotinib arm remained at risk (83% of the original sample).

There was no clear selection as to what the best piecewise curve for crizotinib was, and there was no clear benefit of piecewise modelling over the standard parametric models. Therefore, crizotinib piecewise modelling was not applied in the health economic model.

The extrapolated PFS hazard plots are presented in Figure 71. PFS hazards show a plateau for crizotinib after 100 months. This is caused by the hazards getting close to zero with a log-logistic distribution. PFS hazards show a plateau for lorlatinib from month 75 to month 140. This is caused because the PFS curves crosses the OS, and therefore, the PFS and the OS display the same hazards.

Figure 70 Smoothed Hazard – PFS – Lorlatinib

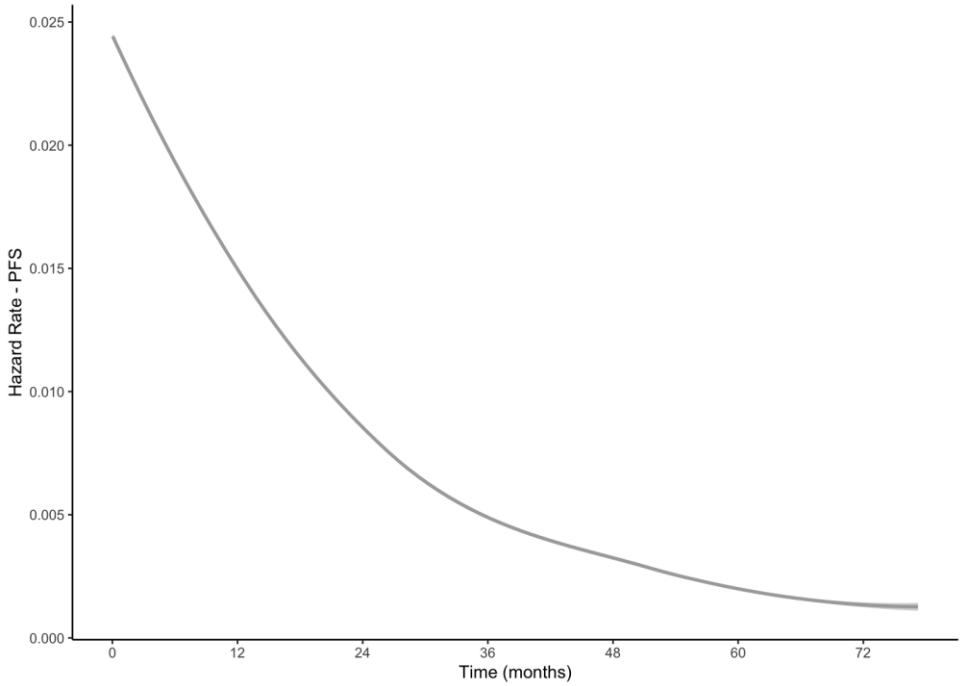


Figure 71 Smoothed Hazard – PFS – Crizotinib

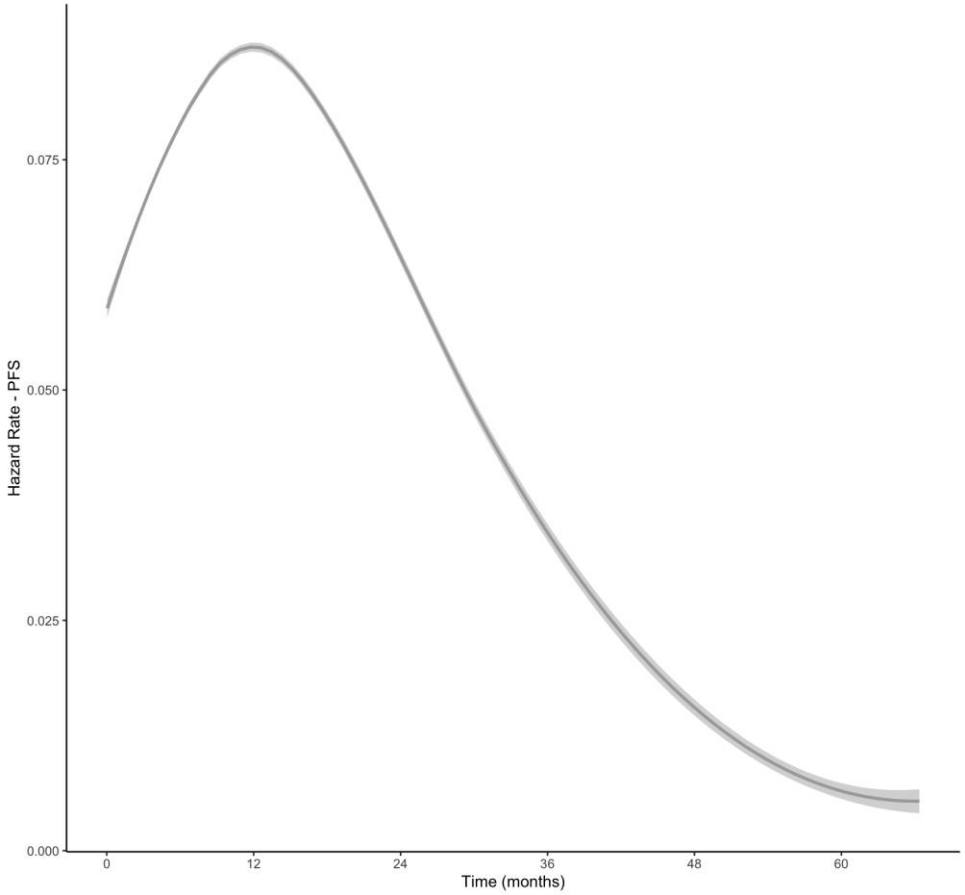
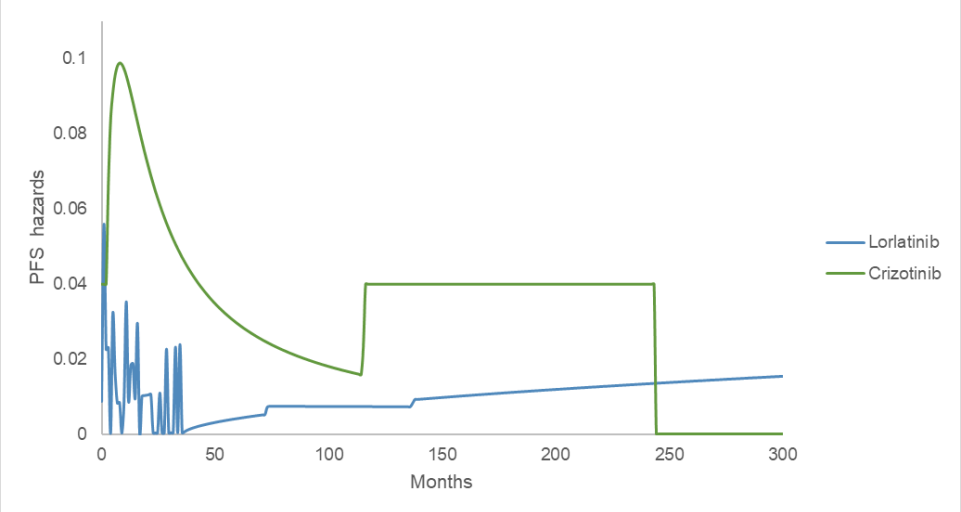


Figure 72 Hazard plot for modelled PFS extrapolations



D.1.7 Validation and discussion of extrapolated curves

Based the test of proportional hazards where the proportional hazards assumptions seemed to be violated, separate curve models were chosen. A flexible approach using

piecewise models for the base case was chosen for lorlatinib based on the smoothed hazard plots, visual fit assessments and expected clinical plausibility, while standard parametric models were chosen for crizotinib.

The 36-month piecewise Weibull curve was selected for the lorlatinib base case as this curve represents the second-best statistical fit to observed data combined with plausible long-term extrapolation for lorlatinib compared with the other curves, which are likely to be clinically implausible (> 13% alive and progression-free after 30 years). The 36-month piecewise gamma curve is also considered plausible, but it leads to extrapolations above the equivalent parametric OS during most of the time horizon. The standard exponential curve was not considered as it is too conservative during the early months, especially at the median (6.1 years) and 5-year points.

For the crizotinib arm, the standard log-logistic model provided the best statistical fit, while the Weibull provided the worst statical fit. Given the best statical fit, the log-logistic curve was selected for crizotinib, which was also expected to better align with the flexibility of the piecewise model used for lorlatinib. The choice of survival extrapolation does not have a large impact on the survival estimate as Kaplan–Meier PFS data were more complete (≤ 1% of patients alive and progression-free at 10 years across all curves except for generalized gamma and Gompertz).

D.1.8 Adjustment of background mortality

Background mortality was adjusted for in OS.

D.1.9 Adjustment for treatment switching/cross-over

Not relevant.

D.1.10 Waning effect

Not considered in the base case. Included as scenario analysis.

D.1.11 Cure-point

Mixture-cure was considered for the analysis during the creation of the global model. However, feedback from a UK advisory board stated that mixture-cure was not an appropriate method in this case. Also, mixture-cure requires the use of external data on the survival, PFS in this case, of ‘cured’ patients.

Therefore, it was not found appropriate to use mixture-cure for PFS using general population mortality statistics to represent the PFS of ‘cured’ patients. While a scenario could be considered which applied an additional hazard to the general population mortality, external data for estimating this additional hazard for PFS was not readily available. While mixture-cure may be considered appropriate to model OS for lorlatinib patients, it was not considered appropriate for PFS. Therefore, a mixture-cure model is also not available for this Danish submission.

D.2 Extrapolation of overall survival

D.2.1 Data input

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

For the base pooled CROWN + Study 1001 Kaplan–Meier data was used for lorlatinib extrapolations to ensure more mature OS data for lorlatinib in 1st line treatment. Extrapolations were also carried out on the CROWN data alone.

D.2.2 Model

For the base case, standard parametric OS curves were fitted independently to lorlatinib using pooled CROWN + Study 1001 Kaplan–Meier data for lorlatinib.

The OS curves were also independently fitted to each arm of the CROWN data alone for scenario testing. The independently fitted curves were chosen based on the proportional hazards testing.

D.2.3 Proportional hazards

The log-cumulative hazard plot of OS is presented in Figure 73 The curves cross several times early in the plot, suggesting that the proportional hazards assumption is violated for OS. The Schoenfeld residual plot presented in Figure 74 shows that the HR between lorlatinib and crizotinib initially decreases between 0 and 13 months and then begins to increase. However, the Schoenfeld individual p-value is over 0.05. The survival time points in the quantile–quantile plot in Figure 75 do not appear to be evenly scattered around the straight line, suggesting that there is evidence that the accelerated failure time assumption is violated. Overall, it seemed plausible that the proportional hazards assumption was violated, suggesting that fitting separate parametric survival models is justified.

Figure 73 Log-cumulative hazard plot for OS

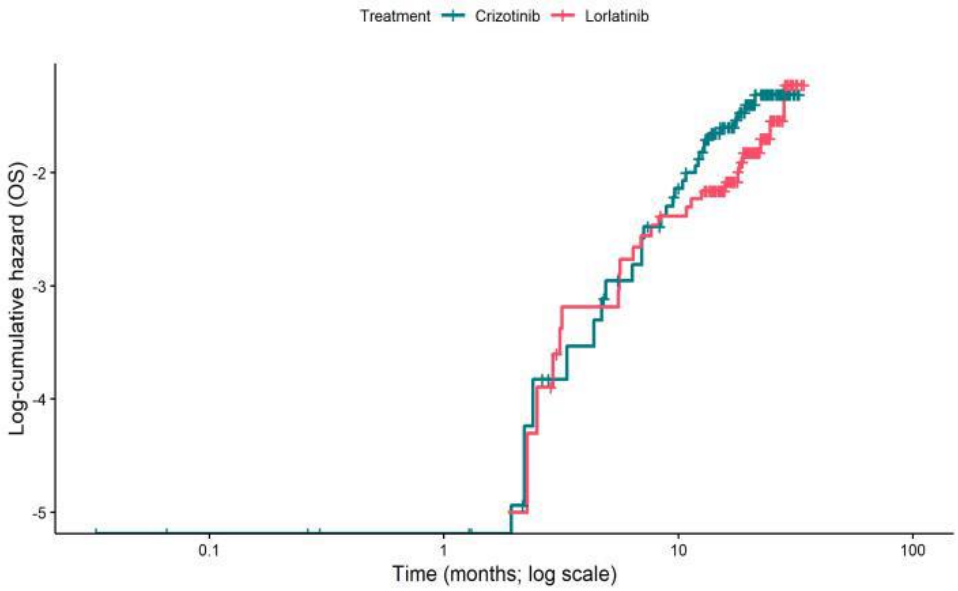


Figure 74 Schoenfeld residual plot

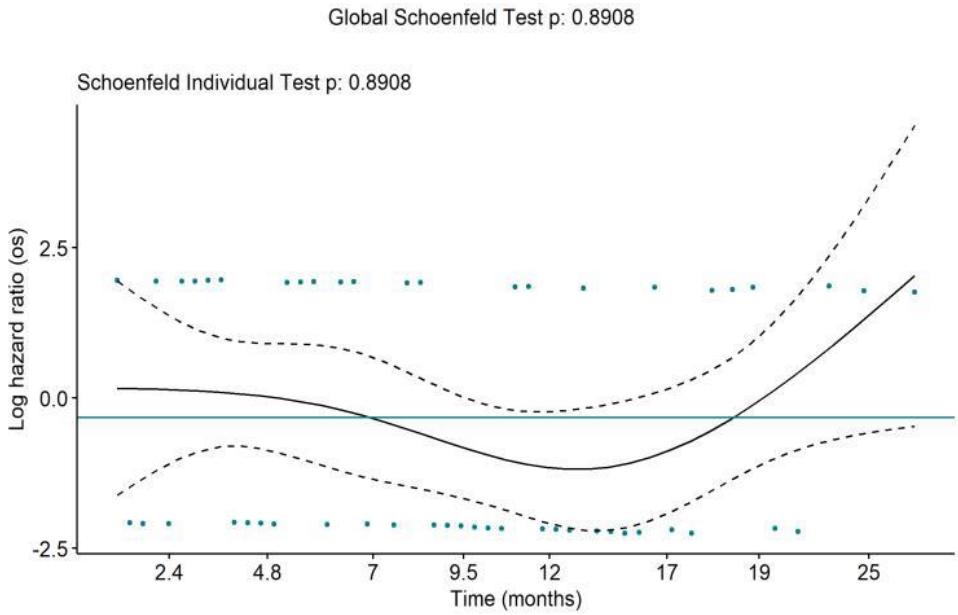
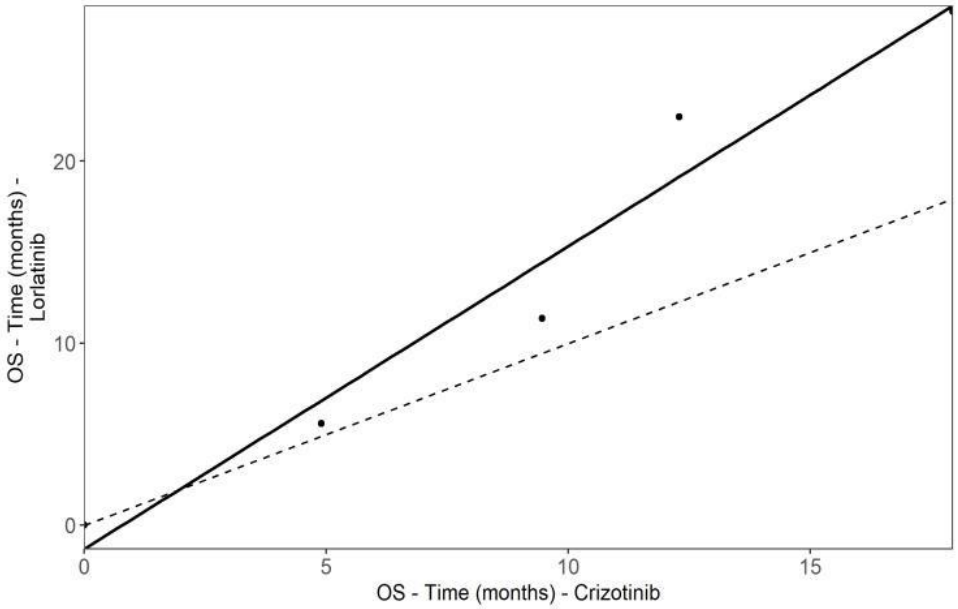


Figure 75 Quantile–quantile plot for OS



D.2.4 Evaluation of statistical fit (AIC and BIC)

The Akaike information criterion (AIC) and Bayesian information criterion (BIC), which provide an indication of the statistical goodness-of-fit of the parametric models to the observed portion of the data, may not be considered as informative as is typical in curve selection given the immaturity of the CROWN survival data. Furthermore, as shown in Table 76, Table 77, and Table 78 the AIC/BIC across parametric models are within 5 points of each other. This suggests there is not a large difference in the goodness-of-fit to the observed data.

Table 76 Fit statistics of OS extrapolation – lorlatinib using CROWN

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	269.29	1	272.30	1
Generalized gamma	270.32	3	279.33	7
Gompertz	271.27	6	277.27	5
Log-logistic	271.12	4	277.12	3
Log-normal	269.85	2	275.86	2
Weibull	271.27	7	277.28	6
Gamma	271.25	5	277.26	4

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

Table 77 Fit statistics of OS extrapolation – lorlatinib using pooled CROWN + Study 1001

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	373.95	3	380.32	1
Generalized gamma	372.33	1	385.08	5
Gompertz	374.74	4	384.30	3
Log-logistic	375.32	5	384.89	4
Log-normal	373.08	2	382.62	2
Weibull	375.92	6	385.48	6
Gamma	375.94	7	385.50	7

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

Table 78 Fit statistics of OS extrapolation – crizotinib using CROWN

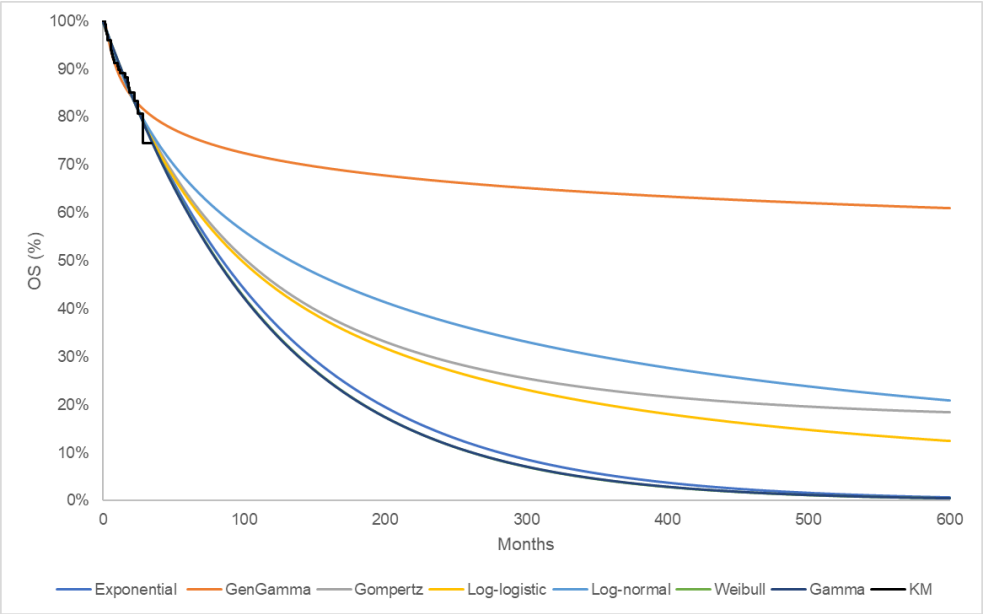
Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	308.95	3	311.94	1
Generalized gamma	307.14	1	316.11	4
Gompertz	310.76	7	316.74	7
Log-logistic	309.50	4	315.48	3
Log-normal	307.29	2	313.27	2
Weibull	310.45	6	316.43	6
Gamma	310.21	5	316.19	5

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

D.2.5 Evaluation of visual fit

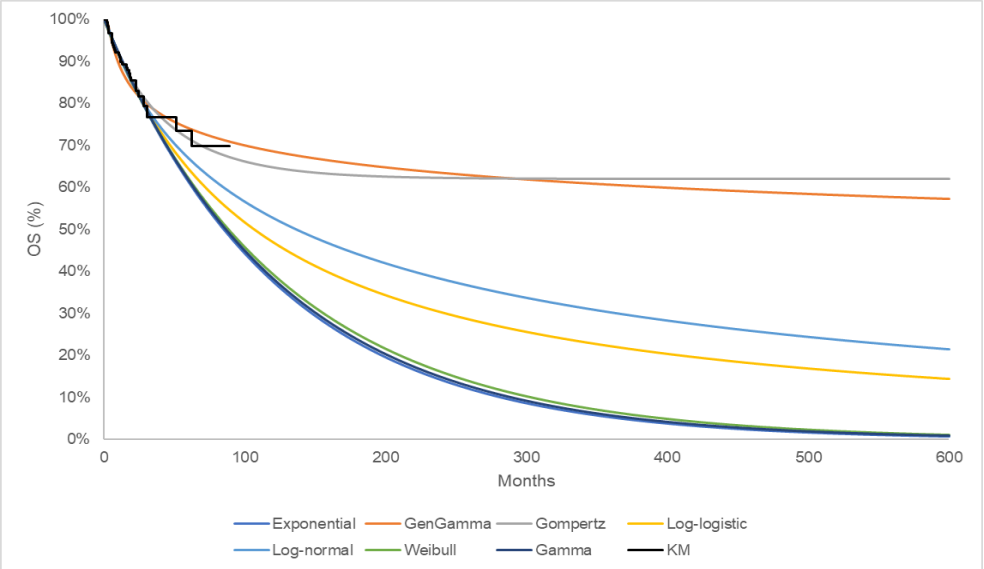
The visual fits for the extrapolations are found here below in Figure 76, Figure 77, and Figure 78, which present OS extrapolations for lorlatinib using CROWN, lorlatinib using pooled CROWN and Study 1001, and crizotinib using CROWN, respectively.

Figure 76 Overall survival extrapolations for lorlatinib – CROWN



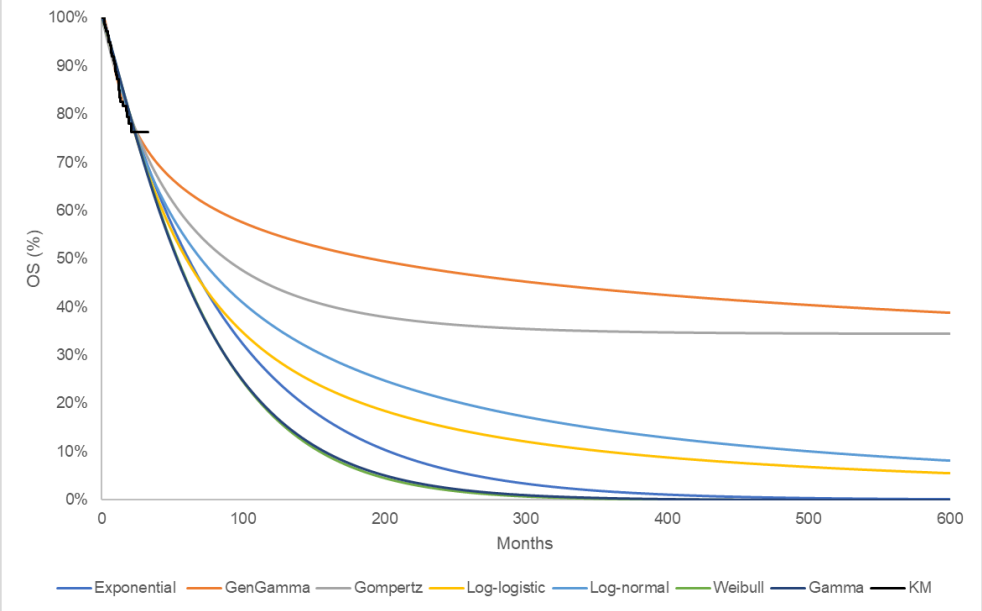
Abbreviations: KM, Kaplan–Meier; OS, overall survival.

Figure 77 Overall survival extrapolations for lorlatinib – Pooled CROWN + Study 1001



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

Figure 78 Overall survival extrapolations for crizotinib – CROWN



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

D.2.6 Evaluation of hazard functions

The OS hazards plot is presented in Figure 79 for both lorlatinib and crizotinib. It is acknowledged that the DMC prefers the hazard plots to be separated for intervention and comparator, however, separate figures were not available for OS, thus the hazards were presented for both lorlatinib and crizotinib in the figure below.

The plot suggests that the risk of death decreases slightly between 0 and 15 months and then begins to increase for lorlatinib, and that the risk of death increases between 0 and 10 months and then decreases after for crizotinib. The smoothed hazard plot suggests that the hazard functions in the lorlatinib and crizotinib arms are different to each other and that fitting separate parametric survival may therefore be justified. The lorlatinib hazard seems to start at a plateau for the first 18 months, while an increased hazard is noticed from month 18 and onwards.

The extrapolated hazard plots are presented in Figure 80. The steps in the OS hazards are caused by the background mortality.

Figure 79 Smoothed and unsmoothed hazard plots of overall survival

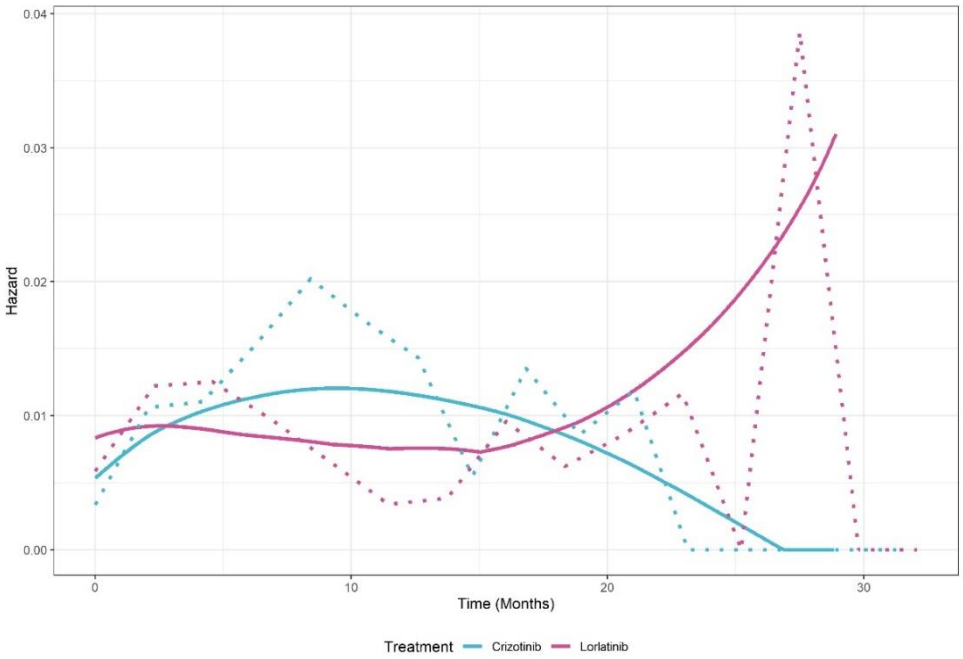
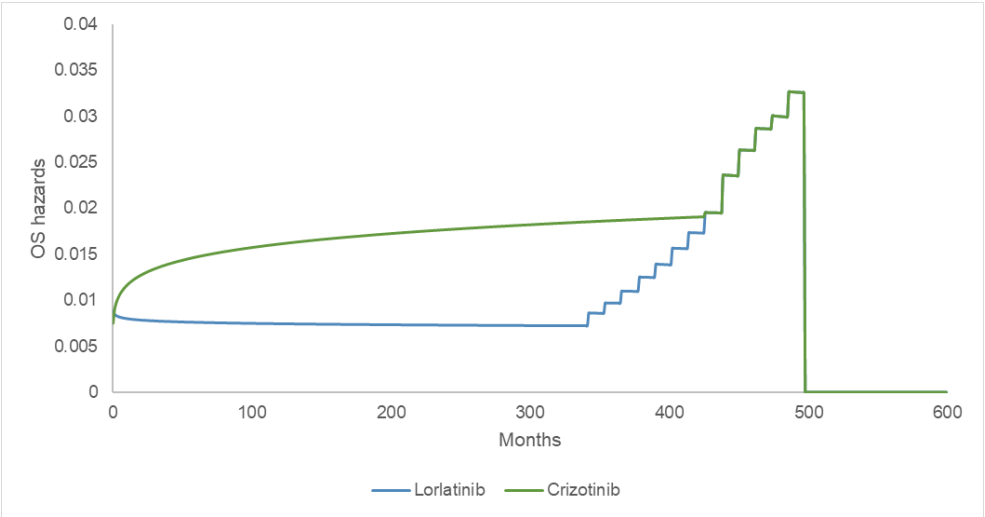


Figure 80 Hazard plot for modelled OS extrapolations



D.2.7 Validation and discussion of extrapolated curves

Considering the CROWN and Study 1001 pooled extrapolations, the results indicate that Gompertz, generalized gamma, log-logistic and log-normal curves were likely to produce outcomes, which could be expected to be clinically implausible (more than 20% and 10% of patients remain alive after 30 years in the lorlatinib and crizotinib arms, respectively).

The gamma OS curve (CROWN or pooled) struggles to stay above the Weibull 36-month piecewise PFS curve, so is not a coherent selection. The Weibull OS curve (pooled CROWN + Study 1001) is selected as a compromise, as it is more consistent with the

selected PFS curve, although it is also imperfect in that it meets the selected PFS curve between around 6 and 10 years. Therefore, Weibull can be considered a conservative selection.

D.2.8 Adjustment of background mortality

Background mortality is applied as per DMC guidelines using the 'General mortality' sheet of the DMCs addendum to the health economic model.

D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

D.2.10 Waning effect

Not considered in the base case. Included as scenario analysis.

D.2.11 Cure-point

Not applicable.

D.3 Extrapolation of time on treatment

D.3.1 Data input

Time on treatment was based on CROWN data from the October 2023 data cut.

D.3.2 Model

Standard parametric OS curves were fitted independently to lorlatinib using pooled CROWN + Study 1001 Kaplan–Meier data for lorlatinib. The parametric extrapolations were not used in the base case, as a hazard ratio between PFS and ToT was used to describe the ToT instead.

D.3.3 Proportional hazards

Figure 81 presents the log-cumulative hazard plot for time on treatment. The curves do not cross, suggesting that the proportional hazard assumption is not violated. However, the Schoenfeld residual plot (Figure 82) shows that the HR between lorlatinib and crizotinib decreases over time, and the p-value is less than 0.05, suggesting that the proportional hazards assumption is violated. Given that there are inconsistences in these plots and that patient-level data are available for both treatment arms, fitting separate parametric survival models to each treatment arm may be appropriate.

The QQ plot presented in Figure 83 gives an approximately straight line, suggesting there is little evidence that the AFT assumption is violated. However, the smoothed hazard plot presented in section D.3.6 suggests the hazard functions in the treatment arms are different and that fitting separate parametric models is justified.

Figure 81 Log-cumulative hazard for time on treatment

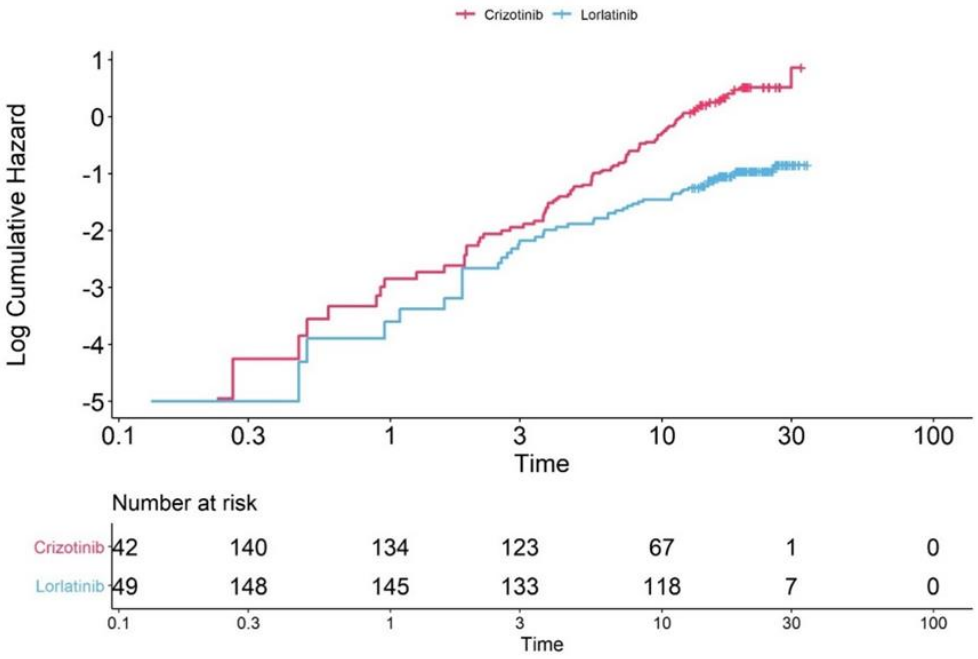


Figure 82 Schoenfeld residual plot for time on treatment

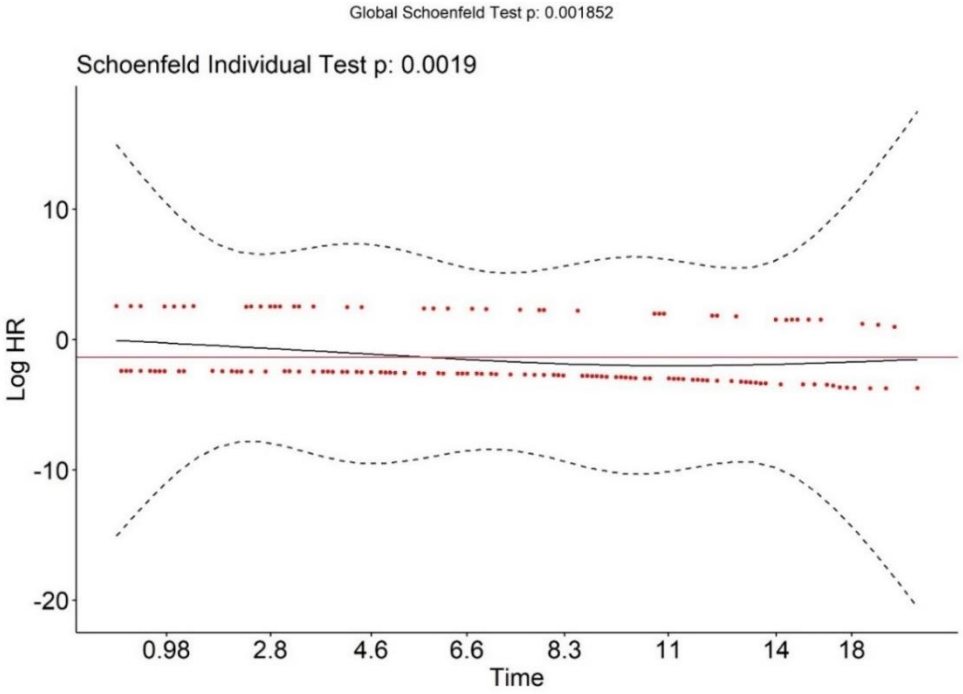
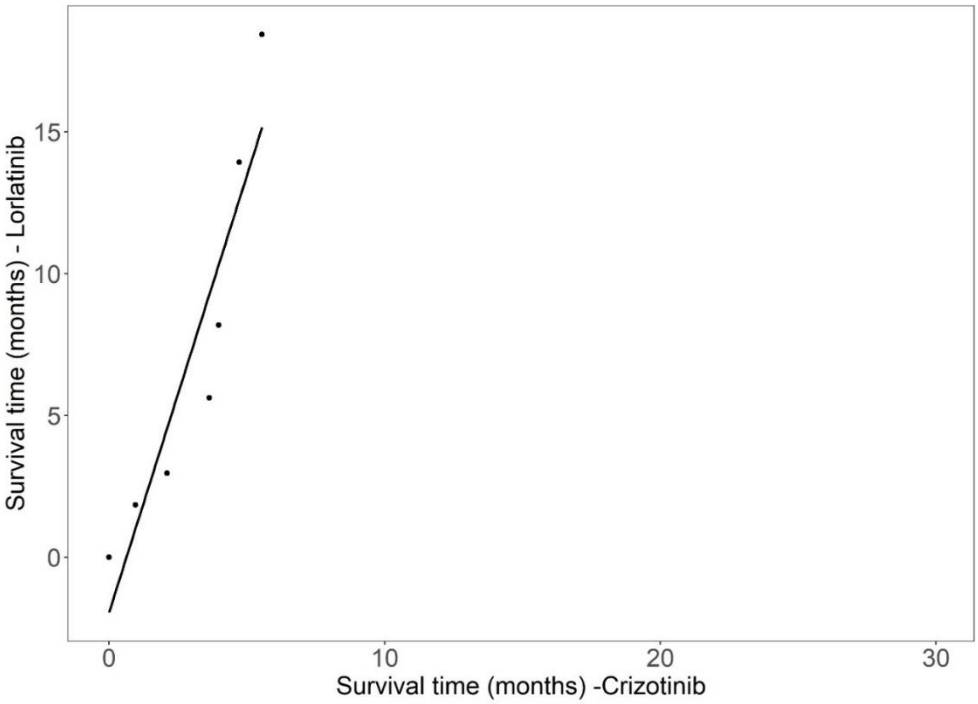


Figure 83 Quantile–quantile plot for time on treatment



D.3.4 Evaluation of statistical fit (AIC and BIC)

The AIC/BIC do not largely differ for lorlatinib and crizotinib, which is aligned with visual inspection, which are presented in Table 79 and Table 80

Table 79 Fit statistics of ToT extrapolation – lorlatinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	814.62	7	817.63	7
Generalised gamma	794.34	2	803.35	3
Gompertz	797.56	4	803.57	4
Log-logistic	795.14	3	801.15	2
Log-normal	792.60	1	798.61	1
Weibull	797.61	5	803.62	5
Gamma	799.30	6	805.30	6

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BICR: blinded independent central

Table 80 Fit statistics of ToT extrapolation – crizotinib

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	999.39	5	1002.34	5
Generalised gamma	992.75	2	1001.62	4
Gompertz	994.48	4	1000.39	3
Log-logistic	985.27	1	991.18	1
Log-normal	993.92	3	999.83	2

Weibull	1001.32	7	1007.23	7
Gamma	1001.06	6	1006.97	6

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

D.3.5 Evaluation of visual fit

For crizotinib, most of the curves provides reasonable visual fit. For lorlatinib it is seen that Gompertz flattens out at a plateau just below 50%, which is considered to be unreasonable. Remaining options could provide a reasonable fit.

Figure 84 Time on treatment extrapolations for lorlatinib – CROWN

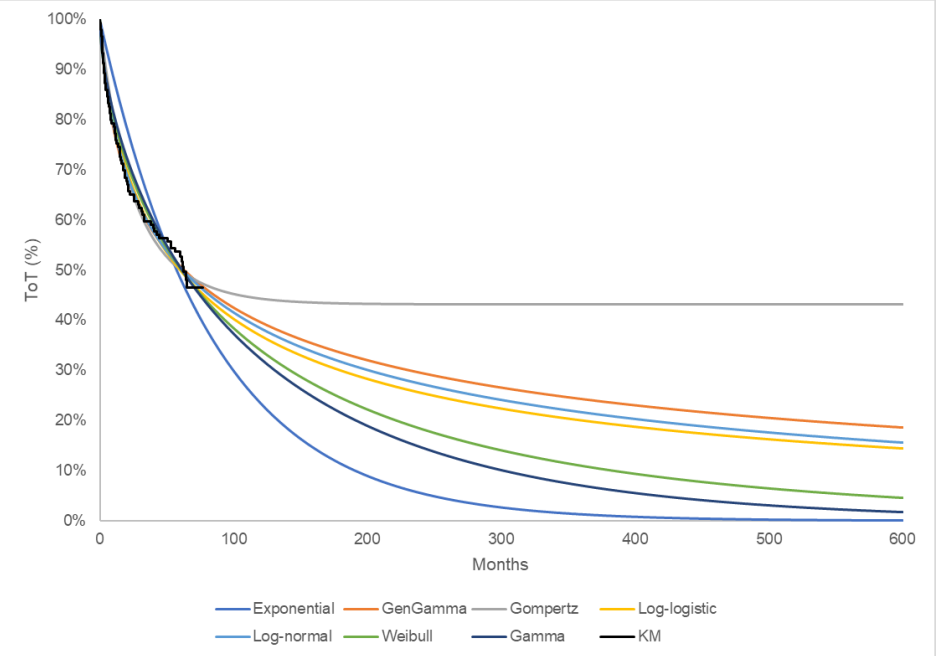
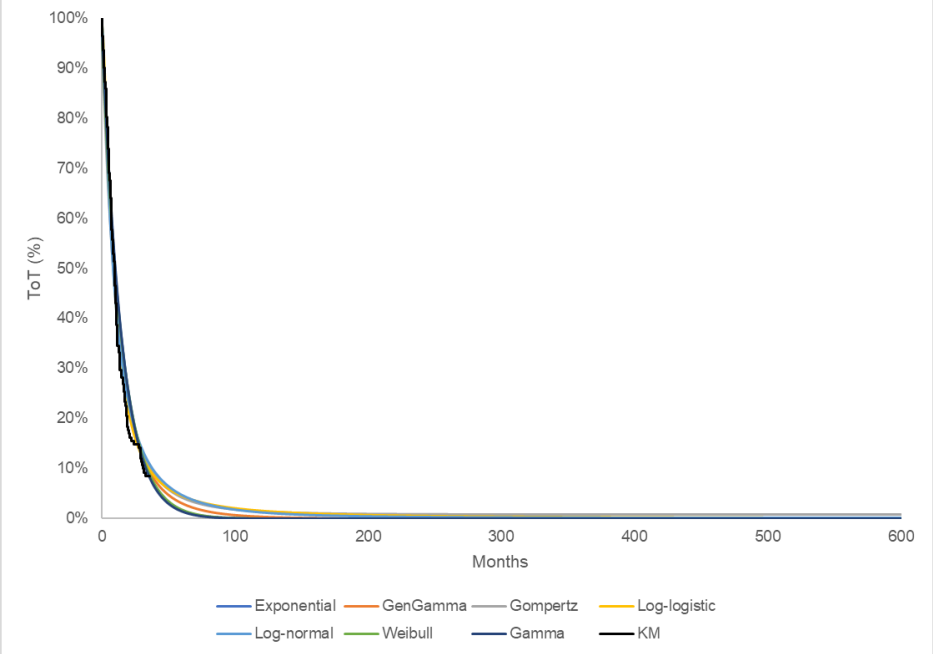


Figure 85 Time on treatment extrapolations for crizotinib – CROWN



D.3.6 Evaluation of hazard functions

The hazard plots for ToT are presented in Figure 86. It is acknowledged that the DMC prefers the hazard plots to be separated for intervention and comparator, however, separate figures were not available for ToT, thus the hazards were presented for both lorlatinib and crizotinib in the figure below.

The smoothed hazard plot shows that the risk of treatment discontinuation decreases over time for lorlatinib; for crizotinib, it increases between 0 and 12 months and then decreases after. These plots suggest the hazard functions in the treatment arms are different and that fitting separate parametric models is justified.

A hazard plot for a set of exponential extrapolations is presented in Figure 87.

Figure 86 Smoothed and unsmoothed hazard for time on treatment

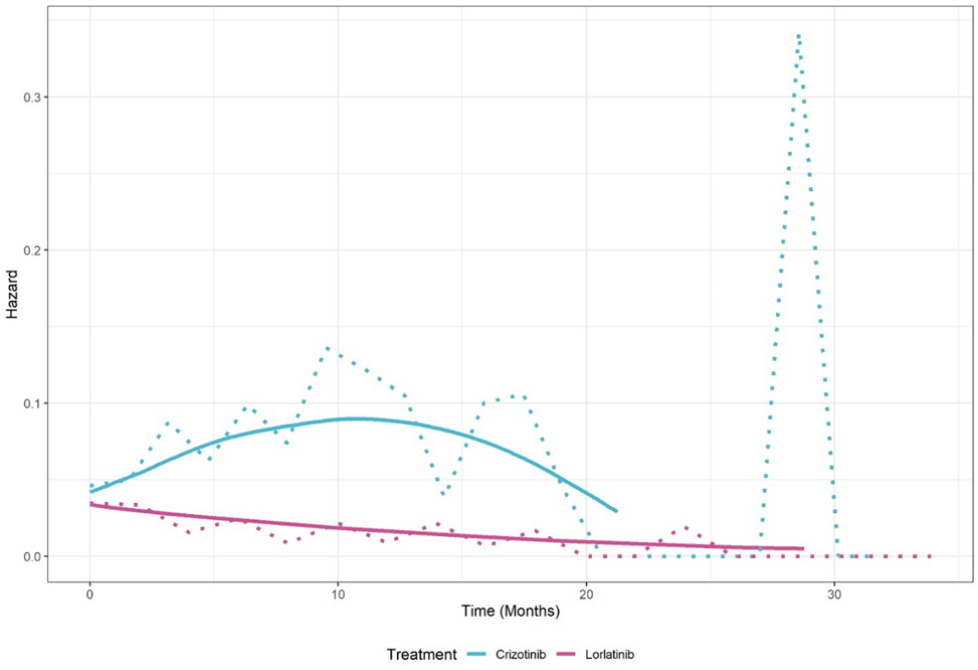
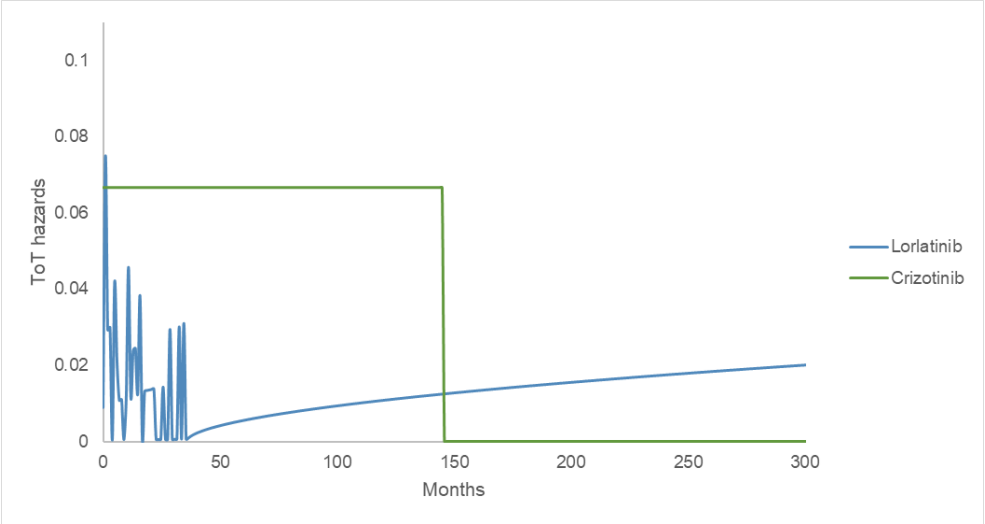


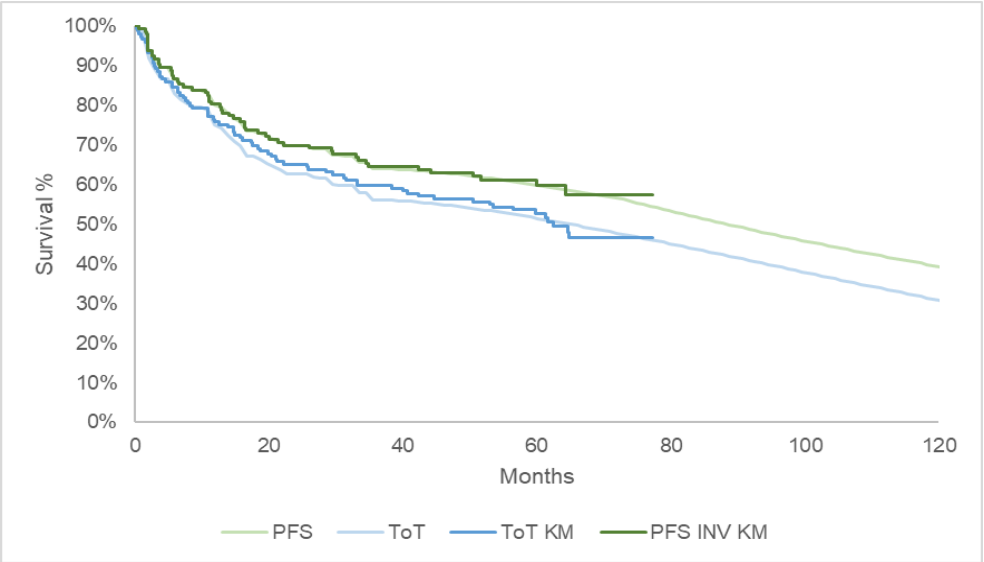
Figure 87 Hazard plot for exponential extrapolations of ToT



D.3.7 Validation and discussion of extrapolated curves

Figure 88 presents the PFS and ToT Kaplan–Meier curves side by side and shows that the ToT curve is consistently below the PFS curve in CROWN. This is likely due to the unusually long duration of treatment for lorlatinib compared with second generation ALK inhibitors; the greater the duration of treatment with an ALK inhibitor, the greater the likelihood of stopping treatment. Pfizer believes that CROWN data is the most robust source informing the relationship between PFS and ToT and this relationship should be reflected in cost-effectiveness modelling. Therefore, the ToT was estimated by applying a HR to PFS INV. The parametric curves were explored in scenario analysis.

Figure 88 Extrapolated PFS INV and ToT vs Kaplan–Meier curves from CROWN



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

D.3.8 Adjustment of background mortality

Not relevant.

D.3.9 Adjustment for treatment switching/cross-over

Not relevant.

D.3.10 Waning effect

Not relevant.

D.3.11 Cure-point

Not relevant

Appendix E. Serious adverse events

In this table for Serious Adverse Events for all causalities for lorlatinib, crizotinib and alectinib, there is a large difference between the reported events in the two trials. In CROWN all SAEs are listed from latest CSR with a follow-up of 60 months. For ALEX it has not been possible to find data for SAEs later than 2017 in the EMA assessment report and only SAEs occurring in at least 2 patients are listed (53). As many of SAE in CROWN only is reported in one person there is a clear imbalance.

Serious adverse events	Lorlatinib (N=149)		Crizotinib (N=142)		Alectinib (N=152)		Crizotinib (N=151)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
[redacted]	[redacted]		[redacted]		59 (38.8)	(16)	48 (31.8)	(16)
[redacted]	[redacted]		[redacted]		5 (3)		4 (3)	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		2 (1)		1 (1)	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		NR		NR	
[redacted]	[redacted]		[redacted]		1 (1)		3 (2)	
[redacted]	[redacted]		[redacted]		NR		NR	

[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	2 (1)	0
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
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[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	2 (1)	0
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	2 (1)	0
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR

[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
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[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
Nausea	NR	NR	0	3 (2)
Vomiting	NR	NR	0	2 (1)
Deep vein thrombosis	NR	NR	0	2 (1)
Confusional state	NR	NR	1 (1)	2 (1)
Lung infection	NR	NR	3 (3)	0
Blood creatine increase	NR	NR	2 (1)	0
Acute kidney injury	NR	NR	4 (3)	0

Abbreviation: NR, Not reported.

Table below covering Serious Adverse Events in CROWN and ALTA-1L, include Treatment-emergent SAEs in more than 2% in either arm for ALTA-1L from the second interim analysis with cut-off June 28, 2019 and a follow-up of 24.9 (0-34.1) months for brigatinib and 15.2 (0.1-36.0) months for crizotinib (Table 72 in the EMA assessment report for brigatinib) (54). The discrepancy in reporting period and events reported (>2%) makes comparison difficult.

Serious adverse events	Lorlatinib (N=149)		Crizotinib (N=142)		Brigatinib (N=136)		Crizotinib (N=137)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	65 (43.6)		45 (31.7)		45 (33.1)		51 (37.2)	
[redacted]	[redacted]	[redacted]	[redacted]		6 (4.4)		5 (3.6)	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
[redacted]	[redacted]	[redacted]	[redacted]		3 (2.2)		6 (4.4)	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
[redacted]	[redacted]	[redacted]	[redacted]		2 (1.5)		3 (2.2)	
[redacted]	[redacted]	[redacted]	[redacted]		4 (2.9)		5 (3.6)	
[redacted]	[redacted]	[redacted]	[redacted]		NR		NR	
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[redacted]	[redacted]	[redacted]	[redacted]	1 (0.7)	3 (2.2)
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Abbreviation: NR, Not reported.

Appendix F. Health-related quality of life

As mentioned in section 10, 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, EORTC QLQ-LC13 and EQ-5D-5L in the CROWN trial. Completion rates for the EORTC QLQ-C30 and QLQ-LC13 were ≥ 96% through Cycle 18 in both treatment arms, with similar completion rates for the EQ-5D-5L. All HRQL data are presented up to the September 2021 data cut-off as per CROWN protocol, HRQL data was not collected beyond the 3-year follow-up.

Lorlatinib demonstrated improvement in emotional functioning and no significant or clinically meaningful deterioration in cognitive functioning versus crizotinib, irrespective of the presence of CNS AEs or presence of baseline metastases.(56)

Summary of the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments are presented below, while the EQ-5D-5L data was presented in detail in section 10.

F.1 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).

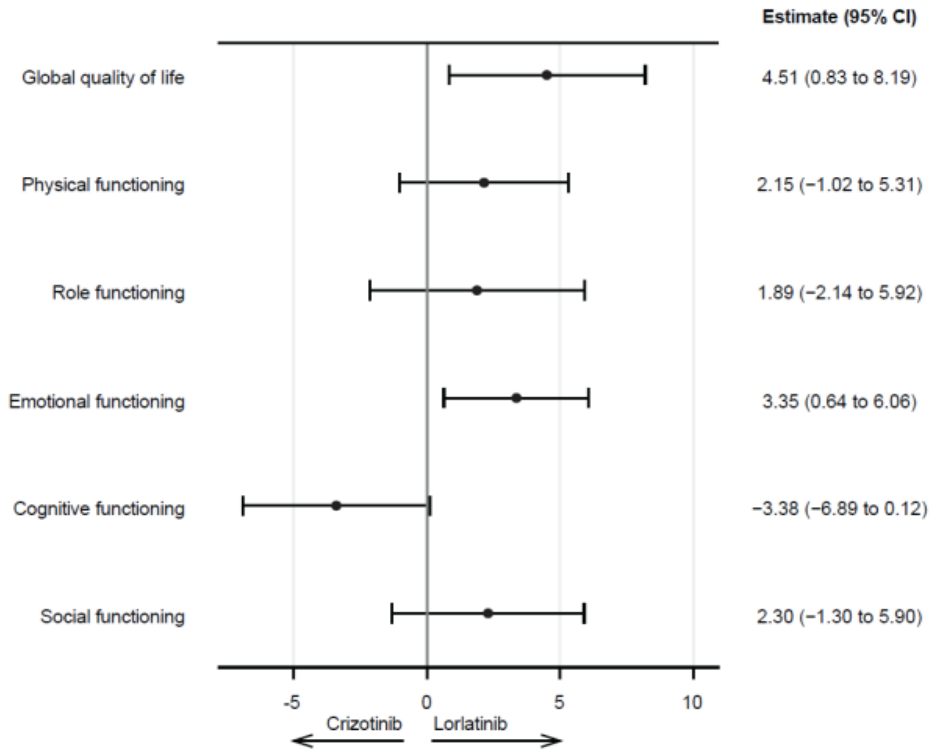
Mean baseline scores in global QoL were 64.6 (standard error [SE] ± 1.82) in the lorlatinib arm and 59.8 (SE ± 1.90) in the crizotinib arm supporting the findings from the March 2020 data cut-off. At the September 2021 data cut, patients in the lorlatinib group had significantly greater overall improvement from baseline in global quality of life and emotional functioning and showed a non-significant improvement in physical and role functioning, except cognitive functioning, compared with those who received crizotinib (Figure 89). 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 90A). In a post-hoc analysis, median time to deterioration in global quality of life from EORTC QLQ-C30 was 24.7 months (95% CI: 6.5, NR) for lorlatinib and 12.0 months (95% CL: 6.5, NR) for crizotinib (Figure 90B).(33)

Compared with crizotinib, global QoL and emotional functioning significantly improved in patients without baseline brain metastases and no changes in EORTC QLQ-C30 scores were observed in those with baseline brain metastases.(56) These results were not clinically meaningful, given the high baseline functioning scores. However, these results confirmed that the robust intracranial efficacy of lorlatinib is not associated with a significant deterioration in patient's global QoL, and that overall QoL is preserved with lorlatinib versus crizotinib, if not improved, regardless of baseline brain metastasis status.(56)

Lorlatinib demonstrated improvement in emotional functioning and no significant or clinically meaningful deterioration in cognitive functioning, irrespective of presence of CNS adverse events (AEs).(56) Cognitive functioning scores slightly declined over time in patients with or without CNS AEs. However, this was not clinically meaningful. Emotional functioning scores generally improved over time, independent of presence or absence of CNS AEs.(56)

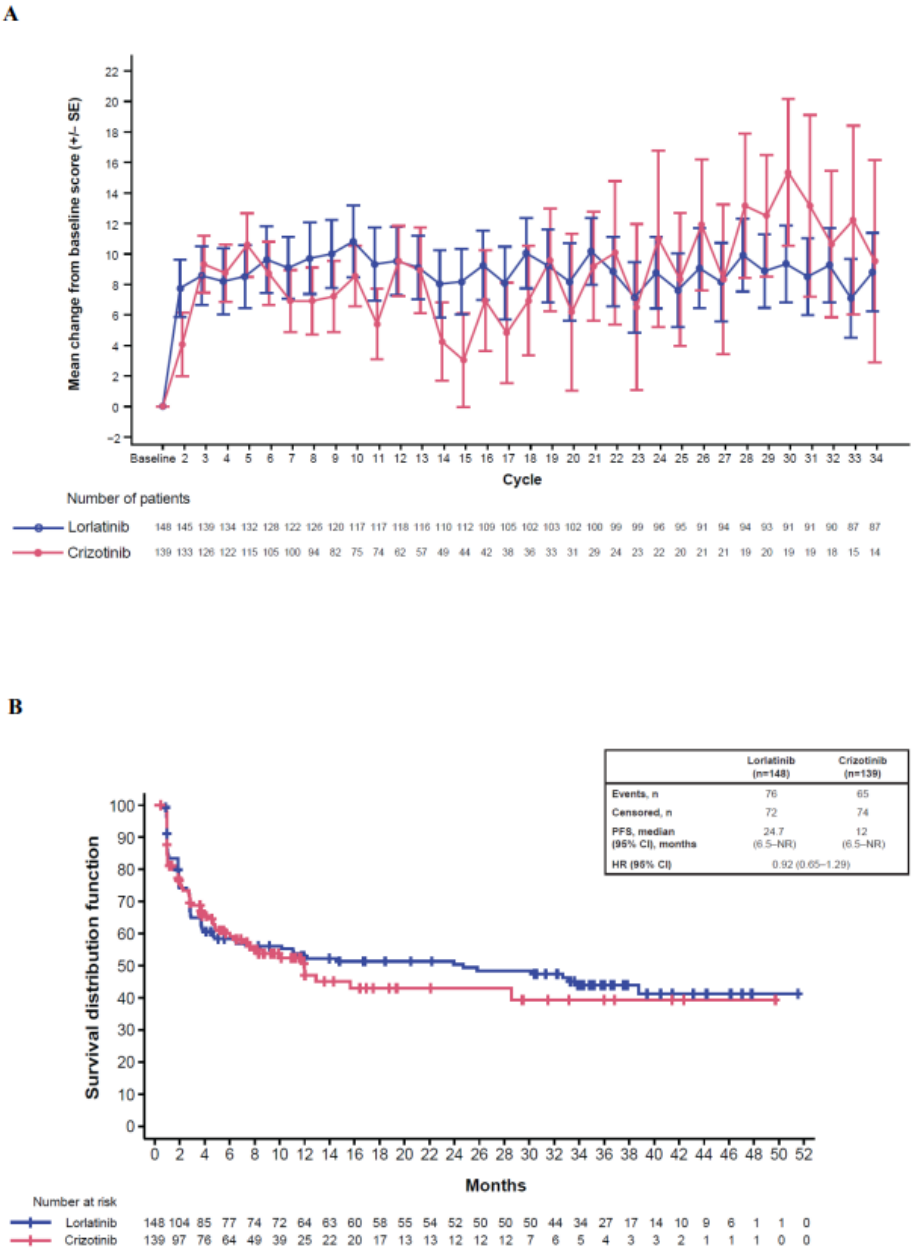
Consistent with previous data showing that CNS AEs with lorlatinib were mostly Grade 1 or 2, and more than half of all CNS AEs resolved without intervention or with lorlatinib dose interruption, these longitudinal PRO data demonstrate that occurrence of CNS AEs did not result in a clinically meaningful difference in patient-reported QoL(56)

Figure 89 Forest plot for difference in change from baseline EORTC QLQ-C30 for global quality of life and functioning scales, PRO analysis set, 20 September 2021 data cut-off



Source: Solomon et al. 2023 (Supplementary).(33)

Figure 90 Global quality of life from EORTC QLQ-C30: (A) mean change from baseline over time and (B) Kaplan–Meier estimates of time to deterioration PRO analysis set, 20 September 2021 data cut-off



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.

Notes: 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 before the date of the first dose of study treatment. Higher scores signify lower burden.

Source: Solomon et al. 2023 (Supplementary).(33)

F.2 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.

Baseline mean scores for symptoms of pain in the chest, dyspnoea and cough reported in the September 2021 data cut were similar between treatment arms.(33) Similarly, the TTD in the composite endpoint was not different between treatment arms, as presented in Table 81 and Figure 91.

Using a longitudinal mixed effects regression analysis, no clinically meaningful differences were observed in any QLQ-LC13 symptoms; however, in favour of lorlatinib, numerical differences were observed for coughing (Figure 91).(33)

Compared with crizotinib, there were no differences between treatment groups in any symptom scores of QLQ-LC13 between patients with and without baseline brain metastases.(56)

Table 81 TTD in composite of pain in chest, dyspnoea and cough from EORTC QLQ-LC13, PRO analysis set, September 2021 data cut-off

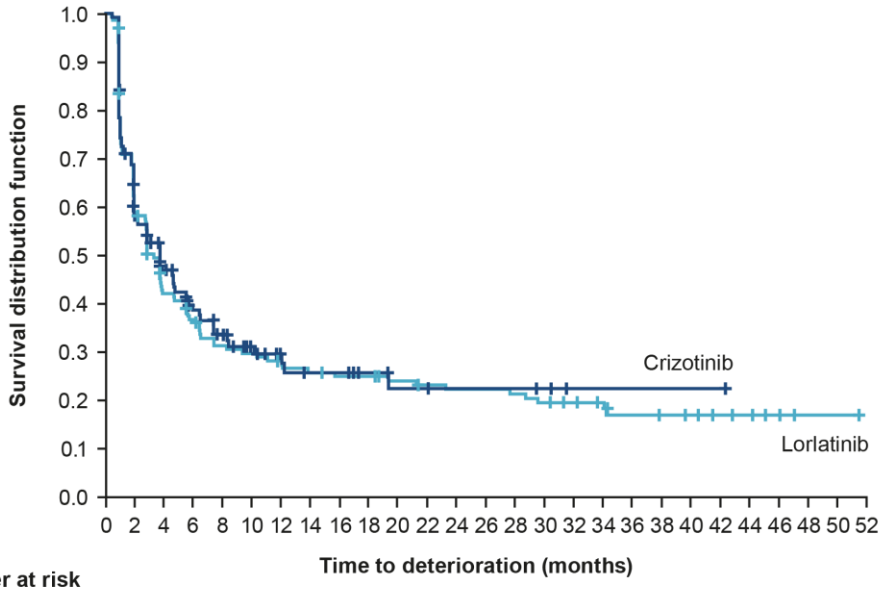
Variable	Lorlatinib (N = 146)	Crizotinib (N = 139)
Patients with event		
n (%)	112 (76.7)	92 (66.2)
Type of event		
Deterioration of chest, dyspnoea and cough, n (%)	112 (76.7)	92 (66.2)
Patients censored		
n (%)	34 (23.3)	47 (33.8)
Reason for censoring		
No deterioration, n (%)	34 (23.3)	47 (33.8)
Probability of being event free at 12 months		
Probability, (95% CI) [a]	0.281 (0.208, 0.358)	0.294 (0.211, 0.382)
Kaplan–Meier estimates of time to event (months)		
Quartiles		
Q1, (95% CI) [b]	1.0 (1.0, 1.9)	1.0 (1.0, 1.9)
Median, (95% CI) [b]	3.3 (2.1, 4.7)	3.7 (2.0, 5.5)
Q3, (95% CI) [b]	15.7 (6.5, 34.3)	NE (7.4, NE)
Comparison versus crizotinib, stratified analysis [c]		
HR (95% CI) [d]	1.07 (0.811, 1.421)	

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.

Notes: [a] CIs were derived using the log-log transformation with back transformation to original scale. [b] CIs were calculated using the Brookmeyer and Crowley method. [c] Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomisation from IRT. [d] HR based on Cox proportional hazards model; under proportional hazards, HR < 1 indicates a reduction in hazard rate in favour of lorlatinib compared to crizotinib.

Source: Solomon et al. 2023 (Supplementary).(33)

Figure 91 Kaplan–Meier Plot of TTD in composite of pain in chest, dyspnoea and cough from EORTC QLQ-LC13 in CROWN, PRO analysis set, September 2021 data cut-off



Number at risk

Lorlatinib	146	82	56	48	40	38	35	32	30	30	27	25	24	24	23	21	18	16	13	11	10	6	5	3	1	1	0
Crizotinib	139	77	54	39	29	20	15	12	12	9	7	7	6	6	6	4	1	1	1	1	1	1	0	0	0	0	0

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: Solomon et al. 2023.(33)

Appendix G. Probabilistic sensitivity analyses

Table 82 present data and assumptions (point estimate, and lower and upper bound) for the selected probability distributions used in the probabilistic analysis.

Table 82 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
RDI (%) - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
RDI (%) - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
RDI (%) - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - CROWN dose distribution - 100 mg	[redacted]			[redacted]
Lorlatinib - CROWN dose distribution - 75 mg	[redacted]			[redacted]
Lorlatinib - CROWN dose distribution - 50 mg	[redacted]			[redacted]
Lorlatinib - CROWN dose distribution - 25 mg	[redacted]			[redacted]
Lorlatinib - CROWN dose distribution - 0 mg	[redacted]			[redacted]
Administration costs - IV	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment drug costs: Pemetrexed 100mg	[redacted]			[redacted]
Subsequent treatment drug costs: Pemetrexed 500mg	[redacted]			[redacted]
Subsequent treatment drug costs: Cisplatin 50mg	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment drug costs: Cisplatin 100mg	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - clinical practice subsequent treatment % - VEGF-R	[redacted]	[redacted]	[redacted]	[redacted]

Alectinib - clinical practice subsequent treatment % - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - clinical practice subsequent treatment % - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - clinical practice subsequent treatment % - Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - clinical practice subsequent treatment % - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - clinical practice subsequent treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - clinical practice subsequent treatment % - Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - clinical practice subsequent treatment % - Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - clinical practice subsequent treatment % - VEGF-R	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - clinical practice subsequent treatment % - VEGF-R	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - trial subsequent treatment % - VEGF-R	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - trial subsequent treatment % - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - trial subsequent treatment % - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - trial subsequent treatment % - Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]

Crizotinib - trial subsequent treatment % - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - trial subsequent treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - trial subsequent treatment % - Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - trial subsequent treatment % - Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - trial subsequent treatment % - VEGF-R	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - trial subsequent treatment % - VEGF-R	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - Ceritinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - trial subsequent treatment % - VEGF-R	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
Ceritinib - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
VEGF-R - subsequent treatment duration (months)	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Oncology outpatient (f) first cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Full blood test first cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Biochemistry first cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]

RU frequency: Oncology outpatient (s) subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: GP visit subsequent cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Cancer nurse subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Full blood test subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Biochemistry subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: CT scan subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: MRI subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: X-ray subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: ECG subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Oncology outpatient (s) subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: GP visit subsequent cycle off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Cancer nurse subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Full blood test subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: Biochemistry subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: CT scan subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: MRI subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU frequency: X-ray subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Oncology outpatient (f) first cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Full blood test first cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Biochemistry first cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Oncology outpatient (s) subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: GP visit subsequent cycle on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Cancer nurse subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Full blood test subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Biochemistry subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]

RU proportion: CT scan subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: MRI subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: X-ray subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: ECG subsequent cycles on treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Oncology outpatient (s) subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: GP visit subsequent cycle off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Cancer nurse subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Full blood test subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: Biochemistry subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: CT scan subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: MRI subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
RU proportion: X-ray subsequent cycles off treatment	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - Oncology outpatient (first)	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - Oncology (subsequent)	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - GP visit	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - Cancer nurse	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - CT scan	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - X-ray	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - MRI	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - unit cost - ECG	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients without CNS metastases (First and subsequent years) - Hospitalizations	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients without CNS metastases (First and subsequent years) - Medical visits	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients without CNS metastases (First and subsequent years) - Laboratory tests	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients without CNS metastases (First and subsequent years) - Imaging techniques	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (First year) - Specific procedures for the treatment of metastases	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (First year) - Hospitalizations	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (First year) - Medical visits	[redacted]	[redacted]	[redacted]	[redacted]

Resource use - Patients with CNS metastases (First year) - Laboratory tests	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (First year) - Imaging techniques	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (Subsequent years) - Specific procedures for the treatment of metastases	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (Subsequent years) - Hospitalizations	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (Subsequent years) - Medical visits	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (Subsequent years) - Laboratory tests	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - Patients with CNS metastases (Subsequent years) - Imaging techniques	[redacted]	[redacted]	[redacted]	[redacted]
Cost per patient hour	[redacted]	[redacted]	[redacted]	[redacted]
Hours per visit	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients that incur transport costs	[redacted]	[redacted]	[redacted]	[redacted]
Average distance to hospital (km, round trip)	[redacted]	[redacted]	[redacted]	[redacted]
Cost per km	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Hypertriglyceridemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Weight increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Increased lipase level - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Hypercholesterolemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Aspartate aminotransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Gamma-glutamyltransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Hypertension - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Anaemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Amylase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Neutropenia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Blood creatine phosphokinase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Neutrophil count decreased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Peripheral neuropathy - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Cognitive effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Lorlatinib - Mood effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Hypertriglyceridemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Weight increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Increased lipase level - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Hypercholesterolemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE - Crizotinib - Aspartate aminotransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Gamma-glutamyltransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Hypertension - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Anaemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Amylase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Neutropenia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Blood creatine phosphokinase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Neutrophil count decreased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Peripheral neuropathy - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Cognitive effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Crizotinib - Mood effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Hypertriglyceridemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Weight increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Increased lipase level - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Hypercholesterolemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Aspartate aminotransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Gamma-glutamyltransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Hypertension - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Anaemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Amylase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Neutropenia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Blood creatine phosphokinase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Neutrophil count decreased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Peripheral neuropathy - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Cognitive effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Alectinib - Mood effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Hypertriglyceridemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Weight increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Increased lipase level - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Hypercholesterolemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Aspartate aminotransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Gamma-glutamyltransferase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE - Brigatinib - Hypertension - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Anaemia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Amylase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Neutropenia - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Blood creatine phosphokinase increased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Neutrophil count decreased - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Peripheral neuropathy - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Cognitive effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE - Brigatinib - Mood effects - events (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Hypertriglyceridemia	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Increased lipase level	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Hypercholesterolemia	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Peripheral neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Cognitive effects	[redacted]	[redacted]	[redacted]	[redacted]
AE duration - Mood effects	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib: Mean treatment exposure	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib: Mean treatment exposure	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Hypertriglyceridemia	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Increased lipase level	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Hypercholesterolemia	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]	[redacted]

AE costs - Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Peripheral neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Cognitive effects	[redacted]	[redacted]	[redacted]	[redacted]
AE costs - Mood effects	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival HR: Crizotinib vs. Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival HR: Crizotinib vs. Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR: Crizotinib vs. Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR: Crizotinib vs. Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS BICR is not available for the October 2023 data cut. To use PFS BICR select the HR to apply to crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Post-CNS progression survival (months)	[redacted]	[redacted]	[redacted]	[redacted]
TA536: Progression-free utility value	[redacted]	[redacted]	[redacted]	[redacted]
TA536: Progressed utility value	[redacted]	[redacted]	[redacted]	[redacted]
TA670: Progression-free utility value	[redacted]	[redacted]	[redacted]	[redacted]
TA670: Progressed utiility value	[redacted]	[redacted]	[redacted]	[redacted]
TA670: Non-CNS progressed utility by treatment - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
TA670: Non-CNS progressed utility by treatment - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
TA670: Non-CNS progressed utility by treatment - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
TA670: CNS progressed utility by treatment - Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]
TA670: CNS progressed utility by treatment - Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
TA670: CNS progressed utility by treatment - Alectinib	[redacted]	[redacted]	[redacted]	[redacted]
USER: Progression-free utility (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]
USER: Progression-free utility (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]
USER: Progressed utility (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]
USER: Progressed utility (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]
USER: CNS-progressed utility (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]
USER: CNS-progressed utility (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Utility - brain metastases - Roughley et al. (2014)	[redacted]	[redacted]	[redacted]	[redacted]
Utility - contralateral lung metastases - Roughley et al. (2014)	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Hypertriglyceridemia	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Increased lipase level	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Hypercholesterolemia	[redacted]	[redacted]	[redacted]	[redacted]

AE - utility decrement: Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Peripheral neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Cognitive effects	[redacted]	[redacted]	[redacted]	[redacted]
AE - utility decrement: Mood effects	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib median treatment beyond progression (months)	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib Median time on treatment excluding treatment beyond progression (months)	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib Median time on treatment excluding treatment beyond progression (months)	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib Median treatment beyond progression (months)	[redacted]	[redacted]	[redacted]	[redacted]
Brigatinib Median treatment beyond progression (months)	[redacted]	[redacted]	[redacted]	[redacted]
OS Exponential rate: TreatmentLorlatinib	-4.81000			Multivariate normal
OS Gen.gamma mu: TreatmentLorlatinib	2.80000			Multivariate normal
OS Gen.gamma sigma: TreatmentLorlatinib	0.89000			Multivariate normal
OS Gen.gamma Q: TreatmentLorlatinib	-3.68000			Multivariate normal
OS Gompertz shape: TreatmentLorlatinib	-0.02000			Multivariate normal
OS Gompertz rate: TreatmentLorlatinib	-4.65000			Multivariate normal
OS Log-logistic shape: TreatmentLorlatinib	0.03000			Multivariate normal

OS Log-logistic scale: TreatmentLorlatinib	4.67000	Multivariate normal
OS Log-normal meanlog: TreatmentLorlatinib	4.92000	Multivariate normal
OS Log-normal sdlog: TreatmentLorlatinib	0.63000	Multivariate normal
OS Weibull shape: TreatmentLorlatinib	-0.03000	Multivariate normal
OS Weibull scale: TreatmentLorlatinib	4.86000	Multivariate normal
OS Gamma shape: TreatmentLorlatinib	-0.01000	Multivariate normal
OS Gamma rate: TreatmentLorlatinib	-4.84000	Multivariate normal
OS Exponential rate: TreatmentCrizotinib	-4.48121	Multivariate normal
OS Gen.gamma mu: TreatmentCrizotinib	3.28684	Multivariate normal
OS Gen.gamma sigma: TreatmentCrizotinib	0.75739	Multivariate normal
OS Gen.gamma Q: TreatmentCrizotinib	-2.08525	Multivariate normal
OS Gompertz shape: TreatmentCrizotinib	-0.01196	Multivariate normal
OS Gompertz rate: TreatmentCrizotinib	-4.35986	Multivariate normal
OS Log-logistic shape: TreatmentCrizotinib	0.20379	Multivariate normal
OS Log-logistic scale: TreatmentCrizotinib	4.08979	Multivariate normal
OS Log-normal meanlog: TreatmentCrizotinib	4.24794	Multivariate normal

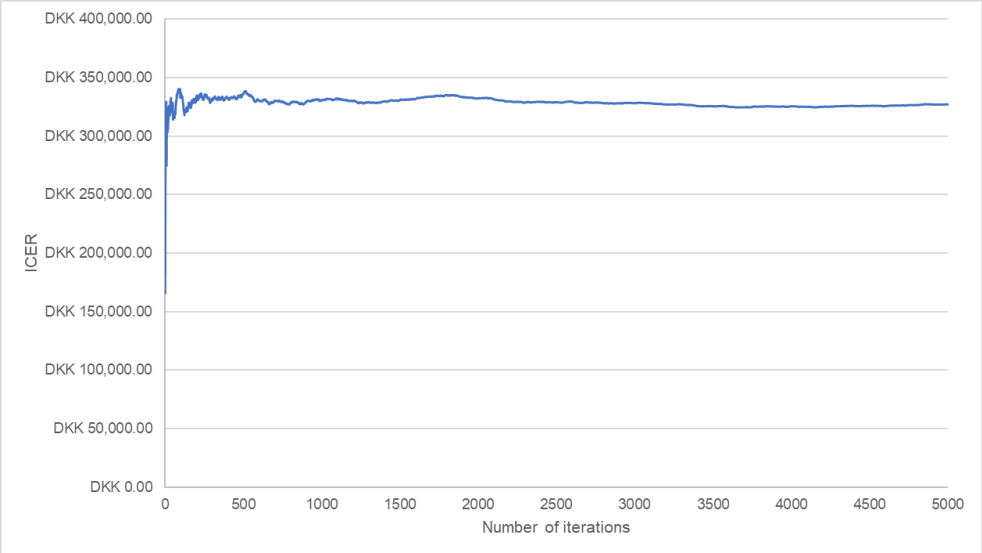
OS Log-normal sdlog: TreatmentCrizotinib	0.43203	Multivariate normal
OS Weibull shape: TreatmentCrizotinib	0.12518	Multivariate normal
OS Weibull scale: TreatmentCrizotinib	4.30472	Multivariate normal
OS Gamma shape: TreatmentCrizotinib	0.18339	Multivariate normal
OS Gamma rate: TreatmentCrizotinib	-4.09027	Multivariate normal
PFS Exponential rate: TreatmentLorlatinib	-4.654	Multivariate normal
PFS Gen.gamma mu: TreatmentLorlatinib	2.937	Multivariate normal
PFS Gen.gamma sigma: TreatmentLorlatinib	0.941	Multivariate normal
PFS Gen.gamma Q: TreatmentLorlatinib	-1.914	Multivariate normal
PFS Gompertz shape: TreatmentLorlatinib	-0.040	Multivariate normal
PFS Gompertz rate: TreatmentLorlatinib	-3.779	Multivariate normal
PFS Log-logistic shape: TreatmentLorlatinib	-0.297	Multivariate normal
PFS Log-logistic scale: TreatmentLorlatinib	4.538	Multivariate normal
PFS Log-normal meanlog: TreatmentLorlatinib	4.597	Multivariate normal
PFS Log-normal sdlog: TreatmentLorlatinib	0.841	Multivariate normal
PFS Weibull shape: TreatmentLorlatinib	-0.437	Multivariate normal

PFS Weibull scale: TreatmentLorlatinib	5.078	Multivariate normal
PFS Gamma shape: TreatmentLorlatinib	-0.497	Multivariate normal
PFS Gamma rate: TreatmentLorlatinib	-5.613	Multivariate normal
PFS Exponential rate: TreatmentCrizotinib	-2.740	Multivariate normal
PFS Gen.gamma mu: TreatmentCrizotinib	2.089	Multivariate normal
PFS Gen.gamma sigma: TreatmentCrizotinib	-0.036	Multivariate normal
PFS Gen.gamma Q: TreatmentCrizotinib	-0.400	Multivariate normal
PFS Gompertz shape: TreatmentCrizotinib	-0.022	Multivariate normal
PFS Gompertz rate: TreatmentCrizotinib	-2.473	Multivariate normal
PFS Log-logistic shape: TreatmentCrizotinib	0.618	Multivariate normal
PFS Log-logistic scale: TreatmentCrizotinib	2.227	Multivariate normal
PFS Log-normal meanlog: TreatmentCrizotinib	2.272	Multivariate normal
PFS Log-normal sdlog: TreatmentCrizotinib	-0.029	Multivariate normal
PFS Weibull shape: TreatmentCrizotinib	0.031	Multivariate normal
PFS Weibull scale: TreatmentCrizotinib	2.748	Multivariate normal
PFS Gamma shape: TreatmentCrizotinib	0.213	Multivariate normal

PFS Gamma rate: TreatmentCrizotinib	-2.505	Multivariate normal

As seen in Figure 92, convergence testing indicated that about 2500 iterations would be enough for the PSA. However, 5000 iterations were chosen to ensure a reliable result.

Figure 92 Convergence testing of PSA based on ICER



Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The systematic literature search for efficacy and safety studies was based on an existing SLR that was updated to October 2024. The first search was conducted in October 2019 with the purpose of summarizing the clinical evidence for first-line treatment in advanced/metastatic ALK+ NSCLC patients. The SLR was then updated in April 2021, in February 2024 and again in October 2024 for the present application. In the previous updates, the following databases were included:

- MEDLINE® and Embase® (using Embase.com)
- MEDLINE In-Process® (using Pubmed.com)
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews (CDSR)
    - The Cochrane Central Register of Controlled Trials (CENTRAL)

The update for the present application was conducted in MEDLINE (via PubMed) and EMBASE (via Ovid) using the search strategy and search strings from the existing SLR. In addition, the website of the HTA agency NICE was searched to identify relevant studies used in similar NICE appraisals. Relevant conferences were also searched to identify any relevant conference material. The conferences that were regarded as relevant are presented in Table 85 along with the search strategy for each conference.

Table 83 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
EMBASE	Ovid	February 2024 to October 2024	09 October 2024
MEDLINE	PubMed	February 2024 to October 2024	07 October 2024

Table 84 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Searched to identify any appraisals with literature that could be used in the present application. Search terms included terms on the relevant patient population and interventions.	11 October 2024

Table 85 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Terms searched February 2024	Terms searched October 2024	Date of search
International Association for the Study of Lung Cancer (IASLC)	https://www.iaslc.org/	Manual search. February 2024 update: from 2018–2023 October 2024 update: 2024 (conference in March 2024)	"Lorlatinib"; PF-06463922; "Crizotinib"; Crizalk®; Xalkori®; PF-02341066; "Ceritinib"; Zykadia®; LDK 378; "Alectinib"; Alecensa®; AF-802 (Alectinib); ALECENSARO (Alectinib); RG-7853 (Alectinib); RO-5452802 (Alectinib); RO-5424802 (Alectinib); CH-5424802 (Alectinib); "Brigatinib"; AP26113; "Ensartinib"; X-396; "TSR-011"; "ASP3026"; X-376; "CEP-28122"; "CEP-37440"; "Entrectinib"; NMS-E628 (Entrectinib); RXDX-101; "Retaspimycin"; Retaspamycin; IPI-504;	“NSCLC”; “Non small cell lung cancer”; “Lung cancer”; “Non-small cell lung cancer”; “ALK+”; “Anaplastic lymphoma kinase’; “ALK-Positive”; “ALK positive”; “Pulmonary adenocarcinoma” AND "Lorlatinib"; PF-06463922; "Crizotinib"; Crizalk®; Xalkori®; PF-02341066; "Alectinib"; Alecensa®; AF-802 (Alectinib); ALECENSARO (Alectinib); RG-7853 (Alectinib); RO-5452802 (Alectinib); RO-5424802 (Alectinib); CH-5424802 (Alectinib);	11 October
American Society of Clinical Oncology (ASCO)	https://www.asco.org/	Manual search. February 2024 update: from 2018–2023 October 2024 update: 2024 (conference in May/June)			11 October
European Cancer Organisation (ECCO)	http://www.ecco-org.eu/	No abstract submission			11 October
European Society for Medical	http://www.esmo.org/	Manual search.			11 October

Oncology (ESMO)	February 2024 update: from 2018–2023 October 2024 update: 2024 (conference in September 2024)	Pemetrexed; Alimta®; “NSCLC”; “Non small cell lung cancer”; “Lung cancer”; “Non-small cell lung cancer”; “ALK+”; “Anaplastic lymphoma kinase’; “ALK-Positive”; “ALK positive”; “Pulmonary adenocarcinoma”	"Brigatinib"; AP26113.

H.1.1 Search strategies

Table 86 and Table 87 present the different searches and updates in PubMed, while Table 88 and Table 89 present the different searches in Embase. Table 90 presents the search from the Cochrane library conducted in the existing SLR and previous updates, which was not updated in the present application.

As seen in Table 88 and Table 89, the search string used in the update from February 2024 was adjusted slightly in the October 2024 update. This was done to adapt the search string to Embase via Ovid as the February 2024 update was conducted in Embase via Embase.com. Search results from the two databases were merged using the reference management software Rayyan and duplicates were removed. All titles and abstracts were reviewed for information that clearly met the inclusion and exclusion criteria stated in Table 91. First-level screening was conducted by two reviewers. The full text of studies that passed the first level of screening was retrieved and reviewed by two reviewers using the same inclusion/exclusion criteria. Any disagreements in terms of relevance were discussed with an independent third reviewer.

Table 86 Search strategy for PubMed.com (original SLR and first update)

No.	Query	Original SLR from October 31, 2019	Update SLR from April 22, 2021
#1	Carcinoma, Non-Small-Cell Lung[mh] OR nsclc[tiab]	61,625	71,499
#2	Neoplasms[mh] OR Carcinoma, Squamous Cell[mh] OR Adenocarcinoma[mh]	3,232,661	3,445,930
#3	Lung[mh]	266,998	280,403
#4	#2 AND #3	51,464	32,901
#5	(lung[tiab] OR pulmon*[tiab] OR bronchial[tiab]) AND (cancer* [tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	302,902	337,545
#6	#4 OR #5	349,128	351,318
#7	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	62,092	72,252
#8	#6 AND #7	61,857	72,002
#9	#1 OR #8	72,746	84,216
#10	lorlatinib[tiab] OR "pf-06463922"[tiab]	126	233
#11	crizotinib[tiab] OR xalkori[tiab] OR "pf-02341066"[tiab] OR "pf-2341066"[tiab]	2,042	2,478
#12	ceritinib[tiab] OR zykadia[tiab] OR "ldk 378"[tiab] OR "ldk378"[tiab]	408	517
#13	alectinib[tiab] OR alecensa[tiab] OR "af802"[tiab] OR "af-802"[tiab] OR "ch5424802"[tiab] OR "rg7853"[tiab] OR "ro5424802"[tiab] OR "unii-lij4ct1z3y"[tiab]	431	609
#14	brigatinib[tiab] OR "ap26113"[tiab]	141	217
#15	ensartinib[tiab] OR "x-396"[tiab]	21	33
#16	"tsr-011"[tiab]	7	7
#17	"asp3026"[tiab] OR "asp-3026"[tiab]	18	20
#18	"x-376"[tiab]	5	3

#19	"cep-28122"[tiab]	2	2
#20	"cep-37440"[tiab]	6	6
#21	entrectinib[tiab] OR "rxdx-101"[tiab]	63	164
#22	retaspimycin[tiab] OR "ipi-504"[tiab]	41	41
#23	pemetrexed[tiab] OR alimta[tiab] OR “ly231514”[tiab]	3,027	3,407
#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	5,370	6,429
#25	#9 AND #24	3,090	3,681
#26	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	322,146	374,955
#27	#25 AND #26	102	69

Table 87 Search strategy for PubMed.com (February 2024 update and October 2024 update)

No.	Query	Update SLR from February 2024	Update SLR from October 2024
#1	Carcinoma, Non-Small-Cell Lung[mh] OR nsclc[tiab]	92,887	96,918
#2	Neoplasms[mh] OR Carcinoma, Squamous Cell[mh] OR Adenocarcinoma[mh]	39,37,083	3,878,639
#3	Lung[mh]	310,461	314,257
#4	#2 AND #3	38,557	38,096
#5	(lung[tiab] OR pulmon*[tiab] OR bronchial[tiab]) AND (cancer* [tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	407,719	422,942
#6	#4 OR #5	422,476	437,542
#7	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	92,832	97,148
#8	#6 AND #7	92,560	96,868
#9	#1 OR #8	107,621	112,315

#10	lorlatinib[tiab] OR "pf-06463922"[tiab]	548	623
#11	crizotinib[tiab] OR xalkori[tiab] OR "pf-02341066"[tiab] OR "pf-2341066"[tiab]	3,269	3,401
#12	ceritinib[tiab] OR zykadia[tiab] OR "ldk 378"[tiab] OR "ldk378"[tiab]	704	724
#13	alectinib[tiab] OR alecensa[tiab] OR "af802"[tiab] OR "af-802"[tiab] OR "ch5424802"[tiab] OR "rg7853"[tiab] OR "ro5424802"[tiab] OR "unii-lij4ct1z3y"[tiab]	1,083	1,163
#14	brigatinib[tiab] OR "ap26113"[tiab]	423	453
#15	ensartinib[tiab] OR "x-396"[tiab]	113	125
#16	"tsr-011"[tiab]	7	7
#17	"asp3026"[tiab] OR "asp-3026"[tiab]	20	22
#18	"x-376"[tiab]	4	5
#19	"cep-28122"[tiab]	2	2
#20	"cep-37440"[tiab]	7	7
#21	entrectinib[tiab] OR "rxdx-101"[tiab]	395	452
#22	retaspimycin[tiab] OR "ipi-504"[tiab]	43	43
#23	pemetrexed[tiab] OR alimta[tiab] OR “ly231514”[tiab]	4,177	4,314
#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	8,706	9,129
#25	#9 AND #24	13	18
#26	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	8,708	9,133
#27	#25 AND #26	377,875	344,459
#28	#26 AND #27	118	111
#29	#28 AND ("2024/02/27"[Date - Publication] : "3000"[Date - Publication])	-	68

Table 88 Search strategy for EMBASE (original SLR and first update – search via Embase.com)

No.	Query	Original SLR from October 31, 2019	Update SLR from April 22, 2021
#1	'non small cell lung cancer'/exp OR nsclc:ab,ti	157,602	176,163
#2	'neoplasm'/exp OR 'squamous cell carcinoma'/exp OR 'adenocarcinoma'/exp	4,768,098	5,178,939
#3	'lung'/exp	318,965	342,260
#4	#2 AND #3	69,149	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	316,824	352,559
#6	#4 OR #5	358,285	397,977
#7	'non small cell':ab,ti OR 'non-small-cell':ab,ti OR 'nonsmall cell':ab,ti	97,764	109,341
#8	#6 AND #7	96,865	108,378
#9	#1 OR #8	160,544	183,866
#10	'lorlatinib'/syn OR lorlatinib:ab,ti OR 'pf-06463922'	521	819
#11	'crizotinib'/syn OR crizotinib:ab,ti OR xalkori:ab,ti OR 'pf-02341066' OR 'pf-2341066'	7,716	9,141
#12	'ceritinib'/syn OR ceritinib:ab,ti OR zykadia:ab,ti OR 'ldk 378' OR 'ldk378'	1,687	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'	1,528	2,096
#14	'brigatinib'/syn OR brigatinib:ab,ti OR 'ap26113'	758	1,045
#15	ensartinib:ab,ti OR 'x-396'	225	167
#16	'belizatinib'/syn OR belizatinib:ab,ti OR 'tsr-011'	56	61
#17	'asp3026' OR 'asp-3026'	113	116
#18	'x-376'	14	16

#19	'cep-28122'	36	38
#20	'cep-37440'	32	34
#21	'entrectinib'/syn OR entrectinib:ab,ti OR 'rxdx-101'	340	701
#22	'retaspimycin'/syn OR retaspimycin:ab,ti OR 'ipi-504'	460	474
#23	'pemetrexed'/syn OR pemetrexed:ab,ti OR alimta:ab,ti OR 'ly231514'	13,782	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	21,571	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)	2,216,470	2, 7,536
#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	10,241,982	11,312,679
#27	#25 OR #26	10,508,282	11,601,794
#28	#9 AND #24 AND #27	8,746	10,442
#29	letter:it OR editorial:it OR note:it	2,465,436	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)	2,662,758	2,858,082
#31	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5,345,075	5,579,673
#32	'case report*':ab,ti OR 'case series':ab,ti	571,347	642,817
#33	#29 OR #30 OR #31 OR #32	10,696,076	11,380,516
#34	#28 NOT #33	7,076	1,733

Table 89 Search strategy for EMBASE (February 2024 update and October 2024 update)

No.	Query in Embase.com (used in the february 2024 update)	Query in Embase via Ovid (used in the October 2024 update)	Update SLR from February 2024	Update SLR from October 2024
#1	'non small cell lung cancer'/exp OR nsclc:ab,ti	exp non small cell lung cancer/OR nsclc.ab,ti.	129,783	213,514
#2	'neoplasm'/exp OR 'squamous cell carcinoma'/exp OR 'adenocarcinoma'/exp	exp neoplasm/ OR exp squamous cell carcinoma/ OR exp adenocarcinoma/	4,376,049	5,871,742
#3	'lung'/exp	exp lung/	298,065	409,758
#4	#2 AND #3	2 AND 3	63,336	89,833
#5	((lung OR pulmon* OR bronchial) NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ab,ti	((lung OR pulmon$ OR bronchial) adj3 (cancer$ OR carcin$ OR neoplasm$ OR tumour$ OR tumor$ OR squamous OR adenocarcinoma$)).ab,ti.	279,118	446,521
#6	#4 OR #5	4 OR 5	316,619	501,157
#7	'non small cell':ab,ti OR 'non-small-cell':ab,ti OR 'nonsmall cell':ab,ti	non small cell.ab,ti. OR non-small-cell.ab,ti. OR nonsmall cell.ab,ti.	82,786	151,284
#8	#6 AND #7	6 AND 7	81,985	150,049
#9	#1 OR #8	1 OR 8	136,010	238,754

#10	'lorlatinib'/syn OR lorlatinib:ab,ti OR 'pf-06463922'	syn lorlatinib/OR lorlatinib.ab,ti. OR pf-06463922	281	383
#11	'crizotinib'/syn OR crizotinib:ab,ti OR xalkori:ab,ti OR 'pf-02341066' OR 'pf-2341066'	syn crizotinib/ OR crizotinib.ab,ti. OR xalkori.ab,ti. OR pf-02341066 OR pf-2341066	6,215	6,998
#12	'ceritinib'/syn OR ceritinib:ab,ti OR zykadia:ab,ti OR 'ldk 378' OR 'ldk378'	syn ceritinib/ OR ceritinib.ab,ti. OR zykadia.ab,ti. OR ldk 378 OR ldk378	1,218	1,477
#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'	syn alectinib/ OR alectinib.ab,ti. OR alecensa.ab,ti. OR af802 OR af-802 OR ch5424802 OR rg7853 OR ro5424802 OR unii-lij4ct1z3y	995	2,069
#14	'brigatinib'/syn OR brigatinib:ab,ti OR 'ap26113'	syn brigatinib/ OR brigatinib.ab,ti. OR ap26113	460	872
#15	ensartinib:ab,ti OR 'x-396'	ensartinib.ab,ti. OR x-396	111	297
#16	'belizatinib'/syn OR belizatinib:ab,ti OR 'tsr-011'	syn belizatinib/ OR belizatinib.ab,ti. OR tsr-011	53	58
#17	'asp3026' OR 'asp-3026'	asp3026 OR asp-3026	108	127
#18	'x-376'	x-376	15	37
#19	'cep-28122'	cep-28122	34	40
#20	'cep-37440'	cep-37440	29	44
#21	'entrectinib'/syn OR entrectinib:ab,ti OR 'rxdx-101'	syn entrectinib/ OR entrectinib.ab,ti. OR rxdx-101	209	925
#22	'retaspimycin'/syn OR retaspimycin:ab,ti OR 'ipi-504'	syn retaspimycin/ OR retaspimycin.ab,ti. OR ipi-504	452	372
#23	'pemetrexed'/syn OR pemetrexed:ab,ti OR alimta:ab,ti OR 'ly231514'	syn pemetrexed/ OR pemetrexed.ab,ti. OR alimta.ab,ti. OR ly231514	11,840	9,489
#24	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR	17,931	18,922

	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	18 OR 19 OR 20 OR 21 OR 22 OR 23		
#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 OR '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) NOT ('case study'/de OR 'case report':ab,ti OR 'abstract report'/de OR 'letter'/de)	(exp clinical trial/ OR exp randomized controlled trial/ OR randomization/de OR single blind procedure/de OR double blind procedure/de OR crossover procedure/de OR placebo/de OR ((randomi#ed adj2 controlled trial$).ab,ti.) OR rct.ab,ti. OR random allocation.ab,ti. OR randomly allocated.ab,ti. OR allocated randomly.ab,ti. OR (((allocated OR assign$) adj2 random).ab,ti.) OR ((single adj blind$).ab,ti.) OR ((double adj blind$).ab,ti.) OR (((treble OR triple) adj3 blind$).ab,ti.) OR placebo$.ab,ti. OR prospective study/de OR exp clinical study/ OR case control study/de OR family study/de OR longitudinal study/de OR retrospective study/de OR (prospective study/de NOT exp randomized controlled trial/) OR cohort.ab,ti. OR cohort analysis/de OR ((cohort adj1 (study OR studies)).ab,ti.) OR ((case control adj1 (study OR studies)).ab,ti.) OR ((follow up adj1 (study OR studies)).ab,ti.) OR ((observational adj1 (study OR studies)).ab,ti.) OR ((epidemiologic$ adj1 (study OR studies)).ab,ti.) OR ((cross sectional adj1 (study OR studies)).ab,ti.) OR exp register/ OR regist$.ab,ti.) NOT (case study/de OR case report.ab,ti. OR abstract report/de OR letter/de)	12,915,712	13,608,560

#26	#9 AND #24 AND #25	9 AND 24 AND 25	5,467	7,791
#27	letter:it OR editorial:it OR note:it	letter.pt. OR editorial.pt. OR note.pt.	2,289,905	3,174,801
#28	(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)	(review.pt. OR exp review literature as topic/ OR literature review.ti.) NOT (meta-analysis.pt. OR meta-analysis as topic/ OR systematic review.ti OR systematic literature review.ti. OR meta-analysis.ab,ti. OR meta analysis.ab,ti.)	2,502,373	3,350,056
#29	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	exp animal/ NOT (exp animal/ AND exp human/)	5,055,077	5,327,030
#30	'case report*':ab,ti OR 'case series':ab,ti	case report$.ab,ti. OR case series.ab,ti.	510,949	839,957
#31	#27 OR #28 OR #29 OR #30	27 OR 28 OR 29 OR 30	10,031,076	12,263,858
#32	#26 NOT #31	26 NOT 31	10,858	7,100
#33	#26 NOT #31 AND [01-04-2021]/sd NOT [01-03-2024]/sd	limit 32 to dc=20240227-20241010	3,072	335
#34	'iruplinalkib'/exp OR 'envonalkib'/exp OR 'fl 006' OR fl006 OR 'wx 0593' OR wx0593 OR 'q b3139' OR qb3139 OR envonalkib OR iruplinalkib	exp iruplinalkib/ OR exp envonalkib/ OR fl 006 OR fl006 OR wx 0593 OR wx0593 OR q b3139 OR qb3139 OR envonalkib OR iruplinalkib	43	40
#35	#9 AND #25 AND #34	9 AND 25 AND 34	13	19
#36	#35 NOT #31	35 NOT 31	13	17
#37	#33 OR #36	33 OR 36	3,086	349
#38	(#33 OR #36) AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	(33 or 36) AND lim conference abstract/ OR lim conference paper/ OR lim conference review/	800	0

#39	(#33 OR #36) AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2022-2024]/py	(33 or 36) and lim conference abstract/ or lim conference paper/ or lim conference review/AND 2024:py	516	0
#40	#37 NOT #38	37 NOT 38	2,286	349
#41	#39 OR #40	39 OR 40	2,802	349

Table 90 Search strategy for Cochrane library: Wiley interscience (original SLR and previous updates. This search was not updated in the present application)

S. No.	Query	Hits		
		Original SLR October 31, 2019	Update SLR April 22, 2021	Update SLR February 27, 2024
1	[mh "Carcinoma, Non-Small-Cell Lung"] or nsclc:ti,ab,kw	9,950	11,318	14,025
2	[mh Neoplasms] or [mh "Carcinoma, Squamous Cell"] or [mh Adenocarcinoma]	72,188	82,548	123,386
3	[mh Lung]	4,084	4,299	6,387
4	#2 and #3	259	283	558
5	((lung or pulmon* or bronchial) near/3 (cancer* or carcin* or neoplasm* or tumour* or tumor* or squamous or adenocarcinoma*)):ti,ab,kw	21,790	23,814	28,599
6	#4 or #5	21,858	23,889	28,712
7	("non small cell" or "non-small-cell" or "nonsmall cell"):ti,ab,kw	12,431	13,833	16,406
8	#6 and #7	12,276	13,633	16,173
9	#1 or #8	12,968	14,420	17,092
10	(lorlatinib or "pf-06463922"):ti,ab,kw	19	33	60
11	(crizotinib or xalkori or "pf-02341066" or "pf-2341066"):ti,ab,kw	300	357	449
12	(ceritinib or zykadia or "ldk 378" or "ldk378"):ti,ab,kw	65	71	77
13	(alectinib or alecensa or "af802" or "af-802" or "ch5424802" or "rg7853" or "ro5424802" or "unii-lij4ct1z3y"):ti,ab,kw	104	130	176
14	(brigatinib or "ap26113"):ti,ab,kw	62	91	129
15	(ensartinib or "x-396"):ti,ab,kw	15	21	29
16	"tsr-011":ti,ab,kw	1	0	0
17	("asp3026" or "asp-3026"):ti,ab,kw	0	0	0

18	"x-376":ti,ab,kw	0	0	0
19	"cep-28122":ti,ab,kw	0	0	0
20	"cep-37440":ti,ab,kw	0	0	0
21	(entrectinib or "rxdx-101"):ti,ab,kw	9	16	30
22	(retaspimycin or "ipi-504"):ti,ab,kw	6	6	6
23	(pemetrexed or alimta or "ly231514"):ti,ab,kw	1,790	2,147	2,584
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	2,090	2,517	3,083
25	#9 and #24	1,060	2,014	2,482
26	#9 and #24 with Cochrane Library publication date from Oct 2019 to May 2021, in Trials	-	490	-
	#25 with Cochrane Library publication date Between Mar 2021 and Mar 2024, in Trials	-	-	568

H.1.2 Systematic selection of studies

The inclusion/exclusion criteria were used to screen the identified results (see Table 91). Studies assessing a mixed population were included only if relevant outcomes data were reported for patients with advanced/metastatic ALK-positive NSCLC receiving first-line therapy, including both chemo-treated and a treatment-naïve population. Studies of combinations of the intervention of interest with non-pharmacological therapy were also included. Some adaptations of the inclusion and exclusion criteria were made in the October 2024 update to ensure that the inclusion and exclusion criteria reflected Danish clinical practice. In terms of populations, in addition to the populations excluded in the existing SLR, studies on a 100% Asian population were excluded in the October 2024 update. Also, studies that included a mixed population (early stages and advanced stages) had to report results separately for advanced ALK-positive NSCLC to be included. In terms of interventions, the October 2024 update only included interventions relevant in a Danish setting i.e., lorlatinib, alectinib and brigatinib.

Table 91 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	• Adult patients with advanced/metastatic (Stage IIIb or IV) ALK+ NSCLC • First-line setting with no prior treatment with ALK inhibitors, but <50% patients can be treated with prior chemotherapeutic regimens	• Paediatric patients • Disease other than advanced/metastatic ALK+ NSCLC • Early-stage NSCLC in adjuvant or neoadjuvant setting • Treatment-resistant/failed/second-line or later setting NSCLC	Studies with a 100% Asian population were excluded
Intervention	The following therapies either alone or in combination with any other treatment: • Lorlatinib/PF-06463922 • Crizotinib/PF-02341066b • Ceritinib/LDK 378 • Alectinib • Brigatinib/AP26113 • Ensartinib/X-396 • Iruplinalkib/WX-0593 • Envonalkib/CT-711/TQ-B3139	• All non-pharmacological interventions • Interventions not included in the list • Radiotherapy • Surgery • Neoadjuvant	Studies with the following interventions: Ceritinib/LDK 378,Crizotinib/PF-02341066b, Ensartinib/X-396, Iruplinalkib/WX-0593 and Envonalkib/CT-711/TQ-B3139 were excluded in the October 2024 update
Comparators	No restrictions	No exclusion on comparators	None
Outcomes	Baseline outcomes such as • Age, male, metastatic sites (bone, brain/CNS metastases, liver and other), race, prior surgery, prior therapy, prior radiotherapy, current smokers, never smokers, ex-smokers/former	Studies assessing only pharmacodynamics and pharmacokinetics Studies assessing outcomes not	None

	smokers, cancer stages (IIIb and IV), ECOG Performance Status, disease subtype, BIRC and INV assessed: • Overall response • Complete response • Partial response • Stable disease • Disease progression • Disease control rate • Cumulative incidence rate of CNS progression • Overall survival • Event-free survival/progression-free survival • Overall death/mortality • Time to progression • Time to response • Duration of response BIRC, INV assessed in patients with or without[c] brain metastases and Asian[c] subgroup: • Overall response • Complete response • Partial response • Stable disease • Disease progression • Disease control rate • Cumulative incidence rate of CNS progression • Overall survival • Event-free survival/progression-free survival • Time to CNS progression • Time to response • Duration of response	relevant to the review

	• Time to next treatment[d] • Time to discontinuation[d] • Quality of life • Tolerability • Safety • Discontinuation rates due to AEs • Dose reduction rate due to AEs • Median duration of treatment		
Study design/publication type	• RCTs irrespective of blinding status • Non-RCTs • Single-arm studies • Cohort studies (both prospective and retrospective) • Long-term follow-up studies • Systematic reviews and meta-analyses of RCTs[a]/non-RCTs[a]	• Preclinical studies • Comments, letters, editorials • Case reports, case series • Non-systematic review	RCT's were preferred over other types of study designs in the October 2024 update
Language restrictions	Not limited by language of publication[e]	None	None

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; ALK+, anaplastic lymphoma kinase-positive; BIRC, Blinded Independent Central Review; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; INV, investigator; NSCLC, non-small-cell lung cancer; RCTs, randomised controlled trials; SLR, systematic literature review. Table notes: [a]Systematic reviews and meta-analyses of RCTs and non-RCTs will be included and flagged. Bibliographies of these systematic reviews will be screened to check if literature searches had missed any potentially relevant studies. [b]Only extracted for RCTs. [c]Applicable only for RCT data extraction. [d]This applies exclusively to data extraction for non-RCT and other observational studies, not for RCTs. [e]Non-English publications will be explored if sufficient evidence from English language studies is not identified.

H.1.2.1 Results from the original SLR, 2021 update and February 2024 update

In the original SLR and previous updates, a total of 10,500 potentially relevant titles or abstracts were identified. 940 of the studies were identified as duplicates and excluded. The remaining 9,560 studies were screened based on the information reported in their titles and/or abstracts. Of these, 7,475 records were excluded, and 2,085 records were included. These 2,085 records were further assessed for their eligibility by full-text screening, which resulted in the exclusion of 1,857 publications and the inclusion of 228 publications. Additionally, 11 citations were identified through grey literature searches.

After duplicate removal and linking across the original and updated SLR, 89 studies (10 RCTs and 79 non-RCTs) were extracted from 239 publications.

In the update from 27 February 2024, a total of 3,488 relevant citations were identified for review. Out of the total studies, 247 were identified as duplicates and subsequently excluded. The remaining 3,241 studies underwent screening based on the information presented in their titles and/or abstracts; 443 full text citations were considered for inclusion. Of these, a total of 366 references were excluded and 77 reports were included. Additionally, seven citations were identified through grey literature searches. After removing duplicates and conducting a linking procedure, 41 studies were extracted from an initial pool of 84 publications. Amongst these, 10 studies were RCTs, while the other 31 were non-RCT in nature. Of the 10 RCTs from 45 publications, eight were updates to previously identified RCTs and two were newly identified in this review. No relevant non-English citations were identified.

The total evidence represented from the previous updates was 12 studies, which were extracted from an RCT perspective. Out of the 12 RCTs extracted from 145 publications, eight were updates to previously identified RCTs, and two were newly identified. Additionally, two studies were found without newly identified links. Therefore, only subgroup data were updated for these two studies. Of the 41 non-RCTs from 77 publications, three were updates to previously identified non-RCTs and 28 were newly identified.

A PRISMA flow diagram from the original SLR and updates is presented in Figure 93 and the references reported as included from the February 2024 update are presented in Table 92.

Figure 93 PRISMA flow diagram from the original SLR and the previous searches.

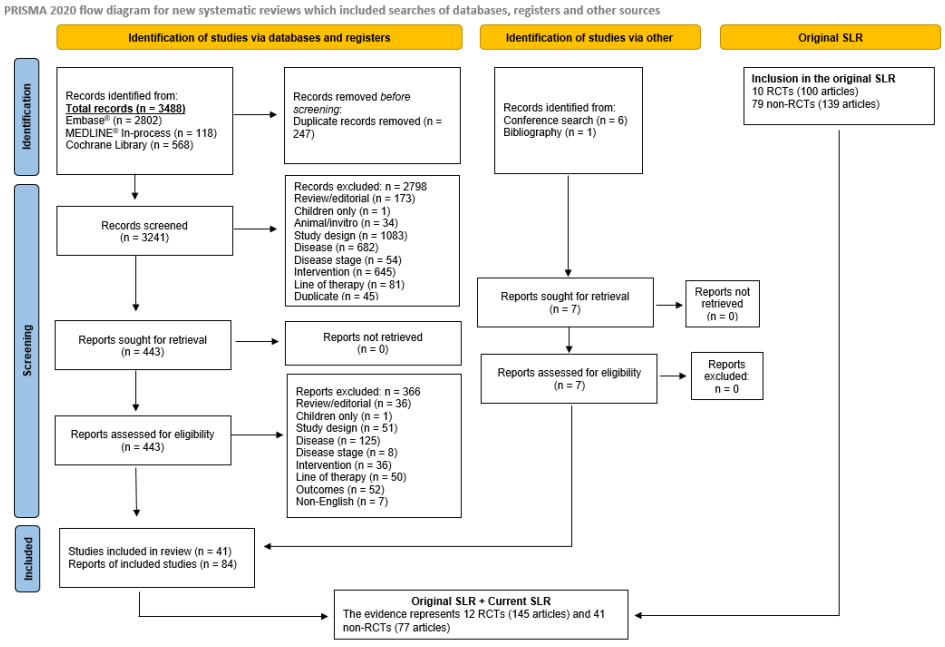


Table 92 RCT studies and associated publications identified in the February 2024 update

S. No.	Primary study (author and year)	Trial name	Linked publications	Included in the present application?
1	Shi 2024(66)	INSPIRE	Shi 2023	No
2	Yang 2023 (67)	NR	Zhang 2022	No
3	Camidge 2020 (68)	ALTA-1L	Campelo 2021, Popat 2021a, Ahn 2020, Cranmer 2020, Califano 2020, Campelo 2020, Camidge 2020b, Griesinger 2020a, Gupta 2020, Ng 2020 Popat 2020, Ahn 2019, Camidge 2019, Campelo 2019a, Campelo 2019b, Califano 2019a, Califano 2019b, Wong 2019, Yang 2019, Camidge 2018a, Camidge 2018b, Popat 2018, Popat 2016a, Beaumont 2024, Gupta 2022, Ahn 2022, Campelo 2023a, Camidge 2023a, Camidge 2023b, Camidge 2022, Campelo 2023b, Griesinger 2022, Tiseo 2022, Camidge 2021, Popat 2021b, Griesinger 2020b, Griesinger 2019, Popat 2022	Yes
4	Selvaggi 2020 (23)	eXalt3	Selvaggi 2021, Horn 2018a, Horn 2018b, Horn 2018c, Horn 2018d, Horn 2017a, Horn 2017b, Wu 2017, Horn 2021	No
5	Shaw 2020 (32)	CROWN	Mazieres 2021, Soo 2021, Solomon 2020, Shaw 2018, Shaw 2017, Mazieres 2022, Solomon 2022a, Solomon 2023(33), Bauer 2023, Bearz 2022a, Solomon 2022b, Solomon 2022c, Soo 2023, Bearz 2024, Lu 2023, Qing 2022, Felip 2022, Liu 2022, Zhou 2021, Solomon 2021, Bearz 2021, Bearz 2022b, Zhou 2023, Liu 2023	Yes
6	Camidge 2019 (36)	ALEX	Mok 2021, Hoffknecht 2020, Mok 2020, Peters 2020, Perol 2019, Dziadziuszko 2019, Mok 2019, Thomas 2019a, Camidge 2018, Dziadziuszko 2018, Gadgeel 2018, Hsu 2018, Kim 2018, Mok 2017a, Mok 2017b, Mok 2017c, Perol 2018, Peters 2017, Shaw 2017, Wong 2019, Dziadziuszko 2022, Noé 2022	Yes
7	Cho 2019 (69)	ASCEND-8	Cho 2021, Cho 2020, Liang 2019, Cho 2018, Cho 2017a, Cho 2017b, Dziadziuszko 2017, Cho 2023	No

8	Zhou 2019 (46)	ALESIA	Zhou 2018a, Zhou 2018b, Zhou 2022	No
9	Solomon 2018 (70)	PROFILE -1014	Wilner 2019, Chan 2018, Li 2018, Nishio 2018, Mok 2017, Thorne-Nuzzo 2017, Solomon 2016, Felip 2015, Solomon 2015, Mok 2014, Nakagawa 2014, Solomon 2014	Yes
10	Wu 2018 (71)	PROFILE -1029	Lu 2017, Zhou 2017, Lu 2016	No
11	Hida 2017 (72)	J-ALEX	Yoshioka 2021, Nakagawa 2020, Seto 2019, Nishio 2018, Kim 2017, Takiguchi 2017, Nokihara 2016, Hotta 2022	No
12	Soria 2017 (73)	ASCEND -4	Lau 2019, Tan 2019, Chan 2018, Li 2018, Author 2017, Castro 2017, Tan 2017, Tan 2021	No

Table 93 Non-RCT studies and associated publications identified in the February 2024 update

S. No.	Primary study (author and year)	Linked studies	Included in the present application?
1	Jeon 2024 (74)	Jeon 2023	No
2	Bratova 2023 (75)	Not linked	No
3	Katgi 2023 (76)	Not linked	No
4	Li 2023 (77)	Not linked	No
5	Madrigal 2023 (78)	Not linked	No
6	Moharana 2023 (79)	Not linked	No
7	Montella 2023 (80)	Not linked	No
8	Poh 2023 (81)	Not linked	No
9	Preeshagul 2023 (82)	Not linked	No
10	Provencio-Pulla 2023 (83)	Not linked	No
11	Schmid 2023 (84)	Schmid 2021, Chotai 2021	No
12	Siringo 2023 (85)	Not linked	No
13	Su 2023 (86)	Not linked	No

14	Swalduz 2023 (87)	Not linked	No
15	Wang 2023 (88)	Not linked	No
16	Yoshida 2023 (J-ALTA) (89)	Nishio 2021, Hida 2021, Murakami 2019, Kondo 2021, Correction to Yoshida 2023, Sugawara 2022, Zhang 2022, Camidge 2023	No
17	Chen 2022 (90)	Not linked	No
18	Chow 2022 (ASCEND-7) (91)	Not linked	No
19	Hizal 2022 (92)	Hizal 2023	No
20	Ma 2022 (93)	Ma 2020	No
21	Ma 2022 (94)	Not linked	No
22	Shi 2022 (95)	Not linked	No
23	Tilkema-Tiebosch 2022 (96)	Not linked	No
24	Zou 2022 (97)	Not linked	No
25	Zou 2022 (98)	Zou 2021	No
26	Krebs 2021 (99)	Not linked	No
27	Li 2021 (100)	Not linked	No
28	Pan 2021 (101)	Not linked	No
29	Takeda 2021 (102)	Not linked	No
30	Yang 2021 (103)	Not linked	No
31	Yin 2021 (104)	Not linked	No
32	Jahanzeb 2020 (105)	Jahanzeb 2018	No
33	Koopman 2020 (106)	Not linked	No
34	Gadgeel 2019 (107)	Peled 2021, Mok 2017	No
35	Huang 2019a (108)	Not linked	No
36	Krebs 2019 (109)	Not linked	No

37	Masuda 2019 (110)	Ohe 2018	No
38	Solomon 2018 (70)	Solomon 2017a, Solomon 2017b, Felip 2019, Peters 2020, Sun 2021	No
39	Wakelee 2018 (111)	Not linked	No
40	Ito 2017 (112)	Not linked	No
41	Kim 2016 (113)	Tan 2017, Author 2016, Felip 2016, Mehra 2016, Tan 2016, Kim 2014a, Kim 2014b, Shaw 2014a, Shaw 2014b, Tan 2014, Thomas 2014, Shaw 2013, Tan 2022	No

The 12 RCT's that were identified in the previous versions of the SLR were reviewed for relevance of inclusion in the NMA presented in the present application. The CROWN study, the ALEX study and the ALTA-1 study were considered relevant and included in the present application. Eight publications on the trials were included in the NMA (Seven publications identified in the previous updates and one identified in the October 2024 update). In addition to the studies identified as being relevant to include in the NMA, Solomon et al. 2018 (70) identified in the previous updates were identified as being relevant for inclusion in the health economic model.

The publications on the RCT's included in the NMA are presented in Table 94.

Table 94 RCTs and publications included in the NMA

RCT	Publications included in the NMA from the February 2024 update
ALEX	Mok 2020 (16) and Peter 2017 (47)
ALTA-1L	Camidge 2021 (19) and Camidge 2018 (38)
CROWN	Solomon 2024 (17), Solomon 2023 (33) and Shaw 2020 (33)

Table 95 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
ALEX	To evaluate the efficacy and safety of alectinib	Randomized, active controlled, multicenter	Treatment-naive ALK-positive advanced	Crizotinib: 151	From clinicaltrials.gov:	From clinicaltrials.gov:

	compared with crizotinib treatment in participants with treatment-naive anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer (NSCLC)	phase III open-label study	NSCLC patients	Alectinib 600mg: 152	Progression-Free Survival (PFS) by Investigator Assessment (assessed every 8 weeks up to 33 months) Percentage of Participants With PFS Event by Investigator Assessment (assessed every 8 weeks up to 33 months)	PFS Independent Review Committee (IRC)-Assessed (assessed every 8 weeks up to 33 months)
ALTA-1L	To compare the efficacy of brigatinib to that of crizotinib	Phase III, randomized, open-label, comparative, multicenter, international study	ALK-positive locally advanced or metastatic NSCLC patients naive to ALK inhibitors	Brigatinib: 137 Crizotinib: 138	From clinicaltrials.gov: Progression-free Survival (PFS). Up to end of study (Up to 56 months)	From clinicaltrials.gov: Confirmed Objective Response Rate (ORR). Baseline up to end of treatment (Up to 36 months)
CROWN	To demonstrate whether lorlatinib given as monotherapy is superior to crizotinib alone in prolonging the progression-free survival	Phase III, randomized, open-label study	Advanced ALK-positive NSCLC patients who are treatment naïve	Lorlatinib: 149 Crizotinib: 147	Progression-Free Survival (PFS) Based on Blinded Independent Central Review (BICR) Assessment. From time of Study Start up to 33 months	Overall Survival (OS). From time of Study Start up to 33 months

H.1.2.2 Results from the October 2024 update

68 hits were identified in PubMed and 349 were identified in Embase i.e., a total of 417 hits. After removing duplicates, 379 were title/abstract screened by two reviewers and 354 were excluded in the first step. 25 hits were full text screened by two reviewers and 2 publications were included. The selection process is illustrated in

Figure 94 and an overview of excluded references is presented in Table 97. The publications included in the systematic search from October 2024 are presented in Table 96.

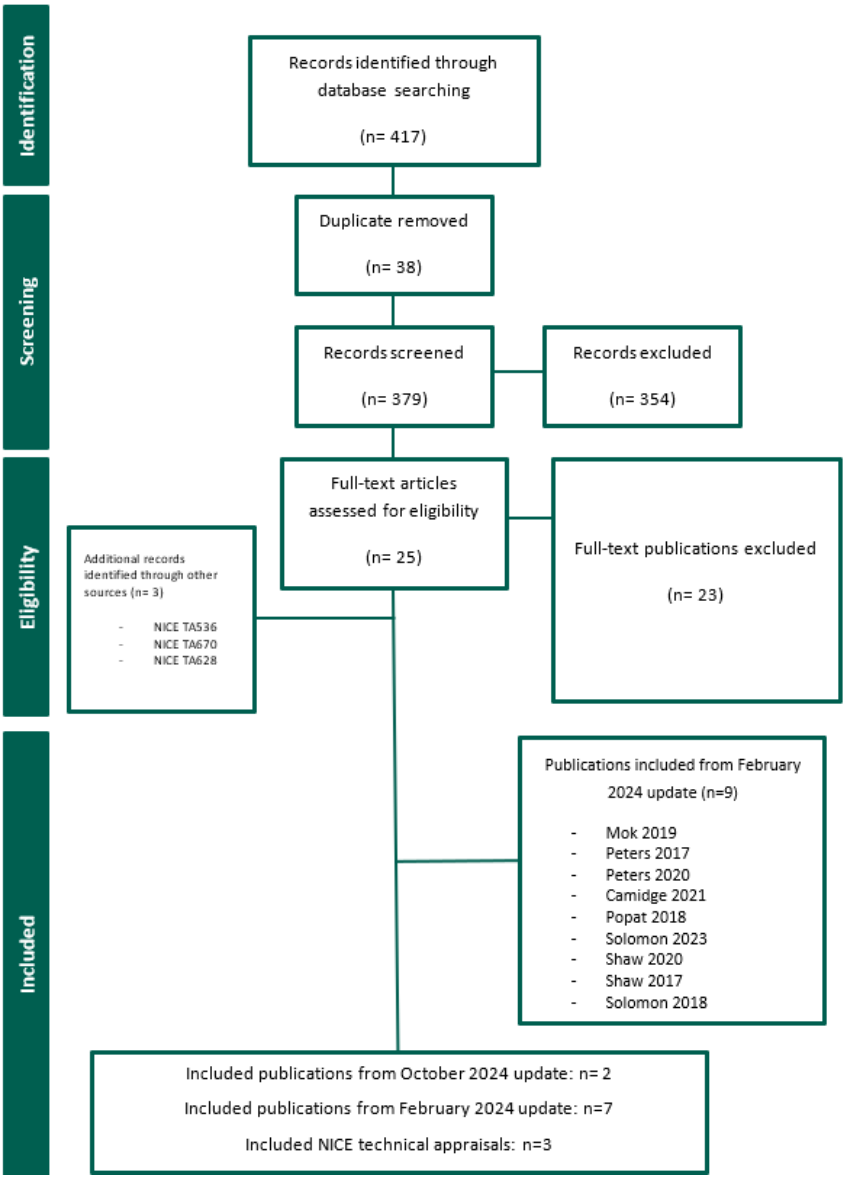
Table 96 Publications included from the systematic search identified in the October 2024 update

Reference	Linked trial	Reason for including
Garcia et al. 2024 (114)	CROWN, ALTA-1L and ALEX	Indirect treatment comparison of all relevant interventions in the relevant population (not applied in the base case)
Solomon et al. 2024 (17)	CROWN	Update on the CROWN study

In addition to the systematic search, the webpage of NICE was searched for technical appraisals relevant for the assessment. From the webpage, TA670 (6) (brigatinib for ALK-positive advanced NSCLC), TA536 (44) (alectinib for untreated ALK-positive advanced non-small-cell lung cancer) and TA628 (115) (lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer) were identified and included in the assessment. From TA628(115), the study by Ou et al. 2014 (43) were identified and used in the present application (only in scenario analysis). The other appraisals were used to identify inputs for the health economic model.

In the search for conference material, two materials were identified. One was already identified in the systematic search (Solomon et al. 2024 (17)) and the other was an update on a trial not included in the present application. Thus, no materials from this search were included.

Figure 94 PRISMA flow diagram from October 2024



H.1.3 Excluded full text references in the update from October 2024

A list of the references excluded after full-text screening from the October 2024 update is presented in Table 97.

Table 97 Excluded full text references and reason for exclusion (October 2024 update)

Reference	Reason for exclusion
Abrahami et al. 2024	Not an RCT
Arnaoutakis et al. 2024	Wrong population (not first-line)

Bauman et al. 2024	Not an RCT
Biber et al. 2024	Wrong population. Includes patients who have been prescribed ALK-inhibitors at any point in therapy. No control for previous treatments.
Bria et al. 2024	Wrong population. Investigating post-alectinib treatments
Cheung et al. 2024	Wrong population. Patients received prior treatments.
Decroisette et al. 2024	Not an RCT
Gulturk et al. 2024	Wrong population (not first-line)
John et al. 2024	Not an RCT
Kilickap et al. 2024	Not an RCT
Lucas et al. 2024	Not an RCT
Mastrantoni et al. 2024	Irrelevant comparator and populations
Mezquita et al. 2024	Not ALK-postive specific
Nduaguba et al. 2024	Wrong population
Nie et al. 2024	Not an RCT
Ou et al. 2024	NMA with interventions and populations not relevant
Priantti et al. 2024	Wrong population. Mixed ALK+ and ROS1+. 84% of patients received lorlatinib as second or later line. 82% were expsoed to one or more ALK TKIs previously.
Qi et al. 2024	Wrong outcome (thrombosis)
Reale et al. 2024	Not an RCT
Schoenmaekers et al. 2024	Does not distinguish between patients with ROS1 and ALK mutations
Solomon et al. 2024	Plain language summary of Solomon et al. 2024 and thus excluded

Tanvetyanon et al. 2024	Wrong outcome and wrong population
Vita et al. 2024	Wrong outcome

H.1.4 Quality assessment

A quality assessment of the RCTs identified in the update from February 2024 was performed using the NICE recommended risk of bias checklist and presented in Table 102.

Table 98 Quality assessment using checklist from NICE

Questions	ALEX	ALTA-1L	CROWN
1. Was randomisation carried out appropriately?	Yes	Yes	Yes
2. Was the concealment of treatment allocation adequate?	Yes	No	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No	No
5. Were there any unexpected imbalances in drop-outs between groups?	No	No	No
6. Is there any evidence to suggest that the authors measured more outcomes than they report ed?	Yes	No	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	Yes	Yes

H.1.5 Unpublished data

No unpublished data was used in the clinical assessment of this application. Further OS data for lorlatinib in 1st line patients was gathered from the study 1001 EXP1(40), which

was only used in the health economic analysis. The results of study 1001 EXP1 is expected to be published soon after the submission of this application.

H.1.5.1 List of ongoing studies on lorlatinib

Table 99 presents the ongoing studies on lorlatinib identified on the webpage of clinicaltrials.gov. The studies were identified with the following search terms:

- Non-small Cell Lung Cancer AND Lorlatinib OR PF-06463922
- Filters: Not yet recruiting, Recruiting, Active, not recruiting

Table 99 Ongoing studies on lorlatinib

Ongoing studies on clinicaltrials.gov
NCT Number, Study Title, Study URL, Study Status, Conditions, Interventions, Sponsor, Collaborators, Study Type
NCT Number,Study Title,Study URL,Study Status,Conditions,Interventions,Sponsor,Study Type
NCT06487078, Analysis of the Effectiveness and Safety of Lorlatinib in Untreated ALK-Positive NSCLC Patients in a French Real-World Context, https://clinicaltrials.gov/study/NCT06487078,NOT_YET_RECRUITING,ALK+ Non-Small-Cell Lung Carcinoma,DRUG: Lorlatinib,Pfizer,OBSERVATIONAL
NCT03909971, A Study of Lorlatinib in ALK Inhibitor-Treated ALK-Positive NSCLC in China, https://clinicaltrials.gov/study/NCT03909971,ACTIVE_NOT_RECRUITING,"Carcinoma, Non-Small-Cell Lung",DRUG: Lorlatinib,Pfizer,INTERVENTIONAL
NCT05144997, Lorlatinib Continuation Study, https://clinicaltrials.gov/study/NCT05144997,ACTIVE_NOT_RECRUITING,Non-Small-Cell Lung Cancer|NSCLC,DRUG: Lorlatinib,Pfizer,INTERVENTIONAL
NCT04127110, Activity of Lorlatinib Based on ALK Resistance Mutations Detected on Blood in ALK Positive NSCLC Patients, https://clinicaltrials.gov/study/NCT04127110,ACTIVE_NOT_RECRUITING,Non Small Cell Lung Cancer,DRUG: Lorlatinib,European Organisation for Research and Treatment of Cancer - EORTC,INTERVENTIONAL
NCT06092086, Lorlatinib as the First-line Treatment in China Advanced ALK+ NSCLC, https://clinicaltrials.gov/study/NCT06092086,RECRUITING,ALK Positive Non-small Cell Lung Cancer,DRUG: Loratinib,Guangdong Association of Clinical Trials,INTERVENTIONAL
NCT03052608, A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC, https://clinicaltrials.gov/study/NCT03052608,ACTIVE_NOT_RECRUITING,"Carcinoma, Non-Small-Cell Lung",DRUG: Lorlatinib|DRUG: Crizotinib,Pfizer,INTERVENTIONAL

NCT06282874, Lorlatinib in Patients With ALK-Positive NSCLC With Brain or Leptomeningeal Metastases, https://clinicaltrials.gov/study/NCT06282874,NOT_YET_RECRUITING,"Carcinoma, Non-Small-Cell Lung|Brain Metastases|Leptomeningeal Metastasis",DRUG: Lorlatinib,Guangdong Association of Clinical Trials,INTERVENTIONAL

NCT06361589, Real World Study of Lolatinib for Advanced ALK+ NSCLC Patients, https://clinicaltrials.gov/study/NCT06361589,RECRUITING,ALK-positive Non-small Cell Lung Cancer|Real World Study,DRUG: Lorlatinib,Sichuan Cancer Hospital and Research Institute,OBSERVATIONAL

NCT06234579, Longitudinal Assessment of Genomic Alterations and Clonal Evolution in ALK-positive NSCLC (Galileo Project), https://clinicaltrials.gov/study/NCT06234579,RECRUITING,ALK Gene Mutation|NSCLC Stage IV|ALK Sensitizing Mutation,DIAGNOSTIC_TEST: Biopsy (tissue or liquid),Fondazione Policlinico Universitario Agostino Gemelli IRCCS,OBSERVATIONAL

NCT04111705, Lorlatinib After Failure of First-line Second-generation ALK Kinase Inhibitor in Patients With Advanced ALK-positive Non-small Cell Lung Cancer, https://clinicaltrials.gov/study/NCT04111705,ACTIVE_NOT_RECRUITING,Non Small Cell Lung Cancer Metastatic,DRUG: Lorlatinib,Intergroupe Francophone de Cancerologie Thoracique,INTERVENTIONAL

NCT04362072, Study of Lorlatinib In People With ALK-positive Non-small Cell Lung Cancer, https://clinicaltrials.gov/study/NCT04362072,ACTIVE_NOT_RECRUITING,Carcinoma|Non-Small-Cell Lung,DRUG: Lorlatinib,Pfizer,INTERVENTIONAL

NCT06378892, A Study to Evaluate the Combination of Platinum-pemetrexed Based Chemotherapy Plus Lorlatinib in ALK Positive Non-Small Cell Lung Cancer (NSCLC) With Exclusively Extracranial Disease Progression on Lorlatinib, https://clinicaltrials.gov/study/NCT06378892,RECRUITING,Non Small Cell Lung Cancer Metastatic|ALK Gene Mutation,DRUG: Lorlatinib,Centro di Riferimento Oncologico - Aviano,INTERVENTIONAL

NCT06410040, A Retrospective Study of the Efficacy and Safety of Lolatinib in ALK+ NSCLC Patients With Brain or Meningeal Metastasis, https://clinicaltrials.gov/study/NCT06410040,ACTIVE_NOT_RECRUITING,ALK-positive Non-small Cell Lung Cancer|Brain Metastases|Meningeal Metastasis,DRUG: Lorlatinib,Sichuan Cancer Hospital and Research Institute,OBSERVATIONAL

NCT06586801, The Patient-Reported Outcomes in ALK Positive Advanced NSCLC in China, https://clinicaltrials.gov/study/NCT06586801,NOT_YET_RECRUITING,Non-small Cell Lung Cancer,OTHER: Patient-reported outcome,Shanghai East Hospital,OBSERVATIONAL

NCT03737994, Targeted Treatment for ALK Positive Patients Who Have Previously Been Treated for Non-squamous Non-small Cell Lung Cancer, https://clinicaltrials.gov/study/NCT03737994,ACTIVE_NOT_RECRUITING,Lung Non-Squamous

Non-Small Cell Carcinoma|Stage IV Lung Cancer AJCC v8|Stage IVA Lung Cancer AJCC v8|Stage IVB Lung Cancer AJCC v8,DRUG: Alectinib|DRUG: Brigatinib|DRUG: Carboplatin|DRUG: Ceritinib|DRUG: Cisplatin|DRUG: Crizotinib|DRUG: Ensartinib|DRUG: Lorlatinib|DRUG: Pemetrexed,National Cancer Institute (NCI),INTERVENTIONAL

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

A search for HRQoL literature was conducted in the present application. As for the literature search for the efficacy and safety assessment in Appendix H, the HRQoL search was based on an existing SLR that was updated to October 2024. The original SLR on HRQoL was from August 2018 and conducted to identify any published literature on relevant utility evidence for patients with ALK-positive advanced NSCLC in the second-line setting. This SLR was then updated on 22 November 2019 to identify any published literature that could be used to generate utilities for patients with untreated ALK-positive advanced NSCLC i.e., in the first-line setting. To adhere with DMC guidelines, we have updated the search from 22 November 2019 to 07 October 2024. The original search was conducted in the following electronic databases:

- Embase® and MEDLINE® (using Embase.com)
- MEDLINE® In-Process (using PubMed.com)
- EconLit® (using Ebsco.com)
- The Centre for Reviews and Dissemination (CRD) York, including the following:
    - Health Technology Assessment Database (HTAD)
    - NHS Economic Evaluation Database (NHS EED)

In the update from October 2024, the search was updated in MEDLINE (via PubMed.com) using the PubMed.com search string from the November 2019 update. In addition to PubMed, the search on the website of NICE was also done with the purpose of identifying relevant appraisals with studies that could be used for utilities in our health economic analysis. In addition, the conference material was also searched using the same strategy as presented in Table 85.

Table 100 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Medline	PubMed	22 November 2019 to 07 October 2024	07 October 2024

Table 101 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Same as mentioned in Appendix G.	11 October 2024

I.1.1 Search strategies

The inclusion and exclusion criteria applied in the HRQoL search are presented in Table 102. Title and abstract screening, full-text screening and data extraction were conducted according to the methods reported for the literature search in Appendix H.1.

Section I.1.1.1 presents the findings from the first search in November 2019 and section I.1.1.2 presents the update from October 2024. All titles and abstracts were reviewed for information that clearly met the inclusion and exclusion criteria stated in Table 102.

Table 102 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes made for the October 2024 update
Population	• Adult patients with advanced/metastatic ALK-positive NSCLC • Treatment naïve (first-line setting)	Other populations	None
Interventions	No specific inclusion criteria	NA	None
Comparators	No specific inclusion criteria	NA	None
Outcomes	• Studies reporting utility values (SF-6D, EQ-5D, HUI, TTO, etc.) • Studies reporting mapped utilities values • Studies reporting elicited utilities from general population	Other studies	None
Study type	• RCTs, nRCTs, and observational studies reporting utility data (as mapped values and/or directly elicited utilities from general population) • Economic evaluations (including HTAs) reporting utility values	Other study types	None
Time limit	No restriction	NA	None

Abbreviations: ALK-positive NSCLC: anaplastic lymphoma kinase positive non-small cell lung cancer; EQ-5D, EuroQol-5 dimension; HTA, health technology assessment; HUI, Health Utilities Index; nRCT, non-randomised controlled trial; RCT, randomised controlled trial; SF-6D, Short-Form 6-D; TTO, time trade-off.

I.1.1.1 First update (22 November 2019)

Table 103 Search strategy for MEDLINE in-process (via PubMed.com) from 2019 November

No.	Query	Results from November 2019
1	Carcinoma, Non-Small-Cell Lung[mh] OR nsclc[tiab]	61,966
2	Neoplasms[mh] OR Carcinoma, Squamous Cell[mh] OR Adenocarcinoma[mh]	3,239,575
3	Lung[mh]	267,376
4	#2 AND #3	31,178
5	(lung[tiab] OR pulmon*[tiab] OR bronchial[tiab]) AND (cancer* [tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	304,081
6	#4 OR #5	317,524
7	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	62,445
8	#6 AND #7	62,210
9	#1 OR #8	73,153
10	(utility[Title/Abstract] OR utilities[Title/Abstract]) NOT ("clinical utility"[Title/Abstract] OR "diagnostic utility"[Title/Abstract])	165,966
11	disutility[Title/Abstract] OR disutilities[Title/Abstract] OR "sf 6"[Title/Abstract] OR sf6[Title/Abstract] OR "short form 6"[Title/Abstract] OR "shortform 6"[Title/Abstract] OR "sf six"[Title/Abstract] OR sfsix[Title/Abstract] OR "shortform six"[Title/Abstract] OR "short form six"[Title/Abstract] OR euroqol[Title/Abstract] OR "euro qol"[Title/Abstract] OR "euroqol 5d"[Title/Abstract] OR "euroqol-5d"[Title/Abstract] OR "euroqol 5-d"[Title/Abstract] OR eq5d[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "health utilities index"[Title/Abstract] OR hui[Title/Abstract] OR hui1[Title/Abstract] OR hui2[Title/Abstract] OR "hui-2"[Title/Abstract] OR hui3[Title/Abstract] OR "hui-3"[Title/Abstract] OR "standard gamble"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "time tradeoff"[Title/Abstract] OR tto[Title/Abstract	15,577
12	standard[Title/Abstract] AND gamble[Title/Abstract]	878
13	Patient Preference[MeSH Terms]	7,707
14	"european quality of life 5 dimension"[Title/Abstract]	0
15	euro*[Title/Abstract] AND "quality of life"[Title/Abstract]	648

16	#10 OR #11 OR #12 OR #13 OR #14 OR #15	185,103
17	#9 AND #16	957
18	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	307,554
19	#17 AND #18	61

Table 104 Search strategy for EMBASE and MEDLINE (via Embase.com) from 2019 November

No.	Query	Results from November 2019
1	'non small cell lung cancer'/exp OR nsclc:ab,ti	158,304
2	'neoplasm'/exp OR 'squamous cell carcinoma'/exp OR 'adenocarcinoma'/exp	4,779,647
3	'lung'/exp	319,440
4	#2 AND #3	69,314
5	((lung OR pulmon* OR bronchial) NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ab,ti	317,864
6	#4 OR #5	359,457
7	'non small cell*':ab,ti OR 'non-small-cell*':ab,ti OR 'nonsmall cell*':ab,ti	98,139
8	#6 AND #7	97,239
9	#1 OR #8	161,178
10	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	4,782,124
11	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5,352,648
12	(review:it OR 'literature review':it) 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)	2,447,480
13	#10 OR #11 OR #12	12,298,310
14	('utility':ab,ti OR 'utilities':ab,ti) NOT ('clinical utilit*':ab,ti OR 'diagnos* utilit*':ab,ti) OR 'disutility':ab,ti OR 'disutilities':ab,ti OR 'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR	263,896

	sfsix:ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR 'euroqol 5d':ab,ti OR 'euroqol-5d':ab,ti OR 'euroqol 5-d':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR 'hui-2':ab,ti OR hui3:ab,ti OR 'hui-3':ab,ti OR 'standard gamble*':ab,ti OR ((standard NEXT/1 gamble*):ab,ti) OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti OR 'patient preference'/exp OR 'european quality of life 5 dimension'/exp OR ((euro* NEAR/4 'quality of life*'):ab,ti)	
15	#9 AND #14	5,540
16	#15 NOT #13	4,841

Table 105 Search strategy for EconLit® from 2019 November

S. No.	Query	Search Options	No. of Hits
S1	"non small cell lung cancer"	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	660,272
S2	TI NSCLC OR AB NSCLC	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	178,776
S3	lung AND (neoplasm OR "squamous cell carcinoma" OR adenocarcinoma)	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	2,666,212
S4	TI (lung OR pulmonary OR bronchial) N3 (cancer OR carcinoma OR neoplasm OR neoplasms OR tumour OR tumor OR squamous OR adenocarcinoma) OR AB (lung OR pulmonary OR bronchial) N3 (cancer OR carcinoma OR neoplasm OR neoplasms OR tumour OR tumor OR squamous OR adenocarcinoma)	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	1,259,115
S5	S3 OR S4	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	3,307,273

S6	TI ("non small cell" OR "non-small-cell" OR "nonsmall cell") OR AB ("non small cell" OR "nonsmall- cell" OR "nonsmall cell")	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	317,969
S7	S5 AND S6	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	315,926
S8	S1 OR S2 OR S7	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	718,573
S9	S8 Source - Econlit	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	123

Table 106 Search strategy for CRD York from 2019 November

S. No.	Query	No. of Hits
1	MeSH DESCRIPTOR Carcinoma, Non-Small-Cell Lung EXPLODE ALL TREES OR (non small cell lung cancer) OR nsclc	818
2	MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES	11,971
3	MeSH DESCRIPTOR Carcinoma, Squamous Cell EXPLODE ALL TREES	214
4	MeSH DESCRIPTOR Adenocarcinoma EXPLODE ALL TREES	872
5	#2 OR #3 OR #4	11,971
6	MeSH DESCRIPTOR Lung EXPLODE ALL TREES OR lung	2,877
7	#5 AND #6	1,346
8	(lung OR pulmon* OR bronch*) NEAR3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)	1,437
9	#7 OR #8	1,438
10	(non small cell) OR (non-small-cell) OR (nonsmall cell)	821
11	#9 AND #10	820

12	#1 OR #11	834
13	(#12) IN NHSEED	334
14	(#12) IN HTA	354

In the update from November 2019, the searches for HRQoL evidence identified a total of 5,713 potentially relevant titles or abstracts (from all the databases searched) but 276 records were removed as duplicates. The remaining 5,437 records were screened based on the information reported in their titles and/or abstracts. Of these, 3,917 were excluded at the primary screening stage as they were not relevant to the research question. A total of 1,520 articles were assessed in full for further evaluation. Of these, 1,507 were excluded, and 13 were included. Additionally, six records from the HTA search and nine records from the bibliography search were included, hereunder NICE TA536, which was applied in the present application. Due to the publication of multiple articles for the same study, 17 unique studies were extracted from the 28 included publications. Across these 17 studies, 13 studies were economic modelling studies reporting utility data and were extracted in the original SLR. Figure 95 shows the PRIMA flow diagram from the existing SLR. Only NICE TA536 from the November 2019 update was applied in the health economic analysis in the present application.

Figure 95 PRISMA flow diagram from November 2019 update.

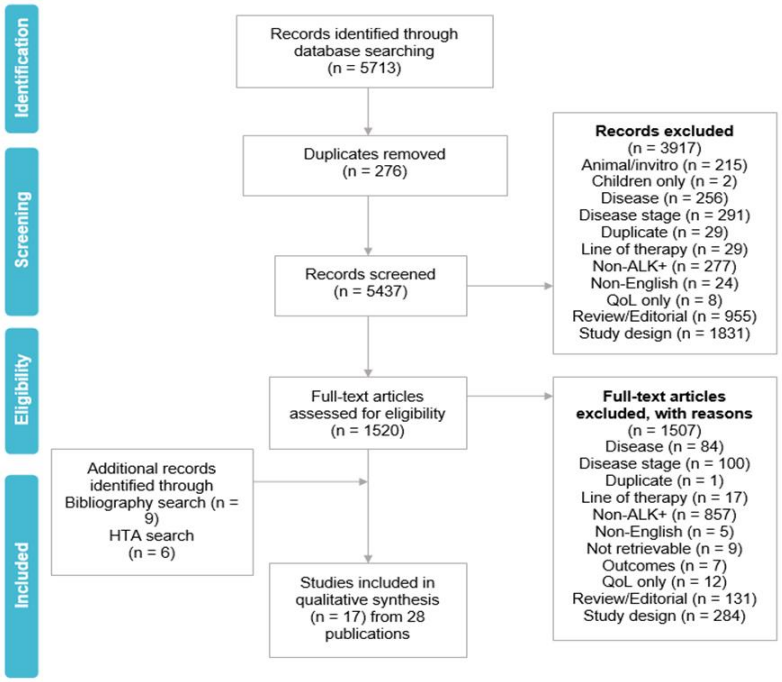


Table 107 Summary of utility results from HRQoL studies identified from the November 2019 update

Study name (Country)	Summary of model		Summary of results	Included in the present application?
	Study type Sample size	Method of Elicitation, Valuation	Utility	
Djalalov 2014 (Canada)	Economic modelling study NR	NR NR	Treatment: value (range) CZT: 0.56 (0.45–0.68) Platinum doublet (CIS and GEM) during treatment: 0.53 (0.42–0.64) Platinum doublet (CIS and GEM) after treatment: 0.61 (0.49–0.74) PEM during treatment: 0.45 (0.36–0.54) PEM after treatment: 0.57 (0.45–0.68) ERL: 0.47 (0.38–0.57) BSC: 0.47 (0.37–0.56)	No
Solomon 2014 (Australia, Belgium, Brazil, Canada, China, Finland, France, Germany, Hong Kong, Ireland, Italy, Japan, Republic of Korea, Luxembourg, Mexico, Netherlands, Norway, Portugal, Russian Federation, Singapore, South Africa, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, US)	Clinical study 343	EQ-5D NR	EQ-5D index scores: mean (SD) At baseline CZT: 0.72 (0.30) Chemo: 0.71 (0.26) On treatment: CZT: 0.81 Chemo: 0.72; p<0.001	No

Lu 2016 (China)	Economic modelling study NR	NR NR	Health state: value (range) PFS: 0.65 (0.26–0.87) PS: 0.47 (0.19–0.58) PFS*: 0.804 OS*: 0.321 Disutility caused by SAEs Febrile neutropenia: -0.42 Neutropenia: - 0.2 Fatigue: -0.07 Diarrhoea: -0.07 Bleeding: -0.19 Nausea and vomiting: -0.12 Rash: -0.1 Hair loss: -0.06 Hypertension: -0.04 *Data extracted from Lu et al., 2018	No
NICE [TA406] 2016 (UK)	HTA 343	EQ-5D TTO	MS Utility values for cost-effectiveness analysis: Utility values for pre-progression PEM patients once off treatment: 0.72 Disutility due to AEs: Elevated transaminases: 0.00 Neutropenia: -0.09 Anaemia: -0.07 Leukopenia: -0.09 Thrombocytopenia: -0.09 Estimated total disutility from the AE profiles: CZT: -0.01 PEM + CIS/CARB: -0.03 ERG	No

			Post progression utility: 0.66 Utility values for pre-progression PEM patients once off treatment ERG analysis informing preferred ICER: 0.81	
SMC [CZT] 2016 (Scotland)	HTA 343	EQ-5D NR	Health state: value PFS for CZT: 0.81 PFS for PEM + CIS or CARB: 0.72 PD for receiving DOC: 0.66 PD for receiving BSC: 0.47	No
Cabrera 2017 (Spain)	Economic modelling study NR	NR NR	First-line of therapy: 0.63	No
Soria 2017 (Australia, New Zealand, Austria, Brazil, China, Colombia, Denmark, France, Germany, Greece, India, Ireland, Italy, Japan, South Korea, Lebanon, Mexico, Netherlands, Norway, Portugal, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, and UK)	Clinical study 376	EQ-5D TTO	EQ-5D score for treatment utility: mean (95% CI) CER: 0.81 (0.78, 0.84) Chemo: 0.77 (0.73, 0.80); p<0.001 Change in overall health status measured using the EQ-5D-5L: mean (95% CI) CER vs Chemo: 0.04 (0.02, 0.07); p=0.0006	No
CADTH [ALC] 2018 (Canada) (116)	HTA 303	NR NR	Progression health state: value ALC: 0.72 CZT: 0.72	No
Carlson 2018 (US)	Economic modelling study	EQ-5D (Specifically EQ-5D-3L)	Health state: value (range) PFS: 0.81 (0.79 - 0.84)	No

	NR	NR	Progression, treated 0.72 (0.70 - 0.75) Progression, BSC: 0.47 (0.38 - 0.57)	
NICE [TA500] 2018 (UK)	HTA NR	EQ-5D TTO	MS Health state utilities: Value (SE) CER PFS (SD or OR): 0.81 (0.015) PD: 0.64 (0.024) CZT PFS (SD or OR): 0.81 PD: 0.64 (0.024) Company corrected base case Mean first-line PD: 0.67	No
NICE [TA536] 2018 (UK)	HTA 303	EQ-5D-3L TTO	Company's updated analysis PFS: 0.814 PD (no CNS progression): 0.725 PD (with CNS progression): 0.520 ERG PFS: 0.814 PD (no CNS progression): 0.725 PD (with CNS progression): 0.520	Yes
SMC [ALC] 2018 (Scotland)	HTA 303	EQ-5D NR	Health state: value PFS: 0.814 PD (no CNS progression): 0.725 PD (with CNS progression): 0.52	No

Soares 2018 (Portugal)	Economic modelling study NR	NR NR	Health state: value (variance) PFS (TKI): 0.814 (0.012) PPS in BSC: 0.470 (0.101)	No
Zhou 2018 (US)	Economic modelling study NR	EQ-5D NR	Health state: value PD: 0.64	No
Liu 2019 (China)	Economic modelling study NR	NR NR	Health state: value (range) PFS: 0.805 (0.644 – 0.966) PS: 0.715 (0.686 – 0.744)	No
Peng 2019 (China)	Economic modelling study NR	NR NR	Health state: value (range) PFS: 0.71 (0.50 – 0.92) PS: 0.67 (0.47 - 0.87)	No
Stefani 2019 (Brazil)	Economic modelling study NR	EQ-5D NR	Health state: value PFS: 0.814 PP non-TKI: 0.660 PP BSC: 0.470	No

Abbreviations: ALC: alectinib; BSC: best supportive care; CARB: carboplatin; CER: ceritinib; Chemo: Chemo; CI: confidence interval; CIS: cisplatin; CZT: crizotinib; DOC: docetaxel; ERG: evidence review group; ERL: erlotinib; EQ-5D: EuroQol 5 dimensions; EQ-5D-3L: EuroQol 5 dimensions 3-level version; EQ-5D-5L: EuroQol 5 dimensions 5-level version; GEM: gemcitabine; HTA: health technology assessment; NR: not reported; PD: progressive disease; PEM: pemetrexed; PFS: progression-free survival; PP: post-progression; PS: progressed survival; SAEs: serious adverse events; SD: standard deviation; SE: standard error; TKI: tyrosine kinase inhibitor; US: United-states.

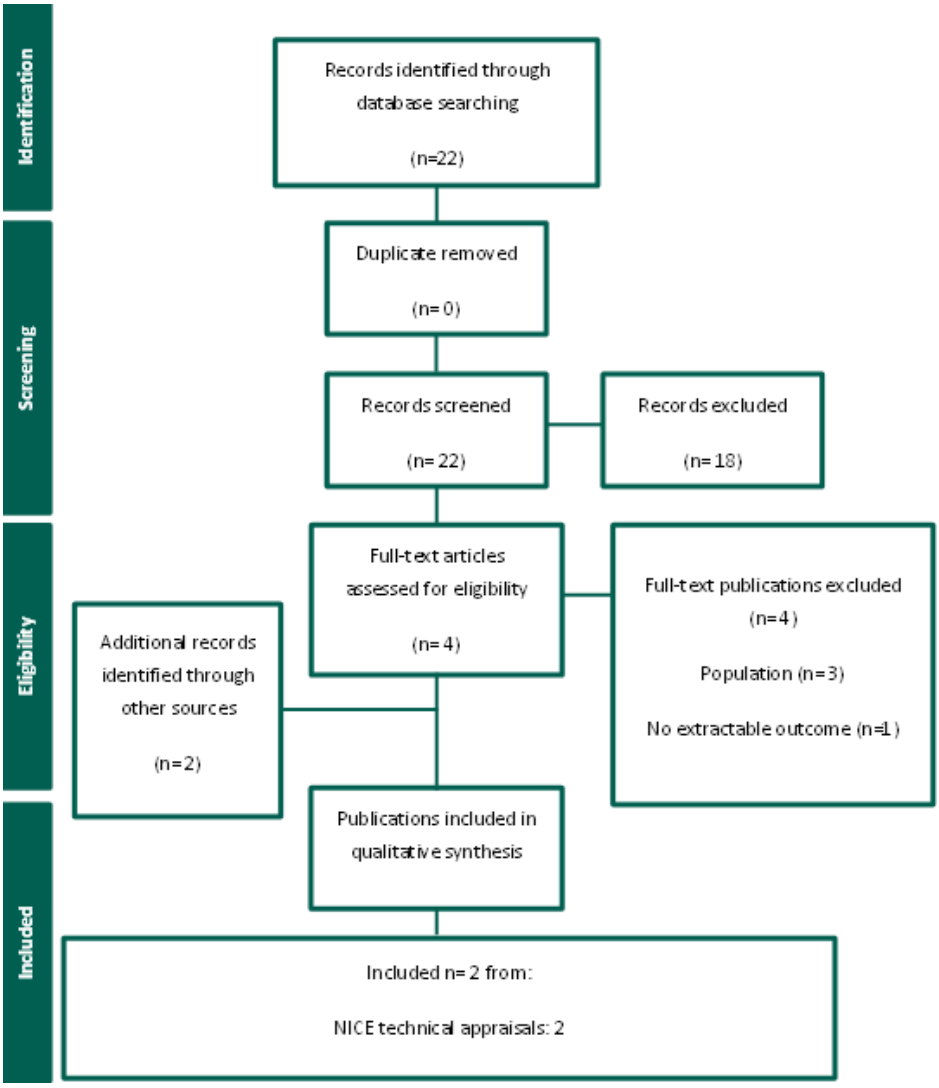
I.1.1.2 Second update (07 October 2024)

Table 108 Search strategy for MEDLINE (via PubMed.com)

No.	Query	Results from October 2024
#1	Carcinoma, Non-Small-Cell Lung[mh] OR nsclc[tiab]	96,918
#2	Neoplasms[mh] OR Carcinoma, Squamous Cell[mh] OR Adenocarcinoma[mh]	3,878,688
#3	Lung[mh]	314,262
#4	#2 AND #3	38,096
#5	(lung[tiab] OR pulmon*[tiab] OR bronchial[tiab]) AND (cancer* [tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	422,967
#6	#4 OR #5	437,567
#7	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	97,155
#8	#6 AND #7	96,875
#9	#1 OR #8	112,322
#10	(utility[Title/Abstract] OR utilities[Title/Abstract]) NOT ("clinical utility"[Title/Abstract] OR "diagnostic utility"[Title/Abstract])	246,651
#11	disutility[Title/Abstract] OR disutilities[Title/Abstract] OR "sf 6"[Title/Abstract] OR sf6[Title/Abstract] OR "short form 6"[Title/Abstract] OR "shortform 6"[Title/Abstract] OR "sf six"[Title/Abstract] OR sfsix[Title/Abstract] OR "shortform six"[Title/Abstract] OR "short form six"[Title/Abstract] OR euroqol[Title/Abstract] OR "euro qol"[Title/Abstract] OR "euroqol 5d"[Title/Abstract] OR "euroqol-5d"[Title/Abstract] OR "euroqol 5-d"[Title/Abstract] OR eq5d[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "health utilities index"[Title/Abstract] OR hui[Title/Abstract] OR hui1[Title/Abstract] OR hui2[Title/Abstract] OR "hui-2"[Title/Abstract] OR hui3[Title/Abstract] OR "hui-3"[Title/Abstract] OR "standard gamble"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "time tradeoff"[Title/Abstract] OR tto[Title/Abstract	26,660
#12	standard[Title/Abstract] AND gamble[Title/Abstract]	997
#13	Patient Preference[MeSH Terms]	11,344

#14	"european quality of life 5 dimension"[Title/Abstract]	92
#15	euro*[Title/Abstract] AND "quality of life"[Title/Abstract]	22,558
#16	#10 OR #11 OR #12 OR #13 OR #14 OR #15	291,760
#17	#9 AND #16	1,946
#18	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	343,897
#19	#17 AND #18	23
#20	#19 AND ("2019/11/22"[Date – Publication]: "3000"[Date - Publication])	22

Figure 96 PRISMA flow diagram from the October 2024 update



A PRISMA diagram illustrating the selection of studies in the update from 2019 and the update from October 2024 is presented in Figure 95 and Figure 96, respectively. 22 hits were identified in PubMed and title/abstract screened in the October 2024 update and 4 were full text screened (see Table 109). None of the full text screened hits were deemed relevant to include in our health economic analysis. In addition, none of the hits from the original SLR were included.

From the NICE website search, in addition to the TA670 appraisal of brigatinib for ALK-positive advanced NSCLC already identified, we identified the TA258 for erlotinib for 1st line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC. Both appraisals were scrutinized for relevant inputs to the health economic analysis and HRQOL evidence. Via the TA670 appraisal of brigatinib, Roughly et al. 2014 (42) was identified (also identified in TA536) and via the TA258 appraisal of erlotinib, Nafees et al. 2008 (117)was identified and both studies were included in the present application.

Table 109 Excluded hits after full text assessment (October 2024 update)

Reference	Reason for exclusion
Mangues-Bafalluy et al. 2024	Not ALK-positive specific and not first-line setting
Wang et al. 2022	Asian population
Mohamed et al. 2024	No HRQoL results for ALK-positive NSCLC reported
Zhang et al. 2024	Asian population

I.1.2 Quality assessment and generalizability of estimates

In the original SLR, quality check of utility studies was performed using the checklist from Papaioannou et al 2013(118). The modelling studies, reporting utility values adapted from other sources, were quality checked using the Drummond and Jefferson checklist. The checklists were completed for each study by a reviewer, followed by a quality check by a senior reviewer. Only the NICE TA536 was included from the original SLR, and the quality assessment of this reference is presented in Table 110.

Table 110 Quality assessment of utility evidence using Papaioannou checklist

No.	Question	NICE TA536
1	Was the research question stated?	Yes
2	Was the economic importance of the research question stated?	Yes

3	Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes
4	Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes
5	Were the alternatives being compared clearly described?	Yes
6	Was the form of economic evaluation stated?	Yes
7	Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes
8	Was/were the source(s) of effectiveness estimates used stated?	Yes
9	Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes
10	Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes
11	Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes
12	Were the methods used to value health states and other benefits stated?	Yes
13	Were the details of the subjects from whom valuations were obtained given?	Yes
14	Were productivity changes (if included) reported separately?	Yes
15	Was the relevance of productivity changes to the study question discussed?	Yes
16	Were quantities of resources reported separately from their unit cost?	Yes
17	Were the methods for the estimation of quantities and unit costs described?	Yes
18	Were currency and price data recorded?	Yes
19	Were details of price adjustments for inflation or currency conversion given?	Yes
20	Were details of any model used given?	Yes
21	Was there a justification for the choice of model used and the key parameters on which it was based?	Yes
22	Was the time horizon of cost and benefits stated?	Yes
23	Was the discount rate stated?	Yes

24	Was the choice of rate justified?	Yes
25	Was an explanation given if cost or benefits were not discounted?	NA
26	Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes
27	Was the approach to sensitivity analysis described?	Yes
28	Was the choice of variables for sensitivity analysis justified?	Yes
29	Were the ranges over which the parameters were varied stated?	Yes
30	Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the Inc. analysis?)	Yes
31	Was an Inc. analysis reported?	Yes
32	Were major outcomes presented in a disaggregated as well as aggregated form?	No
33	Was the answer to the study question given?	Yes
34	Did conclusions follow from the data reported?	Yes
35	Were conclusions accompanied by the appropriate caveats?	Yes
36	Were the generalisability issues addressed?	Yes

I.1.3 Unpublished data

No unpublished data was used for health-related quality-of-life inputs.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

To identify any published literature with input that could be relevant to use in the health economic analysis, we updated an existing SLR to the present application. As with the HRQoL SLR, the existing SLR on costs and resource use was originally conducted in August 2018 to identify any published literature on cost and healthcare resource use evidence for patients with ALK-positive advanced NSCLC in the second-line setting and then updated in November 2019 to identify any published literature on cost and healthcare resource use for patients with untreated ALK-positive advanced NSCLC (first-

line setting). The existing SLR searched the following databases: EMBASE, MEDLINE, MEDLINE In-Process, EconLit and CRD York. In the existing SLR, the search was restricted to citations published over a 10-year period. This restriction was applied to identify the most recent and relevant data inputs required for an economic model and due to the considerable changes observed for costs and resource use, inflation rates, advances in technology (drug therapy, diagnostics, etc.), quality/standard of care and overall standards of living.

In the present update, the search in MEDLINE via PubMed was updated from 2019 to October 2024 using the search string for PubMed.com from the existing SLR. Evidence identified within this review were supplemented by evidence available on the DMC's webpage such as the DMC catalogue with appropriate unit costs from a Danish perspective for the resource use applied in the health economic model and other Danish sources with unit costs relevant in a Danish setting.

J.1.1 Systematic search for costs and health care resource use

Table 111 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
MEDLINE	PubMed.com	November 2019 to October 2024	07 October 2024

J.1.2 Targeted literature search for costs and health care resource use

In addition to the systematic literature search, the search on the website of NICE also targeted inputs for the health economic analysis.

Table 112 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NICE	https://www.nice.org.uk/	None specified	07 October 2024

Abbreviations: National Institute of Health and care Excellence

The inclusion and exclusion criteria for the cost and resource use search are presented in Table 113. Title and abstract screening, and full text screening were done the same way as described in Appendix H.

Table 113 Inclusion and exclusion criteria for the cost and resource use search

PICOS	Inclusion criteria	Exclusion criteria	Adaptation for present application
Population	• Adult patients with advanced/metastatic ALK-positive NSCLC	None specified	None

	• Treatment naïve (first-line setting)		
Interventions	No specific inclusion criteria	None specified	None
Comparators	No specific inclusion criteria	None specified	None
Outcomes	• Studies reporting the resource utilisation and costs • Costs – direct and indirect (unit and total) • Resources – unit and total	None specified	Studies reporting resource use and costs related to treating adult patients with advanced/metastatic ALK-positive NSCLC were included. Studies on diagnostic procedures and similar resource use were excluded.
Study type	• Studies reporting costs and/or resource use • Economic evaluations (including HTAs) reporting costs or resource use • All studies (RCTs, nRCTs and observational) reporting resource utilisation and costs associated with ALK-positive NSCLC were included irrespective of the study design	None specified	None
Time limit	Studies published since 2007	None specified	None
Language	English language	None specified	None
Countries	No restriction	None specified	Danish studies were preferred or studies with health care systems similar to the Danish system. . Asian countries were excluded.

J.1.2.1 November 2019 update

The search strings from Embase and MEDLINE, MEDLINE In-Process, EconLit and CRD York are presented in Table 114, Table 115, Table 116 and Table 117, respectively.

Table 114 Search strategy for Embase® and MEDLINE® from 22 November 2019

S. No.	Search Term	No. of Hits
1	'non small cell lung cancer'/exp OR nsclc:ab,ti	158,304
2	'neoplasm'/exp OR 'squamous cell carcinoma'/exp OR 'adenocarcinoma'/exp	4,779,647
3	'lung'/exp	319,440
4	#2 AND #3	69,314
5	((lung OR pulmon* OR bronchial) NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ab,ti	317,864
6	#4 OR #5	359,457
7	'non small cell*':ab,ti OR 'non-small-cell*':ab,ti OR 'nonsmall cell*':ab,ti	98,139
8	#6 AND #7	97,239
9	#1 OR #8	161,178
10	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	4,782,124
11	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5,352,648
12	(review:it OR 'literature review':it) 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)	2,447,480
13	#10 OR #11 OR #12	12,298,310
14	'cost control'/exp OR 'health care cost'/exp OR 'drug cost'/exp OR 'hospital cost'/exp OR 'cost of illness'/exp OR 'health care utilization'/exp OR 'resource management'/exp OR 'resource allocation'/exp OR ((healthcare NEXT/1 cost*):ab,ti) OR ((unit NEXT/1 cost*):ab,ti) OR price*:ab,ti OR pricing:ab,ti OR ((resource* NEXT/2 allocat*):ab,ti) OR ((health*care NEXT/1 (utilisation OR utilization)):ab,ti) OR (('health care' NEXT/1 (utilisation OR utilization)):ab,ti) OR ((resource NEXT/1 (utilisation OR utilization OR use)):ab,ti) OR ((cost* NEAR/3 (treat* OR therap*)):ab,ti) OR (((total OR direct OR indirect OR medical OR drug OR administration OR laborat* OR diagnos* OR productivity OR illness) NEAR/2 cost):ab,ti) OR 'hospitalization cost'/exp OR 'length of stay'/exp OR 'budget'/exp OR economic:ab,ti OR cost:ab,ti OR 'cost'/mj OR ((low NEXT/1 costs):ab,ti) OR ((high NEXT/1 costs):ab,ti) OR ((cost NEXT/1 estimate*):ab,ti) OR ((cost NEXT/1 variable*):ab,ti) OR hospitalization:ab,ti OR hospitalisation:ab,ti OR 'hospital stay':ab,ti OR ((resource* NEXT/2 (allocat* OR utili* OR use)):ab,ti) OR absenteeism:ab,ti OR presenteeism:ab,ti	1,453,873

15	#9 AND #14	7,538
16	#15 NOT #13	6,009
17	#15 NOT #13 AND [2007-2019]/py	4,862

Table 115 Search strategy for MEDLINE In-Process® from 22 November 2019

S. No	Search terms	No. of Hits
1	Carcinoma, Non-Small-Cell Lung[mh] OR nsclc[tiab]	61,966
2	Neoplasms[mh] OR Carcinoma, Squamous Cell[mh] OR Adenocarcinoma[mh]	3,239,575
3	Lung[mh]	267,376
4	#2 AND #3	31,178
5	(lung[tiab] OR pulmon*[tiab] OR bronchial[tiab]) AND (cancer* [tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	304,081
6	#4 OR #5	317,524
7	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	62,445
8	#6 AND #7	62,210
9	#1 OR #8	73,153
10	Cost Control[MeSH Terms]	32,704
11	Health Care Costs[MeSH Terms]	62,989
12	Drug Costs[MeSH Terms]	15,634
13	Hospital Costs[MeSH Terms]	10,678
14	Cost of Illness[MeSH Terms]	25,977
15	Patient Acceptance of Health Care[MeSH Terms]	145,466
16	Resource Allocation[MeSH Terms]	16,965
17	(healthcare[Title/Abstract]) AND (cost[Title/Abstract] OR costs[Title/Abstract])	35,377
18	(unit[Title/Abstract]) AND (cost[Title/Abstract] OR costs[Title/Abstract])	20,059
19	price[Title/Abstract] OR pricing[Title/Abstract]	29,378
20	(resource[Title/Abstract]) AND (allocation[Title/Abstract] OR allocations[Title/Abstract])	10,522

21	(healthcare[Title/Abstract] OR "health care"[Title/Abstract]) AND (utilisation[Title/Abstract] OR utilization[Title/Abstract])	34,036
22	(resource[Title/Abstract]) AND (utilisation[Title/Abstract] OR utilization[Title/Abstract] OR use[Title/Abstract])	13,711
23	(cost[Title/Abstract] OR costs[Title/Abstract]) AND (treatment[Title/Abstract] OR therapy[Title/Abstract] OR total[Title/Abstract] OR direct[Title/Abstract] OR indirect[Title/Abstract] OR medical[Title/Abstract] OR drug[Title/Abstract] OR administration[Title/Abstract] OR laboratory[Title/Abstract] OR diagnostic[Title/Abstract] OR productivity[Title/Abstract] OR illness[Title/Abstract])	291,234
24	"hospitalization cost"[Title/Abstract] OR "hospitalisation cost"[Title/Abstract]	739
25	Length of Stay[MeSH Terms]	84,406
26	Budgets[MeSH Terms]	13,592
27	economic[Title/Abstract] OR cost[Title/Abstract] OR costs[Title/Abstract]	678,230
28	(Costs and Cost Analysis[MeSH Major Topic]) OR (low[Title/Abstract] AND costs[Title/Abstract]) OR (high[Title/Abstract] AND costs[Title/Abstract]) OR "hospital stay"[Title/Abstract] OR absenteeism[Title/Abstract] OR presenteeism[Title/Abstract]	198,676
29	#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 OR #24 OR #25 OR #26 OR #27 OR # 28	1,039,257
30	#9 AND #29	4,749
31		307,389
32	#30 AND #31	90

Table 116 Search strategy for EconLit® 22 November 2019

S. No.	Query	Search Options	No. of Hits
S1	"non small cell lung cancer"	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	660,272
S2	TI NSCLC OR AB NSCLC	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	178,776

S3	lung AND (neoplasm OR "squamous cell carcinoma" OR adenocarcinoma)	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	2,666,212
S4	TI (lung OR pulmonary OR bronchial) N3 (cancer OR carcinoma OR neoplasm OR neoplasms OR tumour OR tumor OR squamous OR adenocarcinoma) OR AB (lung OR pulmonary OR bronchial) N3 (cancer OR carcinoma OR neoplasm OR neoplasms OR tumour OR tumor OR squamous OR adenocarcinoma)	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	1,259,115
S5	S3 OR S4	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	3,307,273
S6	TI ("non small cell" OR "non-small-cell" OR "nonsmall cell") OR AB ("non small cell" OR "nonsmall- cell" OR "nonsmall cell")	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	317,969
S7	S5 AND S6	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	315,926
S8	S1 OR S2 OR S7	Expanders - Also search within the full text of the articles Search modes - Find all my search terms	718,573
S9	S8	Limiters - Date Published: 20070101-20191231 Expanders - Also search within the full text of the articles Search modes - Find all my search terms	601,288
S26	S9 Source - Econlit	Limiters - Date Published: 20070101-20191231 Expanders - Also search within the full text of the articles	97

	Search modes - Find all my search terms

Table 117 Search strategy for CRD York, 22nd November 2019

S. No.	Query	Hits
1	MeSH DESCRIPTOR Carcinoma, Non-Small-Cell Lung EXPLODE ALL TREES OR (non small cell lung cancer) OR nsclc	818
2	MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES	11,971
3	MeSH DESCRIPTOR Carcinoma, Squamous Cell EXPLODE ALL TREES	214
4	MeSH DESCRIPTOR Adenocarcinoma EXPLODE ALL TREES	872
5	#2 OR #3 OR #4	11,971
6	MeSH DESCRIPTOR Lung EXPLODE ALL TREES OR lung	2,877
7	#5 AND #6	1,346
8	(lung OR pulmon* OR bronch*) NEAR3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)	1,437
9	#7 OR #8	1,438
10	(non small cell) OR (non-small-cell) OR (nonsmall cell)	821
11	#9 AND #10	820
12	#1 OR #11	834
13	(#12) FROM 2007 TO 2019	624
14	(#13) IN NHSEED	199
15	(#13) IN HTA	270

In the existing SLR, a total of 5,518 potentially relevant titles or abstracts were identified. 624 records were removed as duplicates and the remaining 4,894 records were screened based on the information reported in their titles and/or abstracts. Of these, 4,004 were excluded at the primary screening stage as they were not relevant to the research question. A total of 890 articles were assessed in full for further evaluation. Of these, 866 were excluded, and 24 were included. Additionally, nine records from the HTA search were included. Therefore, 33 citations were included in the existing SLR. Due to the publication of multiple articles for the same study, 24 unique studies were extracted from the 33 included publications. Of these 24 studies, 15 studies were economic modelling studies reporting cost and resource use data and were extracted in the

existing SLR. Figure 97 presents the PRISMA flow diagram from the existing SLR. Table 118 presents the results from the existing SLR.

Figure 97 PRISMA flow diagram from November 2019.

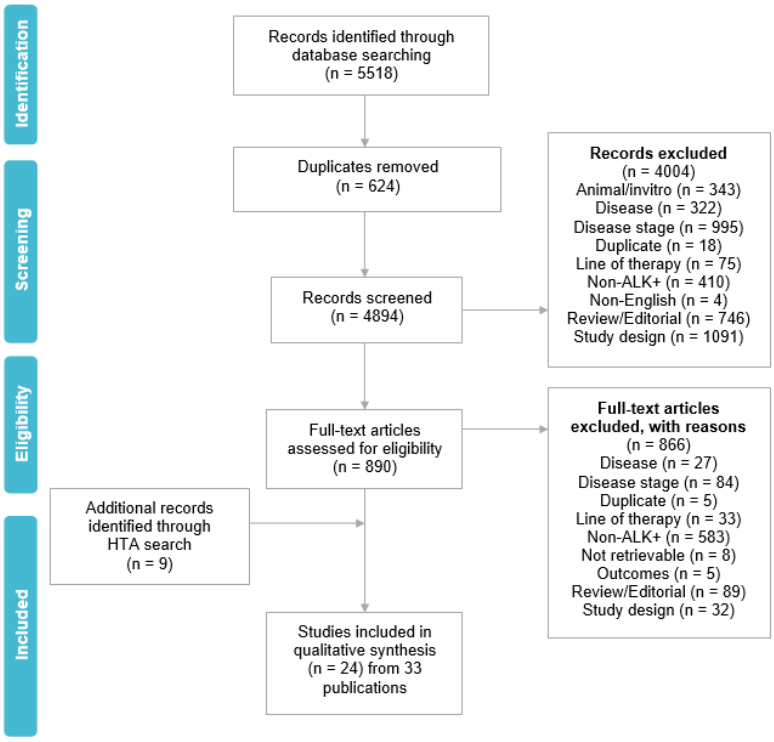


Table 118 Summary of cost and resource use results from November 2019 update

Study name	Summary of model			Summary of results	
	Intervention/ comparator	Country	Study type, Cost year, Currency	Cost Resource use	Cost drivers
Djalalov 2014	CZT Standard care (Platinum doublet: CIS and GEM)	Canada	CUA 2012 Canadian dollars (CA$)	Drug cost ($): value (range) Treatment cost CZT: 7,000 (4,900 – 9,100) Platinum doublet (CIS and GEM): 1,527 (1,069 – 1,985) PEM: 5,900 (4,130 – 7,670) ERL: 2,229 (1,560 – 2,898) BSC: 582 (407 – 757) Testing cost IHC test: 40 (28 – 52) FISH test: 388 (272 – 504) Rebiopsy: 712 (498 – 926) Resource use: NR	Treatment-related utility with CZT and the cost of CZT treatment
Kousoulakou 2015	First line Chemo (PEM + CIS or CARB) (73% patients)	Greece	Cost or resource use analysis 2014 Euro (€)	Cost (€) Per patient cost for PEM + CIS/CARB: 16,331.24 Per patient cost in the future treatment pathway first line (under scenario 1) CZT: 51,245.84 Per patient cost in the future treatment pathway first line (under scenario 2) duration of treatment was 29.3 months; Chemo: 16,331.24 Resource use: NR	AE management and cost of life expectancy
CADTH [CZT] 2015	CZT Standard care (PEM + Platinum)	Canada	HTA NR Canadian dollars ($)	Drug cost ($) Cost of CZT (at the recommended dose of 250 mg twice daily): Cost per day: 293.33 Cost per 28 days: 8,213.34 Cost of PEM (at the recommended dose of 500 mg/m2 on Day 1 of every 21-day cycle): Cost per day: 173.64 Cost per 28 days: 4,862.00 Cost of CIS (at the recommended dose of 75 mg/m2 IV Day 1 every 21 days): Cost per day: 35.57	Post progression probability of mortality, time horizon, extrapolation method of survival effects, and utility values

				Cost per 28 days: 996.10 Resource use: NR	
Lu 2016	CZT Standard Chemo (PEM + CIS)	China	CEA 2016 US dollars (US $)	Drug cost ($) Cost of traditional chemo per cycle other than PEM: 518.4 Cost of CZT per day: 238.1 Cost of follow-up per unit: 55.6 Cost of salvage chemo per cycle: 2352.7 Cost of palliative care in end-of-life: 2042.91 Cost of supportive care per cycle: 337.5 Cost of SAEs in initial chemo per cycle: 507.4 Resource use: NR	Cost of CZT
NICE [TA406] 2016	CZT PEM + Platinum based therapy (CIS or CARB)	UK	HTA 2014-2015 Sterling pound (£)	MS Total cost (£) CZT (CI): 53,223.60 (52,917.11, 53,561.22) PEM + CIS /CARB (CI): 11,045.33 Patients in PFS health state and patients in PD health state cost per month: 192.75 Total cost of palliative care (CI): 7,253 (5,901, 8,742) Total predicted resource use – CZT at list price CZT: 79,884 PEM + CIS/CARB: 21,480 Increment: 58,404 Absolute increment: 63,177 Treating AEs due to chemo with PEM (Total cost) Anaemia: 374.27 Thrombocytopenia: 758.50 Neutropenia: Managed by dose reduction (Cost: Not applicable) Total cost of AEs, by treatment; CZT: 0.00 PEM + CIS/CARB: 82.04 Costs by health state – CZT at list price: Pre-progression: CZT: 61,085 PEM + CIS/CARB: 11,478 Increment cost: 49,607 Absolute increment: 49,607 Post-progression: CZT: 18,799	OS, with the covariate for treatment effect

PEM + CIS/CARB: 10,003
Increment cost: 8,797
Absolute increment: 8,797
Total:
CZT: 79,884
PEM + CIS/CARB: 21,480
Increment cost: 8,797
Increment cost: 58,404
Absolute increment: 58,404
ERG
ERGs revised administration cost, (unit cost per treatment cycle):
CZT: 163
CIS-containing regimens: 413.58
CARB-containing regimens: 325.94
Cost of monitoring in first line: 192.75 per month
Total cost of AEs, by treatment;
CZT: 0.00
PEM + CIS/CARB: 163.20
Resource use:
MS
Patients in PFs and PD health state (frequency per month):
Outpatient Visit: 0.75
General practitioner: 10% of patients per month
Cancer nurse: 20% of patients receive 1 per month
Complete Blood Count: 0.75
Biochemistry: 0.75
CT scan: 30% patients receive 0.75 per month
Chest X-ray: 0.75
ERG
Patients in PFs and PD health state (frequency per month):
Outpatient visit: 0.75
Oncologist visit: NA
General practitioner: 10% of patients per month
Cancer nurse: 20% of patients receive 1 per month
Complete Blood Count: 0.75
Biochemistry: 0.75
CT scan: 30% patients receive 0.75 per month
Chest X-ray: 0.75

SMC [CZT] 2016	CZT PEM + Platinum based therapy (CIS or CARB)	Scotland	HTA NR Sterling pound (£)	Cost (£) Cost per 3-week cycle CZT (250 mg orally twice daily): 3,282 PEM + CIS (IV infusion on Day 1 of each cycle: Cycles 1 to 4: PEM 500 mg/m2, CIS 75 mg/m2): 1,518 PEM maintenance (Cycles 5 onwards PEM 500 mg/m2: 1,440 PEM + CIS (PEM 500 mg/m2, CIS 75 mg/m2): 1,518 Cost per course CZT (250 mg orally twice daily): 52,517 PEM + CIS (IV infusion on Day 1 of each cycle: Cycles 1 to 4: PEM 500 mg/m2, CIS 75 mg/m2): 23,353 PEM + CIS (PEM 500 mg/m2, CIS 75 mg/m2): 6,073 Resource use: NR	Covariates attributed to the OS calculation (such as: alternative crossover methods, alternative methods to model survival, Comparing CZT to PEM maintenance, and patient characteristics)
Kourkoulas 2017	ALC	Greece	Budget Impact NR Euro (€)	Cost (€) Annual Inc. budget impact for ALC First year: 71,371 Second year: 454,469 Third year: 1,245,170 Fourth year: 2,699,802 Fifth year: 4,161,658 Cumulative budget impact for ALC: 8,632,470 (for the 5-year time horizon of the analysis) Resource use: NR	Cost of ALC and the projected market shares
McGahan 2017	CER CZT ALC	Austria	Cost or resource use analysis NR Euro (€) and US Dollar ($)	Cost Cost for CER: €3,748.71* [per 21-day cycle (at recommended dose of 750 mg daily)] Cost for CZT: €4,000 per 21 days Cost for ALC: €4,100 per 21 days Cost for median duration [16.6 months (IQR 7.5–20.9 months)], CER: €62,230 Additional costs for CER for ALK testing Cost for IHC: $US 68.89 Cost for Fish and IHC: $US 279.46 Resource use: NR	NR

				Note: *using 150 mg capsules is available for € 5,355.30 (ex-factory price).	
Burudpakdee 2018	ALC CZT	US	Cost or resource use analysis 2016 US dollars ($)	Cost ($) Phase I: real-world economic burden of brain metastasis Cost with no brain metastases, mean (SD) PPPM (N=207) Total cost: 22,791 (20,116) Inpatient: 6,831 Radiation therapy: 228 Other outpatient service: 4,468 Head/ brain radiology imaging: 189 Other radiology imaging: 1,458 Pharmacy cost: 486 Lung cancer drug cost: 9,131 Cost with brain metastases, Mean PPPM (N=198) Total cost: 29,497 (22,646) Inpatient: 11,057 Radiation therapy: 852 Other outpatient service: 5,834 Head/ brain radiology imaging: 490 Other radiology imaging: 1,939 Pharmacy cost: 699 Lung cancer drug cost: 8,627 Radiation therapy Patients with BM: 9,297 (16,693) Patients with no BM: 2,690 (6,150); p<0.001 Adjusted mean PPPM cost Patients with BM: 24,707 (95% CI: 23,682, 25,866) Patients with no BM: 18,678 (95% CI: 17,187, 19,569) Total mean cost of BM per patient treated with ALC and CZT Mean PPPM cost ALC group (n = 88): 435.32 CZT group (n = 93): 2,733.69 Total mean cost per patient over 24-month follow-up period ALC group (n = 88): 8,390.73 CZT group (n = 93): 49,824.50	Presence or absence of brain metastases

Phase II: the estimated economic burden of BM based on the ALEX trial data
Total mean cost of BM per patient over the study period
ALC group: 8,391
CZT group: 49,824
Cost savings associated with delaying or preventing BM with ALC was estimated at $41,434.
Resource use
Inpatient Stays, PPPM, Mean (SD)
Patients with BM: 0.30 (0.36)
Patients with no BM: 0.19 (0.29) (p = 0.001)
Length of stays in patients with ≥ 1 inpatient stay (in days),
Patients with BM: 8.45 (10.88)
Patients with no BM: 7.99 (10.19) (p =0.292)
Outpatient services, PPPM
ED visits, Mean (SD)
Patients with BM: 0.68 (1.33)
Patients with no BM: 0.40 (0.81) (p = 0.011)
Patients with ≥ 1 ED visit, n (%)
Patients with BM: 130 (65.66)
Patients with no BM: 109 (52.66) (p =0.008)
Radiology imaging procedures, Mean (SD)
Patients with BM: 4.02 (2.67)
Patients with no BM: 3.11 (2.99) (p = 0.001)
Radiation therapy sessions, Mean (SD)
Patients with BM: 0.64 (1.00)
Patients with no BM: 0.33 (0.80) (p <0.001)
Among patients with at least one radiation therapy session, 37.4% of BM patients underwent stereotactic radiation therapy compared to only 1.9% of no BM patients (p < 0.001).
Pharmacy utilisation for non-lung cancer drug treatments, PPPM, Mean (SD)

				Patients with BM: 4.34 (2.86) pharmacy fills Patients with no BM: 3.40 (2.70) pharmacy fills (p =0.001)	
CADTH[ALC] 2018	ALC CZT	Canada	HTA 2017 Canadian dollar (CA$)	Drug Cost ($) ALC Cost per day: 337.33 Cost per 28 days: 9,445.32 CZT Cost per day: 260.00 Cost per 28 days: 7,280.00 Resource use: NR	Time horizon and the choice of parametric curve for OS for ALC
Carlson 2018	ALC CZT	US	CUA 2017 US dollars ($)	Costs (US $): point estimate (range) Treatment cost per week ALC: 3,131 (2,796–3,417) CZT: 3,596 (3,211–3,925) CER: 3,717 (2,023–4,056) Supportive care cost per week CNS metastases: 3,381 (3,043–3,719) No CNS metastases: 788 (709–867) Note: cost related to AEs was not included in this model Resource use: NR	Drug costs (ALC and CZT) and cost-of-care estimates
NICE [TA500] 2018	CER CZT	UK	HTA 2016 Sterling pound (£)	MS Drug cost per month, (£): CER (750 mg orally once daily): 3,861.33 CZT (250 mg orally twice daily): 4,376.79 Drug administration costs (both drugs): 14.26 per month Drug administration costs, first-line treatment (£): CER: 80,325 CZT: 66,097 CER vs CZT: 14,229 Medical costs (£): CER: 18,655 CZT: 17,401 CER vs CZT: 1,254 Total PFS costs (£): 184.42 Total post-progression care costs (£): 267.19 Total terminal care costs (£): 7,328.93 Cost of AEs, by first-line treatment (£):	Total drug acquisition costs and parameters related to drug costs – including relative dose intensity and the list prices of CER and CZT and assumptions about treatment duration.

CER: £340.27
CZT: £218.23
AE cost (£):
Neutropenia: 514.82
Diarrhoea: 382.02
Pulmonary embolism: 1,485.76
Vomiting: 754.13
Hyperglycaemia: 308.44
Alanine transaminase elevation: 308.44
Aspartate aminotransferase elevation: 308.44
Gamma-glutamyl transferase increased; 308.44
Blood alkaline phosphatase increased: 308.44
Health state costs (£):
Medical costs per cycle in PFS: 184.42
Medical costs per cycle in PD: 267.19
One-time terminal care cost: 7,328.93
PF costs (£):
CER: 4,245
CZT: 2,787
CER vs CZT: 1,458
PD costs (£):
CER: 8,320
CZT: 8,307
CER vs CZT: 13
Terminal care costs (£):
CER: 6,089
CZT: 6,307
CER vs CZT: -218
Total costs (£):
CER: 106,954
CZT: 91,970
CER vs CZT: 14,985
ERG
Drug cost (£):
CER: 119,684
CZT: 98,764
Inc. Costs: 20,920
Drug and drug administration costs, initial treatment (£):
CER: 4,471
CZT: 6,000
Inc. Costs: -1,529
Medical costs (£):
CER: 15,078
CZT: 14,704
Inc. Costs: 374

Total costs (£):
CER: 139,573
CZT: 119,687
Inc. Costs: 19,887
Treatment-associated AEs costs (£):
CER: 340
CZT: 218
Inc. Costs: 122
PFS costs (£):
CER: 4,510
CZT: 2,986
Inc. Costs: 1,524
PPS costs (£):
CER: 4,083
CZT: 5,143
Inc. Costs: -1,060
Terminal care costs (£):
CER: 6,485
CZT: 6,575
Inc. Costs: -90
Total costs (£):
CER: 139,573
CZT: 119,687
Inc. Costs: 19,887
Resource use:
Monthly PF cost (frequency of use)
Cancer nurse: 20% of patients (1 visit)
Outpatient visit: 0.75 visits
GP visit: 10% of patients (1 visit)
Full blood count: All patients, 0.75 per month
Computerised tomography scan: 30% of patients, 0.75 per month
X-ray: All patients, 0.75 per month
Serum chemistry: All patients, 0.75 per month
Monthly post-progression costs (frequency of use):
Healthcare provider visits:
Cancer nurse: 10% of patients (1 visit)
Outpatient visit: All patients (1 visit)
GP visit: 28% of patients (1 visit)
Medications:
Steroids (dexamethasone): 50% of patients, 0.5 mg x 160

				NSAIDS (ibuprofen): 30% of patients, 200 mg x 60 Morphine: 75% of patients, 60 mg x 7 Bisphosphonate (alendronate): 7.5% of patients, 5 mg x 28 Dietary supplement: 40% of patients, 350 g x 20 Tests and procedures: Full blood count: All patients, 1 per month Serum chemistry: All patients, 1 per month Computerised tomography scan: 5% of patients, 0.75 per month Home oxygen: 20% of patients, 1 per month X-ray; 30% of patients, 0.75 per month	
NICE [TA536] 2018	ALC CZT	UK	HTA 2015–2016 Sterling pound (£)	Cost per cycle (£): ALC: 1,262 CZT: 1,098 Cost per administration (£): ALC: 9.20 CZT: 9.20 Cost of ALK test: £2,380 Resource use for PFS health state (£): Total cost per month: 324.35 Total cost per weekly cycle: 74.86 Resource use for PD health state (irrespective of progression location). Cost per month Total cost per month: 500.04 Total cost per week: 115.40 Additional resource use for PD health state: brain metastases: Total cost per week for ALC: 146.32 Total cost per week CZT: 127.97 Total Supportive care cost per week of a progression in the CNS for CZT: 243.37 Resource costs for terminal care: Total cost (Total cost of care in each setting): 3,679.37	Utility estimates (not accounting for CNS QoL), the OS distribution utilised (reflecting the conservative assumption used in the base case analysis), PFS extrapolation CNS-related utility value is one of the key drivers

AEs and costs used in the economic model:
Alanine Aminotransferase Increased: 340.36
Aspartate Aminotransferase Increased; 340.36
Cardiac Arrest: 2291.93
QT interval prolongation: 149.08
Neutropenia: 362.66
Pneumonitis: 2783.99
Total cost per week in the PFS health state: 74.86 (60.69 - 89.83)
Total cost per week in the PD health state for CZT: 496.77 (317.41– 473.81)
Total cost per week in the PD health state for ALC: 398.41 (403.65–602.55)
Total cost of end of life: 3,679.37 (1,839.69–5,519.06)

Resource use
Resource use for PFS health state (No. required per month):
Consultant-led outpatient visit/oncologist: 0.75
General practitioner visit: 1
Cancer nurse: 1
Full blood test: 1
Biochemistry: 1
CT scan: 0.5
MRI scan: 0.2
X ray: 0.3
ECG: 1
Resource use for PD health state (irrespective of progression location) (No. required per month):
Consultant-led outpatient visit/oncologist: 1.25
General practitioner visit: 1
Cancer nurse: 1.5
Full blood test: 1.5
Biochemistry: 1.5
CT scan: 0.75
MRI scan: 0.5
X ray: 0.5
Resource use for terminal care/end of life:

				Hospitalisation admission (+excess bed days): 1 (+0.84 excess bed days) Hospice care: 1 Macmillan Nurse (home setting): 50	
Oksuz 2018	ALC Chemo (50% PEM + CIS and 50% PEM + CARB)	Turkey	CUA NR Turkish lira (₺)	Cost (₺) Health state PFS state ALC: 83.36 CZT: 93.33 Chemo: 93.33 Progression state ALC: 756.37 CZT: 919.63 Chemo: 1,144.62 CNS metastasis, weekly: 193.99 Cost of medication administration: 224.6 for 21-day cycles in chemo Resource use: NR	Treatment cost of ALC
Paolini 2018	CZT	Italy	Budget Impact and CEA NR Euro (€)	Cost (€) CZT 250 mg BD cost: Price per pack: 5,900 Treatment cost per 3-week cycle: 4,130 administration cost per 3-week cycle: 0 AE cost: 22 Resource use: NR	Cost of CZT
SMC [ALC] 2018	ALC CZT	Scotland	HTA 2015–2016 Sterling pound (£)	Cost (£) Drug regimen cost per year ALC (600 mg orally twice daily): 65,416 CZT (250 mg orally twice daily): 56,893 Additional one-off cost associated with CNS progression: £20,000 Resource use: NR	Cost of CER
Soares 2018	ALC CZT	Portugal	CUA NR Euro (€)	Monitoring costs per month (€) Medical appointments PFS (at first line): 56,64 PPS (at second line): 41,07 Brain metastasis: 6,319,22 BSC: 114,72 End of life care: 114,72 AEs: 3,204,00 Exams PFS (at first line): 143,39 PPS (at second line): 115,80	Key model driver: PFS and PS

				BSC: 32,57 End of life care: 32,57 Concomitant medication PFS (at first line): 0 PPS (at second line): 4,92 BSC: 21,96 End of life care: 21,96 Urgency entrance PFS (at first line): 0 PPS (at second line): 2,70 BSC: 0 End of life care: 45,74 Out of hospital care (e.g. care home, nursing home or a person´s own home) PFS (at first line): 0 PPS (at second line): 0 BSC: 15,94 End of life care: 583,83 Hospitalisation PFS (at first line): 0 PPS (at second line): 0 BSC: 0 End of life care: 1,766,62 Total PFS (at first line): 200,03 PPS (at second line): 164,49 BSC: 185,19 End of life care: 2,565,44 Resource use: NR	
Zhou 2018	CER CZT Platinum doublet (PEM + CIS/CARB followed by PEM maintenance)	US	CUA 2016 US dollars ($)	Cost ($) Monitoring cost (per month): 315.06 Terminal care cost (one time): 17,426.94 Drug delivery costs IV infusion Chemo IV push additional drug: 63.16 Chemo IV infusion 1 hour: 139.61 Chemo IV infusion additional hour Intra-muscular injection: 28.71 Therapeutic, prophylactic, or diagnostic injection: 25.84 Costs associated with AEs (one-time) CER: 1,239.83 CZT: 2,931.31 Platinum doublet with maintenance: 3,409.69 Medical cost of progression (one-time): 16,316.89 Resource use: NR	Drug and drug administration costs for initial treatment (CER, CZT, and platinum doublet total costs, respectively) and costs associated with post-progression treatment

Liu 2019	CZT ALC CER	China	CUA 2018 US dollars ($) Exchange rate of 1US dollar = 6.61 Yuan	Costs (US $) (range) Drug cost per day CZT: 78.58 (39.29–78.58) CER: 89.76 (44.88–89.76) ALC: 134.87 (134.87–269.74) SAEs cost per cycle: 362 (272–453) Miscellaneous cost Cost of supportive care: 359 (169–845) Cost of follow-up per cycle: 59.2 (44.4–74) Cost of chemo per cycle: 2352.7 (1921.1–4,383.3) Cost of hospice care: 2,176 (845–5,812) Resource use: NR	Cost of chemotherapies (CZT, CER, and ALC)
Massuti 2019	ALC CZT	Spain	Cost or resource use analysis 2018 Euro (€)	Costs (€) Total Average cost per patient (With metastases + Without metastases) ALC: €7627 CZT: €12,575 Difference: €4,949 Cost per patient ALC vs CZT: €4,948.51 patient/ year Average cost per patient (With metastases) ALC: €2,034 CZT: €8,956 Average cost per patient (Without metastases) ALC: €5,593 CZT: €3,619 Management cost per patient (With CNS metastases): €21,637.50 Management cost per patient (Without CNS metastases): €6,173.42 AE cost: ALC vs CZT Average Cost/year difference: -€5,044.26	Appearance of CNS metastasis
Moldaver 2019	ALC	Canada	Cost or resource use analysis, 2018, Canadian dollar (CA $)	Costs (CA $) (range) Cost of treatment: $243,721 to $353,108	Survival

Peng 2019	CER Platinum based therapy (PEM combined with CIS/CARB followed by PEM maintenance)	China	CUA, 2017, US dollars ($) Exchange rate of 1US dollar = 6.59 Yuan	Costs: (US $) (range) Drug cost Platinum drug costs per cycle: 518.40 (362.88–673.92) BSC cost per cycle: 1,415.40 (990.78–1,840.02) Health state cost per year PD: 14,519.00 (10,163.30–18,874.70) Resource use: NR	Cost of CER followed by utility of PFS, cost of PEM, body surface area and the discount rate
Stefani 2019	ALC CZT	Brazil	CUA 2019 Brazilian Real (BRL) Exchange rate of 1 BRL = 0.27 US dollar	Cost (BRL; US $) Monthly drug cost ALC: 26,720; 7,214 CZT: 30,622; 8,268 Disease progression cost CNS progression: 29,029; 7,838 Additional annual follow up costs: 61,819; 16,691 Resource use: CNS progression management was composed by radiotherapy (48%) surgery (28%) diagnostic procedures (17%) hospitalisations and emergency care (7%) and medical honorariums (1%)	SLP health state utility of ALC* *SLP full form was not defined by the author
Truong 2019	CZT	Canada	Cost or resource use analysis, NR, Canadian dollar (CA $)	Cost ($) CZT (Dose level 0) cost per cycle (28 days) by pricing strategy: 8,214 Resource use: NR	Dose reduction resulted in a significantly greater increase in the cost per mg for drugs using flat pricing (of up to 300%) compared to linear pricing

Key: AEs, adverse events; ALC, alectinib; BM, brain metastasis; BRL, Brazilian Real; BSC, best supportive care; CARB, carboplatin; CER, ceritinib; Chemo, Chemotherapy; CI, confidence interval; CIS, cisplatin; CUA, cost-utility analysis; CZT, crizotinib; ED, emergency department; ERG, evidence review group; HTA, health technology assessment; IV, intravenous; NA, not applicable; NR, not reported; PAS, patient access schemes; PAX, paclitaxel; PC, palliative care; PD, progressed disease; PEM, pemetrexed; PFS, progression-free survival; PPPM, per patient per month; SAE, serious adverse events; US, United-States.

J.1.2.2 October 2024 update

Table 119 Search strategy for MEDLINE (via PubMed.com) from October 2024

S. No	Search terms	7 October, 2024
1	Carcinoma, Non-Small-Cell Lung[mh] OR nsclc[tiab]	96,918
2	Neoplasms[mh] OR Carcinoma, Squamous Cell[mh] OR Adenocarcinoma[mh]	3,878,688
3	Lung[mh]	314,262
4	#2 AND #3	38,096
5	(lung[tiab] OR pulmon*[tiab] OR bronchial[tiab]) AND (cancer* [tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	422,967
6	#4 OR #5	437,567
7	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	97,155
8	#6 AND #7	96,875
9	#1 OR #8	112,322
10	Cost Control[MeSH Terms]	34,350
11	Health Care Costs[MeSH Terms]	73,773
12	Drug Costs[MeSH Terms]	17,783
13	Hospital Costs[MeSH Terms]	12,177
14	Cost of Illness[MeSH Terms]	35,325
15	Patient Acceptance of Health Care[MeSH Terms]	178,067
16	Resource Allocation[MeSH Terms]	19,122
17	(healthcare[Title/Abstract]) AND (cost[Title/Abstract] OR costs[Title/Abstract])	70,096
18	(unit[Title/Abstract]) AND (cost[Title/Abstract] OR costs[Title/Abstract])	28,571

19	price[Title/Abstract] OR pricing[Title/Abstract]	45,072
20	(resource[Title/Abstract]) AND (allocation[Title/Abstract] OR allocations[Title/Abstract])	18,612
21	(healthcare[Title/Abstract] OR "health care"[Title/Abstract]) AND (utilisation[Title/Abstract] OR utilization[Title/Abstract])	58,010
22	(resource[Title/Abstract]) AND (utilisation[Title/Abstract] OR utilization[Title/Abstract] OR use[Title/Abstract])	80,662
23	(cost[Title/Abstract] OR costs[Title/Abstract]) AND (treatment[Title/Abstract] OR therapy[Title/Abstract] OR total[Title/Abstract] OR direct[Title/Abstract] OR indirect[Title/Abstract] OR medical[Title/Abstract] OR drug[Title/Abstract] OR administration[Title/Abstract] OR laboratory[Title/Abstract] OR diagnostic[Title/Abstract] OR productivity[Title/Abstract] OR illness[Title/Abstract])	432,029
24	"hospitalization cost"[Title/Abstract] OR "hospitalisation cost"[Title/Abstract]	1,669
25	Length of Stay[MeSH Terms]	106,880
26	Budgets[MeSH Terms]	14,261
27	economic[Title/Abstract] OR cost[Title/Abstract] OR costs[Title/Abstract]	1,040,673
28	(Costs and Cost Analysis[MeSH Major Topic]) OR (low[Title/Abstract] AND costs[Title/Abstract]) OR (high[Title/Abstract] AND costs[Title/Abstract]) OR "hospital stay"[Title/Abstract] OR absenteeism[Title/Abstract] OR presenteeism[Title/Abstract]	283,753
29	#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 OR #24 OR #25 OR #26 OR #27 OR # 28	1,471,395
30	#9 AND #29	3,378
31	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	343,897
32	#30 AND #31	37
33	#32 AND ("2019/11/22"[Date - Publication] : "3000"[Date - Publication])	33

A PRISMA diagram illustrating the selection of studies in the October 2024 update is presented in Figure 98. 33 hits were identified in PubMed and title/abstract screened in the October 2024 update and five were full text screened. None of the full text screened

hits were deemed relevant to include in our health economic analysis (see Table 120). Also, none of the hits identified in the original SLR were included in the present application.

In addition to the systematic search in PubMed.com, the webpage of NICE was searched. The same technical appraisals were identified as reported in the search in Appendix H and none was included from this search.

Figure 98 PRISMA flow diagram for the cost and resource use search (October 2024)

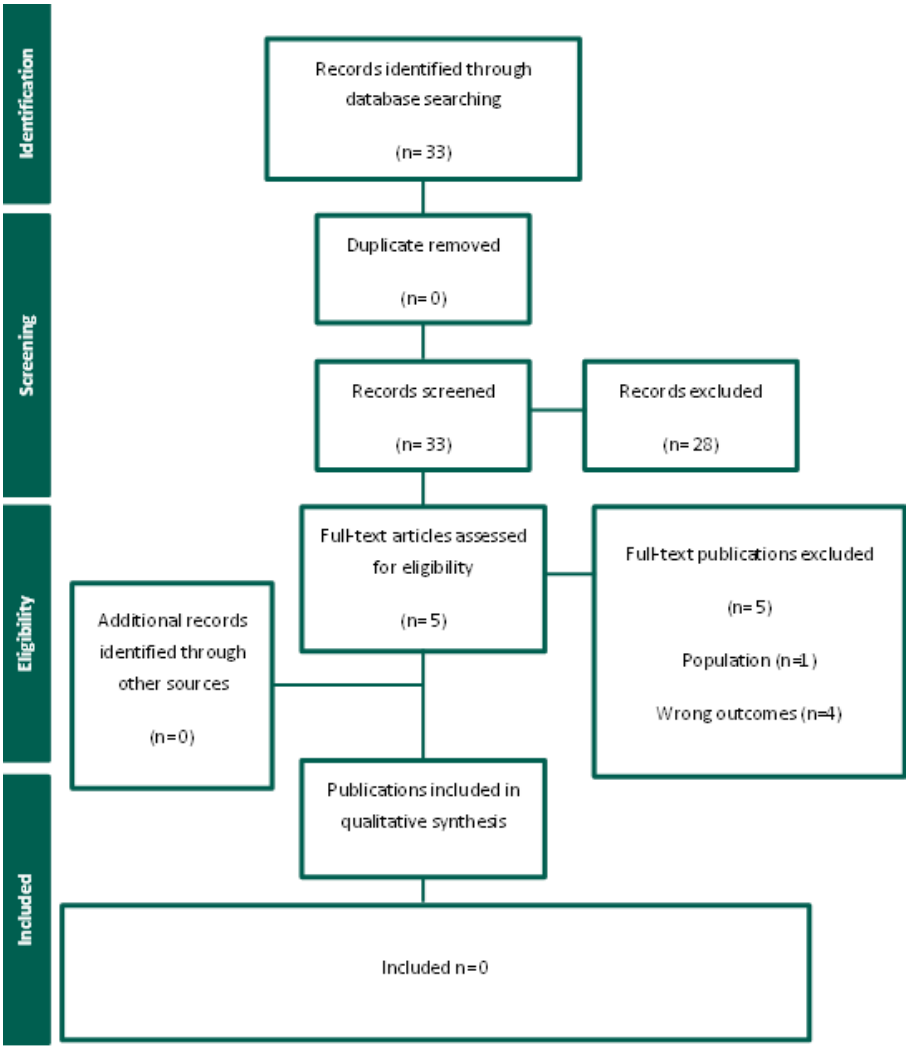


Table 120 Excluded hits after full text assessment (October 2024 update)

Reference	Reason for exclusion
Bestvina et al. 2024	Diagnostic procedures assessed
Abraham et al. 2024	Included costs were drugs, drug administration, and AE costs. The interventions assessed were toripalimab and

	pembrolizumab i.e., the administration costs and AE costs in the study were not relevant for our analysis.
Apter et al. 2024	Israeli health provider perspective
Westerink et al. 2024	No costs or resource use reported
Sridhar et al. 2024	Not ALK-positive NSCLC or first-line setting

J.1.3 Unpublished data

As no relevant literature was found on the resource use of CNS-progressed patients, the study by Le et al. 2023,(45) which is yet to be published in its full length, was used to model the resource use of these patients. The study is based on a UK population. The main finding are presented in an abstract published in 2023. (119)

In order to gain a larger data pool for lorlatinib OS for treatment-naïve ALK-positive patients, results from the Study 1001 EXP1 cohort were pooled with CROWN OS data. Study 1001 is a Phase II open-label, single-arm trial of lorlatinib in patients with ALK-positive NSCLC with varying prior treatment exposure, including a the EXP1 cohort of 30 patients who were treatment naïve. A publication with detailed results from study 1001 EXP1 was not published yet on the date of submission of this DMC application, however, the manuscript is submitted for publication. The mean OS results of Study 1001 EXP1 were presented in the discussion sections of Solomon et al., 2024 (17): Median follow-up for OS of 72.7 months (95% CI, 69.3 to 76.3), and 5-year OS was 76% (95% CI, 57 to 88) in patients with treatment-naïve *ALK*-positive NSCLC.

Appendix K. Overall survival pooled analysis (CROWN + 1001 EXP1)

Study 1001 is a Phase II open-label, single-arm trial of lorlatinib in patients with ALK-positive NSCLC with varying prior treatment exposure, including a cohort of 30 patients who were treatment naïve.(40) Baseline characteristics were similar between the treatment naïve arm of Study 1001 and the lorlatinib arm of CROWN (Section 6.1.2 and Solomon et al 2018).(5, 32) Median duration of follow-up for OS in that group was 72.7 months (95% CI: 69.3, 76.3), the median OS was NR (95% CI: NR, NR) and 5-year OS probability was 76%.(40)

This overall survival data from 30 patients in a treatment naïve cohort was pooled with OS data from the CROWN Phase III trial data. Pooled analysis of OS from CROWN and Study 1001 shows that median OS was not reached and 1-, 3- and 5-year OS rates were 89%, 77% and 73% (Figure 99 and Table 121).(120) With immature OS data in CROWN, this data supports the continued OS benefit of lorlatinib in patients with ALK-positive NSCLC.

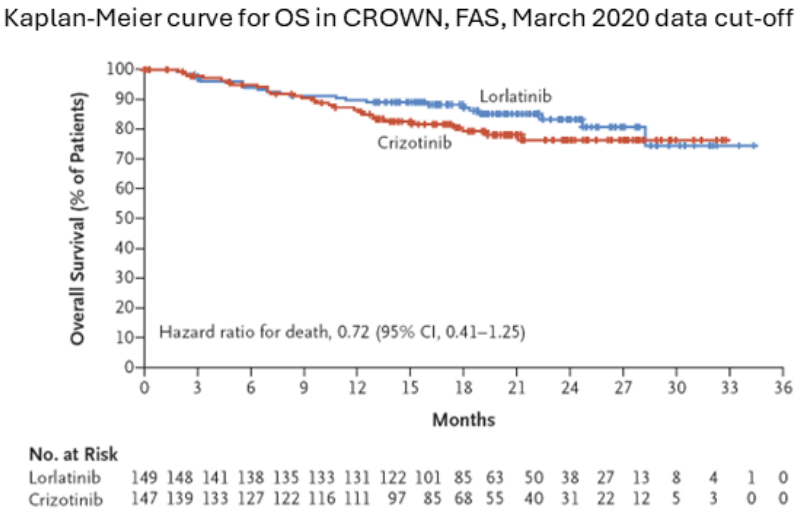
Table 121 OS outcomes in CROWN, Study 100 and pooled analysis

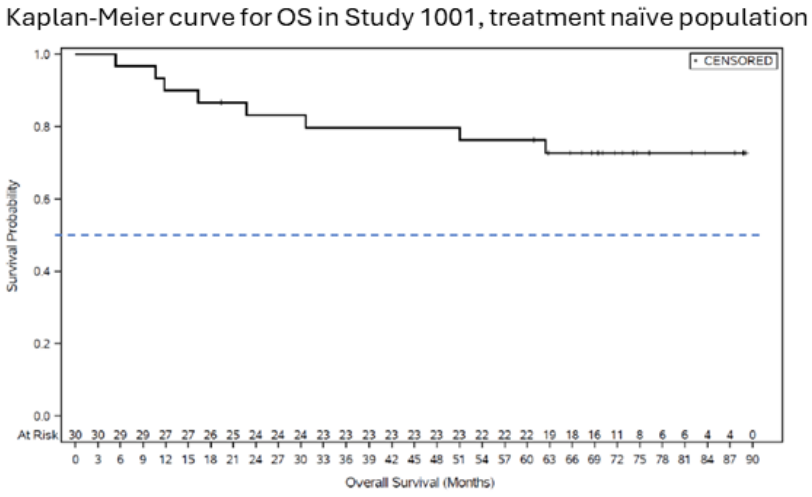
OS outcome	CROWN – 18-month data cut-off (n = 149)(32)	Study 1001 (n = 30)(40)	CROWN + Study 1001 (n = 179)(120)
Median duration of follow-up		72.7 months (95% CI: 69.3, 76.3)	-
Median OS	Not estimable	NR (95% CI: NR, NR)	NR
1-year OS rate	90%	90%	89%
3-year OS rate	-	80%	77%
5-year OS rate	-	76%	73%

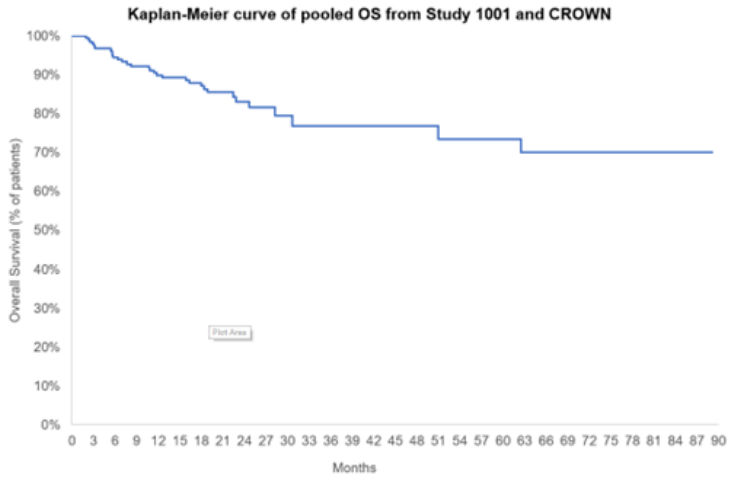
Key: CI, confidence interval; NR, not reached; OS, overall survival.

Source: Ou et al. manuscript in preparation; Pfizer Inc. Data on File, 2024; Shaw et al. 2020; Solomon et al. 2024.(17, 32, 40, 120)

Figure 99 Kaplan–Meier curves for OS for CROWN (top); Study 1001 (middle); CROWN + Study 1001 pooled analysis (bottom)







Source: Shaw et al. 2020; Ou et al. (manuscript in preparation); Pfizer Inc. Data on File, 2004.(32, 40, 120)

Appendix L. Resource use for CNS-progression

The resource use and unit costs used to estimate the one-off CNS progression cost are presented below in Table 122. The resource use was estimated based on UK study by Le et al, which was yet to be published on the date of submission of the application. Applying Danish DRG tariffs to the resource use, a one-off cost of DKK 146,185.70 was applied for CNS-progressions.

Table 122 Estimated resource use for CNS progression patients

	Patients without CNS metastases (First and subsequent years)		Patients with CNS metastases (First year)		Patients with CNS metastases (Subsequent years)		Unit cost	Source
	Patients (%)	Resources/ year (n)	Patients (%)	Resources/ year (n)	Patients (%)	Resources / year (n)		
Specific procedures for the treatment of metastases								
Holocranial brain radiotherapy	0.0%	0	4.0%	5	0%	0	170,533	DRG 2024: 26MP17
Radiosurgery or stereotactic radiotherapy	0.0%	0	43.3%	3	22%	3	7,412	DRG 2024: 27MP10
Surgical resection	0.0%	0	5.7%	1	1%	1	170,533	DRG 2024: 26MP17
None	0.0%	0	47.0%	0	77%	0	0	
Hospitalizations								
General admission (acute complications related to BM)	8.3%	1	16.7%	1	33%	1	45,583	DRG 2024: 04MA07
Radiation oncology	0.0%	0	1.3%	2	7%	2	2,237	DRG 2024: 04MA98
Elective surgery	0.0%	0	5.3%	1	0%	0	7,412	DRG 2024: 27MP10

Visits								
Medical oncology	70.0%	13	70.0%	13	70%	13	1,311	DRG 2024: 04MA98
Emergencies	70.0%	1	70.0%	2	70%	2	1,311	DRG 2024: 04MA98
Radiation oncology (first visit)	30.0%	12	70.0%	16	70%	16	2,237	DRG 2024: 04MA98
Radiation oncology (successive visits)			30.0%	16	30%	16	2,237	DRG 2024: 04MA98
Surgery	0.0%	0	10.0%	2	10%	2	7,412	DRG 2024: 27MP10
Laboratory tests								
Blood count	100.0%	12	100.0%	12	100%	12	0	Assumed included in DRG-tariffs
Biochemistry	100.0%	12	100.0%	12	100%	12	0	Assumed included in DRG-tariffs
Thoracentesis	10.0%	1	10.0%	1	10%	1	1,311	DRG 2024: 04MA98
Imaging techniques								
Bone scan	3.0%	1	3.0%	1	3%	1	3,620	DRG 2024: 36PR07
Cerebral MRI	50.0%	1.7	94.3%	4	94%	4	2,142	DRG 2024: 30PR03
Thorax/abdomen computed tomography	100.0%	4	100.0%	4	100%	4	2,585	DRG 2024: 30PR06
Brain computed tomography	30.0%	1.3	4.0%	2.7	4%	2.7	2,021	DRG 2024: 30PR07

Appendix M. Appendix references

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