Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende alectinib til adjuverende behandling af ALK-positiv ikke-småcellet lungekræft

Post-operative patienter med stadium IB-IIIA-sygdom og høj risiko for tilbagefald

Vers. 1.0

Bilagsoversigt

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

Roche Pharmaceuticals A/S
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Til Medicinrådet,

Høringssvar fra Roche Pharmaceuticals A/S vedrørende Medicinrådets anbefaling vedr. Alecensa (alectinib) til adjuverende behandling af ALK-positiv ikke-småcellet lungekræft.

Roche takker for det fremsendte udkast til Medicinrådets vurderingsrapport af Alecensa (alectinib) til adjuverende behandling af ALK-positiv ikke-småcellet lungekræft. Roche ønsker at kommentere på enkelte dele i Medicinrådets tilgang; både i den kliniske samt den sundhedsøkonomiske vurdering.

I nedenstående afsnit forholder Roche sig til følgende emner enkeltvis:

- Sammenligneligheden mellem populationen i ALINA studiet og den danske population af patienter med tidlige stadier af ALK+ ikke-småcellet lungekræft
- Vurderingen af de forskellige endepunkter
- Den sundhedsøkonomiske vurdering

Sammenligneligheden mellem populationen i ALINA studiet og den danske population (afsnit 2.2.1):

1. Patienter med stadie IB-IIIA sygdom med høj risiko for tilbagefald er en del af indikationen for Alecensa. Det ligger derfor implicit, at der f.eks. er inkluderet flere patienter med N2-sygdom end hvad den generelle danske population vil have, da de jo ikke alle vil være i høj risiko for tilbagefald.
2. De beskrevne forskelle mellem en dansk population og ALINA studiepopulationen må forventes at være aktuelle for både alectinib og kemo-armen. Der må forventes samme risiko for overestimering af effekten af kemo-armen. I vurderingsrapporten tillægges risikoen for overestimering af alectinib højere vægt igennem rapporten - på trods af at ALINA studiet er et randomiseret studie der estimerer den relative effekt mellem alectinib og kemoterapi.
3. Sammenligning af den danske population sker på baggrund af alle danske NSCLC tilfælde i stadie IB-IIIA og der bør tages højde for at der er forskel på denne population og danske patienter med ALK+ NSCLC i stadie IB-IIIA samt den del af populationen med høj risiko for tilbagefald. Det kunne f.eks. være i forhold til udvikling af CNS-metastaser.
4. I forhold til den danske patientpopulation som ikke vil kunne opereres i henhold til danske retningslinjer men i stedet modtager kurativt intenderet kemoradioterapi, har de en væsentligt dårligere prognose end patienter med operable sygdom har (1). Disse patienter har i ALINA studiet fået operation og efterfølgende alectinib og har en væsentligt bedre DFS end de patienter som fik kemoterapi (1,2).

Vurdering af de forskellige endepunkter:

1. Vurdering af DFS (afsnit 2.3.3)
    a. Side 24 - Under vurderingen af DFS sammenlignes DFS data fra ALINA studiet med data fra et dansk abstract af Peter Meldgaard et al (3). Data i abstractet dækker over en lang bredere population end den relevante population der ansøges på, og der er derfor ikke direkte sammenligning med ALINA data, hvilket også beskrives i vurderingsrapporten. Det er uklart hvorfor abstractet stadig er inkluderet i vurderingen samt vurderes relevant at sammenligne med,

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da disse data hverken er peer-reviewed, er på en anden population samt at der er tale om en retrospektiv opgørelse. Abstractet lever ikke op til de krav som Medicinrådet sædvanligvis stiller til ansøgninger, og det er ikke klart hvordan dette abstract er identificeret.

2. Vurdering af OS (afsnit 2.3.4)
    a. Side 25 - Under vurderingen af OS bruges en metaanalyse på EGFR-hæmmere hos postoperative patienter med EGFR-muteret NSCLC til at konkludere at der ikke er korrelation imellem DFS og OS på adjuverende alecensa. EFGR og ALK er to forskellige undergrupper i lungekræft, som har visse ligheder, men som ikke er direkte sammenlignelige. Der er heller ingen generel korrelation mellem effekten af EFGR-hæmmer og ALK-hæmmere. Roche er derfor uforstående overfor brugen af denne metaanalyse i vurderingen af OS.Yderligere, stammer over 50% af patienterne/data i metaanalysen fra et meget tidligt data cut fra ADAURA (4), hvor forfatterne selv skriver at OS data er umodne, da < 5 % af patienterne var døde. Osimeritinib er efterfølgende blevet anbefalet af Medicinrådet, da netop korrelation mellem DFS og OS kunne påvises baseret på ADAURA. Vi opfordrer Medicinrådet til at inddrage den analyse af korrelation mellem DFS/PFS og OS på tværs af studier i NSCLC, som Roche har indsendt. Her indgår nyere data fra ADAURA samt en systematisk tilgang ift. Inddragelse af data/studier.
3. Vurdering af AE (afsnit 2.4)
    a. Side 28 - vurdering af AE - der tages ikke højde for den relativ store andel af patienter som stopper behandling pga AE´er i kemobehandling, dette især i betragtning af den korte eksponeringstid på 4 serier. Dette kan for patienter med restsygdom - øge risikoen for tilbagefald.
4. Samlet vurdering (afsnit 2.5)
    a. Side 29 - Imens vi afventer modne OS data fra ALINA studiet, mener Roche at der i den samlede vurdering bør anerkendes den nuværende kliniske værdi som minimum at tidsforskyde tilbagefald- da prognosen efter tilbagefald er en helt anden.

Sundhedsøkonomi.

1. Probabilistisk sensitivitetsanalyse.
    a. Vi undrer os over, at Medicinrådet ikke mener, at en PSA kan udføres. Det fremgår af vurderingen, at en PSA ikke kan udføres, da vi i Roche ikke har inkluderet relevante parametre i analysen, og her nævnes behandlingsvarighed, nytteværdier og treatment waning. Nytteværdierne er inkluderet i PSA'en. Treatment waning er et funktion/egenskab som Medicinrådet har introduceret i analysen, og ikke en del af Roches analyse. Det må derfor være Medicinrådet der også inkluderer dette i PSA'en. Slutteligt er behandlingsvarigheden inkluderet som KM-kurverne fra ALINA studiet og ikke et gennemsnit. Medicinrådet har ikke sædvanligt efterspurgt eller udført PSA analyse, hvor de respektive punkter på KM-kurverne justeres. Vi opfordrer derfor Medicinrådet til at udføre en PSA.
2. Korrelation mellem DFS og OS.
    a. Medicinrådet har efterspurgt Roche evidens og argumentation for korrelation mellem DFS og OS hos patienter med NSCLC, hvilket vi har efterlevet. Denne evidens fremgår ikke af Medicinrådet vurdering, men i stedet fremgår evidens, hvor det er uklart hvordan disse er identificeret. Vi opfordrer derfor Medicinrådet til at anvende den evidens som er efterspurgt, og som er systematisk fremsøgt.

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2 Wu YL, Dziadziuszko R, Ahn JS, et al. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2024;390(14):1265-1276. doi:10.1056/NEJMoa2310532
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4 Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020;383(18):1711-1723. doi:10.1056/NEJMoa2027071

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19.12.2024

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.01.2025
Leverandør	Roche
Lægemiddel	Alecensa (alectinib)
Ansøgt indikation	Adjuverende behandling af ALK-positiv ikke-småcellet lungekræft
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Alecensa (alectinib):

Tabel 1: Aftalepris

Lægemiddel	Styrke (Paknings-størrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Alecensa	150 mg (224 stk. kapsler)	33.269,72	[redacted]	[redacted]

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

*Tabel 1: Lægemiddeludgift pr. patient**

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Alecensa	150 mg (224 stk. kapsler)	600 mg 2 gange dagligt	[redacted]	[redacted]

*Jævnfør Medicinrådets vurderingsrapport, er komparator kemoterapi (4 serier cisplatin/carboplatin i kombination med vinorelbin i 3,84 måneder). Udgiften for komparator er minimal og er derfor ikke angivet i denne tabel.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Anbefalet		Link til anbefaling
England	Anbefalet		Link til anbefaling

Opsummering

[redacted].

Application for the assessment of alectinib (Alecensa) for ALK-positive early non-small cell lung cancer (NSCLC)

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

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Tables and Figures

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Abbreviations

ALK-positive	Anaplastic lymphoma kinase-positive
IV	Intravenous
NE	Not Estimated
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression free-survival
EGFR	Epidermal Growth Factor Receptor
KRAS	Kirsten RAt Sarcoma
CNS	Central Nervous System
NE	Not Estimated
CT	Computed Tomography
EML4	Echinoderm Microtubule-associated Protein-like 4
TKI	Tyrosine Kinase Inhibitor
BRAF	B-rapidly growing fibrosarcoma
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase
PD-L1	Programmed Cell Death Ligand 1
DLCG	Danish Lung Cancer Group
DLCR	Danish Lung Cancer Registry
DFS	Disease-free survival
DMC	Danish Medicines Council
CNS-DFS	Time to central nervous system recurrence or death
SLR	Systematic Literature Review
CEA	Cost-Effectiveness Acceptability
INV-DFS	Investigator??ssessed DFS
BID	Bis in die (twice a day)
CCOD	Clinical cut-off date
iDMC	independent Data Monitoring Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
PH	Proportional Hazard
AIC	Akaike Information
BIC	Bayesian Information Criterion
IPD	Individual Patient Data
95% CI	95 % Confidence Interval
AE	Adverse Event
SAE	Serious Adverse Event
HRQoL	Health-Related Quality of Life
PRO	Patient-Reported Outcomes
ITT	Intention to treat
PCS	Physical Component Summary
MCS	Mental Component Summary
MIDs	Minimal Important Differences
HSUV	Health state utility values
EQ-5D-5L	EuroQol 5-dimension, 5-level questionnaire
SF-36v2	Short Form-36 version 2
DRG	Diagnose Relative Group
PPP	Pharmacy Purchase Prices
DSA	Deterministic Sensitivity Analyses
PSA	Probabilistic Sensitivity Analyses
CEAC	cost-effectiveness acceptability curves
QALY	Quality Adjusted Life Year
ICER	Incremental cost per QALY gained

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Alecensa
Generic name	Alectinib
Therapeutic indication as defined by EMA	Alecensa as monotherapy is indicated as adjuvant treatment following tumor resection for adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) with high risk of recurrence. Alecensa as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC. Alecensa as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib
Marketing authorization holder in Denmark	Roche Pharmaceuticals A/S
ATC code	L01ED03
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	June 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	• Alecensa as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC. • Alecensa as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

Other indications that have been evaluated by the DMC (yes/no)	Yes, the following indication has been evaluated and is recommended by the DMC: Alecensa as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Aluminum/aluminum (PA/Alu/PVC/Alu) blisters containing 8 hard capsules. Pack size: 224 (4 packs of 56) hard capsules. One capsule contains 150 mg alectinib.

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Alecensa as monotherapy is indicated as adjuvant treatment following tumor resection for adult patients with ALK-positive NSCLC with high risk of recurrence.
Dosage regiment and administration	The recommended dose of Alecensa is 600 mg taken twice daily with food (total daily dose of 1200 mg). Treatment with Alecensa in the adjuvant setting should be continued until disease recurrence, unacceptable toxicity or for 2 years.
Choice of comparator	Adjuvant platinum-based chemotherapy: ● Drug: Cisplatin ○ Cisplatin 75 milligrams per square meter (mg/m^2) on Day 1 every 21 days IV intravenously (IV) until completion of treatment period (four 21-day cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. In combination with one of the following: ● Drug: Vinorelbine ○ Vinorelbine 25 mg/m^2 IV on Days 1 and 8 Q21D until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. ● Drug: Gemcitabine ○ Gemcitabine 1250 mg/m^2 on Days 1 and 8 Q21D IV until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. ● Drug: Pemetrexed ○ Pemetrexed 500 mg/m^2 Day 1 Q21D until completion of treatment period (4 cycles), recurrence of disease,

	unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. For participants who experience unacceptable toxicity with cisplatin, carboplatin can be used. In Denmark, treatment of early ALK-positive NSCLC is limited to surgery followed by platinum-based chemotherapy namely cisplatin and vinorelbine (1). Immunotherapy is not recommended for patients without known ALK-positive NSCLC in neither the neoadjuvant setting nor adjuvant setting (2, 3).
Prognosis with current treatment (comparator)	Patients with ALK-positive NSCLC account for a relatively small population group in Denmark and currently, no data on the prognosis for Danish patients with ALK-positive early NSCLC is available. However, data has shown that patients with ALK-positive early NSCLC have a trend towards poorer outcomes as compared to other molecular actionable targets such as epidermal growth factor receptor (EGFR) and Kirsten RAt Sarcoma (KRAS) but data is limited and shows conflicting results (4, 5). In the metastatic setting, development of Central Nervous System (CNS) metastasis in ALK-positive NSCLC patients has been found - leading to poorer survival and poorer quality of life (6). However, Alecensa has shown efficacy against CNS metastasis in both metastatic and early ALK-positive NSCLC patients leading to a better prognosis (7, 8).
Type of evidence for the clinical evaluation	Head-to-head study.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Intention to treat (ITT) population** *Median DFS* Alectinib: Not Estimated (95% CI: NE, NE) Chemotherapy: 43.1 (95% CI:28.5, NE) HR: 0.24 (95% CI: 0.13–0.43) *Median OS* Alectinib: NE (95% CI: NE, NE) Chemotherapy: NE (95% CI: NE, NE) HR: 0.46 (95% CI: 0.08, 2.25) *Median CNS-DFS* Alectinib: NE (95% CI: NE, NE) Chemotherapy: NE (95% CI: NE, NE) HR: 0.22 (95% CI: 0.08-0.58) **Stage II-IIIA subpopulation** *Median DFS* Alectinib: NE (95% CI: NE, NE) Chemotherapy: 44.4 (95% CI: 27.8, NE) HR: 0.24 (95% CI: 0.13, 0.45)

	Median OS Alectinib: NE (95% CI: NE, NE) Chemotherapy: NE (95% CI: NE, NE) HR: 0.96 (95% CI: 0.14, 6.82) *Median CNS-DFS* Alectinib: NE (95% CI: NE, NE) Chemotherapy: NE (95% CI: NE, NE) HR: 0.24 (95% CI: 0.09-0.65)
Most important serious adverse events for the intervention and comparator	Pneumonia Alectinib: 2.3% Chemotherapy: 0.8% Appendicitis Alectinib: 3.1% Chemotherapy: 0% Nausea Alectinib: 0% Chemotherapy: 1.7% Neutrophil count decreased Alectinib: 0% Chemotherapy: 1.7% Acute myocardial infarction Alectinib: 1.6% Chemotherapy: 0%
Impact on health-related quality of life	Equal with tendency towards improvement
Type of economic analysis that is submitted	Cost utility analysis
Data sources used to model the clinical effects	Alina Study (NCT03456076) (9)
Data sources used to model the health-related quality of life	Alina Study (NCT03456076) (9)
Life years gained	4.27 years
Quality Adjusted Life Year (QALY)s gained	3.57 QALY
Incremental costs	334,348 DKK
ICER (DKK/QALY)	93,699 DKK/QALY

Uncertainty associated with the ICER estimate	The number of patients progressing from adjuvant treatment to metastatic treatment.
Number of eligible patients in Denmark	Approximately 8-10 new patients a year (10)
Budget impact (in year 5)	3.2 mio. DKK

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

3.1 The medical condition

Lung cancer is the most deadly cancer disease in Denmark. In 2022, 5043 Danish patients were diagnosed with lung cancer making the disease one of the most frequent cancer diseases (11, 12). More than 80% of the diagnosed patients have NSCLC and among these patients, approximately 50% have localized (stage I and II) or locally advanced (stage III) disease at the time of diagnosis. Early stage NSCLC is a potentially curative setting where complete tumor resection is still feasible (13, 14).

Early stage NSCLC cancer is typically asymptomatic, with relatively few disease-related symptoms. In Denmark it is defined that for one or more of the following symptoms in persons over 40 years of age with relevant tobacco anamnesis, lung cancer may be suspected and the doctor should consider referring to computed tomography (CT) scans with contrast of thoracic and upper abdomen (15):

- Cough of more than 4-6 weeks duration in a previously pulmonary injury person or changes in the coughing pattern of a person with chronic bronchitis
- Newly arrived shortness of breath with abnormal spirometry with no other obvious explanation for this
- Haemoptysis (regardless of age) and tobacco anamnesis
- Stridor of unknown cause should lead to CT of thoracic and upper abdomen, spirometry and laryngo-bronchoscopy
- General symptoms in the form of fatigue, lack of appetite, weight loss, thrombocytosis
- Other symptoms of lung cancer may be sputum, chest pain, pneumonia, pleural effusion, stokes collar, neuropathy, bone pain and drumstick fingers, shoulder pain

- Hoarseness of more than 3-4 weeks duration without other accompanying symptoms may be a symptom of lung cancer, however, should be examined primarily by an otologist on suspicion of larynx cancer.

In Denmark if lung cancer is suspected, the patient is referred to ”lungekræft i pakkeforløb” (15, 16).

ALK-positive NSCLC

The ALK fusion oncogene is the result of fusion with another partner gene, where the Echinoderm Microtubule-associated Protein-like 4 (EML4) gene is the most common ALK fusion partner and represents a distinct subset of NSCLC (17-19). Based on evidence from patients with advanced or metastatic ALK positive NSCLC, this disease is to some degree associated with specific features such as a never- or light-smoking history, younger age, and adenocarcinoma subtype. ALK-positive NSCLC is often diagnosed at an advanced stage, and more likely to spread to the brain and lymph nodes, indicating a more aggressive tumor biology and disease outcome. Currently available evidence in resected ALK-positive NSCLC suggests similar clinical and social features to that described for advanced ALK-positive NSCLC (4, 18, 20, 21).

In 2023 Holmskov et al., (22) investigated the clinical outcomes of all ALK-positive NSCLC patients in Denmark. Patients were identified using the national pathology database and a total of 209 patients was included in the analysis independent of disease stage. Patients with stage I–IIIA disease accounted for 30% of the study population and OS was not reached (22).

Early-Stage Resected ALK-positive NSCLC

Analyses of the prognostic value of ALK in early-stage NSCLC are conflicting possibly due to small sample sizes and confounders such as the availability and choice of targeted therapy after relapse and differing baseline characteristics between ALK-positive and wild type cohorts such as smoking history (18, 19). Irrespective of the prognostic value of ALK, despite curative-intent surgery followed by conventional adjuvant chemotherapy, many ALK-positive patients will suffer cancer recurrence. Given the success of ALK inhibitor therapy in the advanced and metastatic setting, there is a strong rationale to apply this treatment in the early setting.

Disease recurrence

NSCLC is associated with poor survival even when the diagnosis is made at an early stage due to a high risk of micro metastasis (23). Disease recurrence is common in patients with early-stage NSCLC, even with adjuvant treatment. The five-year recurrence-free survival rate varies depending on the stage of the disease, ranging from 34% for stage III to 80% for stage I to II. Distant recurrence, which is more common than local recurrence, is associated with shorter survival. Patients with lung cancer often experience psychological and social symptoms, such as fear of recurrence, and advanced disease has a significant humanistic burden. Reducing the risk of recurrence and extending disease-free survival is an important goal of therapy (23).

In ALK-positive NSCLC, recurrence in the CNS is particularly prevalent, affecting 50-60% of patients. Brain metastases can cause a variety of disturbing symptoms, including headache, seizures, stroke, loss of neurologic functions from focal neurologic deficits, and considerable loss of autonomy due to neurocognitive and functional deficits. Consequently, brain metastases have a negative impact on prognosis, leading to increased

morbidity and mortality, and significant impairment of quality of life. Current management involves various treatments but conventional local treatments may have limitations, and there can be acute and chronic complications. The use of new generation ALK Tyrosine Kinase Inhibitors (TKI) has shown improved control of brain metastasis. Overall, addressing disease recurrence and managing brain metastases are crucial aspects of treating NSCLC, and advancements in systemic therapies provide hope for better outcomes (9).

3.2 Patient population

The Danish patient population expected to be candidates for adjuvant alectinib is resected ALK-positive NSCLC patients with high risk of disease recurrence.

The following selection criteria define patients with high risk of disease recurrence who are included in the therapeutic indication, and are reflective of the patient population with Stage IB (tumours ≥ 4 cm) – IIIA NSCLC according to the 7th Edition UICC/AJCC staging criteria:

- Tumour size ≥ 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

ALINA (BO40336) did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

In Denmark, the recommendation in the clinical guidelines is to reflex test ALK (among other mandatory biomarkers) at the primary diagnosis for adenocarcinoma plus non-small cell carcinoma, and where the type cannot be definitely decided (16). Further, in minutes from a DaLuPa meeting in January 2022 it is stated that reflex testing for EGFR, ALK, ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), B-rapidly growing fibrosarcoma (BRAF), KRAS and Programmed Cell Death Ligand 1 (PD-L1) is recommended upfront at primary diagnosis for non-squamous NSCLC (24). This to determine suitability for treatment with immunotherapy and targeted therapies.

However, according to Danish expert and the annual lung cancer report, testing of patients in the early setting and for the adjuvant setting is not performed regularly, and testing depends on the oncology department, patient characteristics and tissue available (10, 12). The latest published yearly report by the Danish Lung Cancer Group (DLCG) from the Danish Lung Cancer Registry (DLCR), reports that 36 patients were tested ALK-positive in 2022 which corresponds to 1.6% of all patients tested for ALK (11).

In 2022, 1,245 Danish lung cancer patients underwent resection (surgery exclusive explorative operations). In the same year, the five-year survival rate after surgery was assessed to be 62.9%. For patients undergoing resection at least 9 out of 10 are alive 1 year after surgery, at least 4 out of 5 are alive after 2 years (11).

The ALINA (BO40336) study is the first and only to demonstrate that an adjuvant ALK-inhibitor shows a statistically significant and clinically meaningful improvement in DFS compared with chemotherapy across patients with resected stage IB, II and IIIA ALK+ NSCLC (9). The effect of treatment with alectinib was observed in patients with resected stage IB, II and IIIA ALK-positive NSCLC.

Danish experts have stated that alectinib in the adjuvant setting could fit into the Danish practice and thereby offer a valuable benefit for Danish ALK-positive NSCLC patients with high risk of disease recurrence after surgery. They expect approximately 8-10 patients a year would be candidates for alectinib as adjuvant treatment (10).

As ALK testing and registration in patients with early stage lung cancer has not been standard practice, the incidence will be an estimate based on number of patients with early stage disease, ALK positivity rate and expert opinion. Please refer to Table 1 and Table 2.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark (Lung Cancer) [Ref: DLCG Årsrapport 2022]	4996	4903	5108	5043	Not published yet
Prevalence in Denmark [Nordcan]	13783	14525	15395	N/A	N/A
Number of resections (all pathologies) [Ref: DLCG Årsrapport 2022]	[redacted]	[redacted]	[redacted]	[redacted]	Not published yet
ALK positivity rate [XXXX based on testing in advanced setting] [Ref: DLCG Årsrapport 2022]	[redacted]	[redacted]	[redacted]	[redacted]	Not published yet
Global prevalence*	NA	NA	NA	NA	NA

*Due to global difference in the prevalence of ALK it is not possible calculate exact global numbers

Table 2 Estimated number of patients eligible for treatment

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are eligible for treatment in the coming years	8	8	8	8	8

3.3 Current treatment options

The earlier the stage at the time of diagnosis, the better the prognosis. In Denmark early stage NSCLC is treated surgically with curative intent. For patients with stage I, NSCLC surgical treatment alone is the standard of care. For stage II-III there is a higher risk of disease recurrence and therefore resected patients in these stages are referred to the oncological departments for assessment on eligibility for adjuvant chemotherapy. Patients with stage IIA with a tumortumour diameter of > 4 cm (T2b) should also be considered referred to the oncological department (1).

The current standard adjuvant treatment in Denmark are initiated within 6-8 weeks after surgery and consists of four series of platinum doublet. This can reduce risk of micro metastases and improve survival outcomes compared to surgery alone. The standard of care is cisplatin and vinorelbine, but if the patient is not fit for cisplatin this can be substituted with carboplatin (1).

In 2021, approximately 22% of NSCLC patients undergoing surgery received adjuvant oncological treatment and it is expected that the number of patients receiving multimodal treatment in the early setting will increase in the coming years due to the expected introduction of immunotherapy (3).

3.4 The intervention

Alectinib is a highly selective and potent ALK tyrosine kinase inhibitor.

Overview of intervention (25)	
Therapeutic indication relevant for the assessment	Alecensa as monotherapy is indicated as adjuvant treatment following tumor resection for adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC).
Method of administration	Oral
Dosing	The recommended dose of Alecensa is 600 mg taken orally twice daily with food (total daily dose of 1200 mg).
Dosing in the health economic model (including relative dose intensity)	100%
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment with Alecensa in the adjuvant setting should be continued until disease recurrence, unacceptable toxicity or for 2 years.
Necessary monitoring, both during administration and during the treatment period	Standard of care
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	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. ALK-testing of NSCLC patients is applied in the Danish practice. No additional test are necessary.
Package size(s)	Aluminum/aluminum (PA/Alu/PVC/Alu) blisters containing 8 hard capsules. Pack size: 224 (4 packs of 56) hard capsules. One capsule contains 150 mg alectinib.

3.4.1 The intervention in relation to Danish clinical practice

The current adjuvant treatment algorithm for NSCLC in Denmark in currently chemotherapy, potentially follow by immunotherapy depending on PD-L1 status and lack of EFGR

mutations or ALK-translocations (26). For the subset of ALK-positive NSCLC patients in Denmark, adjuvant treatment will instead be alectinib for up to 2 years. Several ALK-positive inhibitors are recommended by the Danish Medicines Council (DMC) in the advanced or metastatic setting e.g. Crizotinib, Brigatinib, Lorlatinib as well as alectinib (27). Additional information of the impact of later treatment lines depending on type of disease recurrence is described later in this application.

3.5 Choice of comparator(s)

Overview of comparator	
Generic name	Cisplatin
ATC code	L01XA01
Mechanism of action	Cisplatin inhibits DNA synthesis by producing intrastrand and interstrand cross links in DNA. Protein and RNA synthesis are also inhibited to a lesser extent. Although the principal mechanism of action of cisplatin appears to be inhibition of DNA synthesis, other mechanisms, including enhancement of tumor immunogenicity, may be involved in its antineoplastic activity. Cisplatin also has immunosuppressive, radio sensitising, and antimicrobial properties.
Method of administration	Intravenous infusion.
Dosing	A typical dose is 20 mg/m^2 BSA or more when cisplatin is used in combination therapy.
Dosing in the health economic model (including relative dose intensity)	100 %
Should the medicine be administered with other medicines?	Yes
Treatment duration/ criteria for end of treatment	Until the completion of the treatment period (4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	10 mg/10 ml, 50 mg/50 ml and 100 mg/100 ml presentations in Type I amber glass vials and Onco-Tain vials. Packs contain a single vial.

Overview of comparator	
Generic name	Vinorelbine
ATC code	L01CA04

Overview of comparator	
Mechanism of action	Vinorelbine is a cytostatic drug of the vinca alkaloid family. Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. The induction of the tubulin spiralization is less than that produced by vincristine. Vinorelbine blocks mitosis at phase G2-M, causing cell death in interphase or at the following mitosis
Method of administration	Intravenous infusion
Dosing	Typically, 25-30 mg/m^2 body surface area, administered once weekly.
Dosing in the health economic model (including relative dose intensity)	100 %
Should the medicine be administered with other medicines?	Yes
Treatment duration/ criteria for end of treatment	Until the completion of the treatment period (4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	1 ml of concentrate for solution for infusion : 1 vial 5 ml of concentrate for solution for infusion : 1 vial

Overview of comparator	
Generic name	Gemcitabine
ATC code	L01BC05
Mechanism of action	Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation). Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is

	essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.
Method of administration	Intravenous infusion
Dosing	1,250 mg/m^2 body surface area on Days 1 and 8 of the treatment cycle (21 days).
Dosing in the health economic model (including relative dose intensity)	100 %
Should the medicine be administered with other medicines?	Yes, cisplatin has been used at doses between 75-100 mg/m^2 once every 3 weeks.
Treatment duration/ criteria for end of treatment	Until the completion of the treatment period (4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	Cartons each holding 1, 5 or 10 single-dose infusion bags of 120 ml, 130 ml, 140 ml, 150 ml, 160 ml, 170 ml, 180 ml, 200 ml or 220 ml, respectively.

Overview of comparator	
Generic name	Pemetrexed
ATC code	L01BA04
Mechanism of action	Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.
Method of administration	Intravenous infusion
Dosing	500 mg/m^2 of body surface area administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.
Dosing in the health economic model (including relative dose intensity)	100 %

Should the medicine be administered with other medicines?	Corticosteroid; should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day. Vitamin supplementation; oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) must be taken on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.
Treatment duration/ criteria for end of treatment	Until the completion of the treatment period (4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	Powder in Type I glass vial. Rubber stopper. Pack of 1 vial.

3.6 Cost-effectiveness of the comparator(s)

The comparator is a four 21-days cycles of chemotherapy. Chemotherapy as adjuvant treatment for ALK+ patients have not been evaluated by the DMC as the treatment was implemented before the existence of DMC. However, is has been the standard treatment for patients for a long time. At the same time the costs of a chemotherapy treatment regimen of four 21 days cycle are low. Thus, chemotherapy would be considered highly cost-effective, and an additional cost-effectiveness analysis of chemotherapy has not been carried out. According to the guidelines of the DMC (28).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application (9).

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
Disease-free survival (DFS) **ALINA (BO40336)**	CCOD: June 26, 2023 Follow-up: 30.88	DFS is defined as the time from randomization to the first documented recurrence of disease or new primary	Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm, and the Kaplan-

	months (sd: 12.71))	NSCLC or death from any cause, whichever occurs first	Meier curve will be constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm
Overall survival (OS) **ALINA (BO40336)**	CCOD: June 26, 2023 Follow-up: 30.88 months (sd: 12.71))	OS is defined as the time from randomization to death from any cause.	Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm, and the Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm
Time to central nervous system recurrence or death (CNS-DFS) **ALINA (BO40336)**	CCOD: June 26, 2023 Follow-up: 30.88 months (sd: 12.71))	CNS-DFS is defined as the time from randomization to the first documented recurrence of disease in the CNS or death from any cause, whichever occurred first.	Same as for DFS.

Validity of outcomes
Both the primary endpoint DFS, secondary endpoint OS and exploratory endpoint CNS-DFS are validated, well established endpoints within oncology and have been assessed multiple times by DMC.

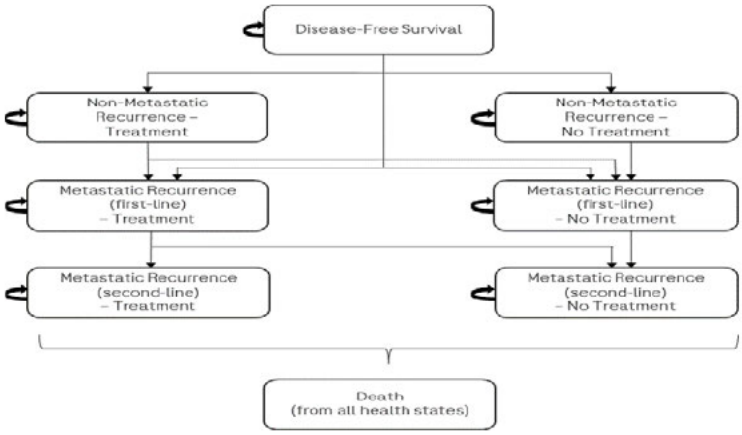
4. Health economic analysis

4.1 Model structure

A systematic literature review (SLR) was conducted to identify and summarise the modelling methods and structures that have been used to evaluate the cost-effectiveness of early-stage NSCLC interventions. The SLR identified 36 studies that conduct an economic evaluation of which only 25 studies utilise an economic model. The majority of these studies utilised a Markov model (Markov model = 17, microsimulation = 7, decision tree = 1). In terms of the structure and assumptions made, however, considerable variation exists across them (e.g. time horizon: 1 year-lifetime; cycle length: 1 month-1 year). Due to this variation, the CEA does not only leverage these past studies to inform certain aspects of the model, but also bases decisions on certain matters on what it deemed was the most appropriate choice from a clinical and economic standpoint.

The CEA utilises a cohort-level semi-Markov model. In comparison to the use of a cohort-level decision tree, the advantage of a Markov model is that the elapse of time is not implicit and cumbersome to model. This is especially an issue in the case of early-stage NSCLC where we can expect the majority of patients to survive for many years before experiencing an event. However, in comparison to an individual-level model, a limitation of a cohort-level model is that health states do not implicitly have memory on what point in time and from which health state a patient had made their transition. This prevents the model from being able to account for the history of patients in determining health state transitions, healthcare resource use and costs and quality of life. Despite this limitation, individual-level based models are more complicated mathematically and data intensive and, therefore, considered overly complex for the stated decision problem.
As per the DMC guidance (28), the cost-effectiveness analysis applied a restricted Danish societal perspective, using the best available clinical and economic evidence. Local Danish data inputs were used wherever available. The current model was based on results from the ALINA trial.

Figure 1 Health State Diagram of the Cost-Effectiveness Model



4.2 Model features

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Intent-to-treat (stage Ib (tumour size ≥ 4cm)-IIIa ALK-positive NSCLC)	Study population from ALINA (BO40336) Clinical cut-off date (CCOD): June 26, 2023 (9).
Perspective	Limited societal perspective	According to DMC guidance (28).
Time horizon	Lifetime (40 years)	To capture all health benefits and costs in line with DMC guidelines (28). Based on mean age at diagnosis in the Danish population (40 years).

		Validated by Danish clinical expert.
Cycle length	Monthly	The CEA uses a short cycle length to granularly capture transitions without half-cycle corrections.
Half-cycle correction	No	Monthly cycle length is enough to capture differences.
Discount rate	3.5 %	According to DMC guidance (28).
Intervention	ALECENSA (Alectinib)	
Comparator(s)	Platinum-based chemotherapy	According to national treatment guidelines. Validated by Danish clinical expert (10).
Outcomes	OS, DFS, PFS and HRQoL	

4.3 Time Horizon

The DMC method guideline states that the selected time horizon should be long enough to reflect all important differences in costs and efficacy between the technologies being compared. The model uses a lifetime horizon of 40 years, considered to represent a lifetime horizon for patients. Given the mean age of 55 years in the ALINA trial, 40 years was considered a fair approximation of a lifetime time horizon.

4.4 Perspective

The perspective of the economic model is a restricted Danish societal perspective, which includes costs related to drug acquisition, drug administration, monitoring, adverse events & supportive care. Indirect costs are not included in line with the DMC's guidelines (28).

5. Overview of literature

5.1 Literature used for the clinical assessment

This application is based on the head-to-head study ALINA (BO40366) which compare adjuvant alectinib with platinum-based chemotherapy in patients with resected ALK-positive NSCLC. Hence, a systematic literature review has not been performed.
Data from the interim analysis of ALINA (BO40366) have been published in NEJM, April 2024 (9). Details are listed in Table 5 below.

Table 5 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*
Full paper Yi.Long W et al., Alectinib in Resected ALK-Positive Non–Small-Cell Lung Cancer. NEJM. 2024 Apr; 390(14): 1265-1276. (9)	ALINA	NCT03456076	Start: 16/08/18 Completion: 19/11/26 Data cut-off: 26/06/23 Future data cut-off: 30/11/26	Adjuvant alectinib vs. platinum-based chemotherapy for patients with ALK- positive NSCLC

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

Health-related quality of life data was obtained from the ALINA study with the intervention and comparator of interest. See section 10.1

5.3 Literature used for inputs for the health economic model

Two SLRs has been conducted to inform the health economic analysis. One SLR to identity clinical efficacy of ALK+ treatments in NSCLC and one SLR to identity utility of subsequent treatment line. This SLRs is outlined in in appendix I and J. All external literature used in the health economic model is identified through those SLRs – expect for Danish unit costs.

Table 6 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
Camidge D, 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. Journal of Thoracic Oncology. 2019:1233-43 Camidge D, Kim H, Ahn M, Yang J, Han J, Hochmair M, et al. Brigatinib versus crizotinib in ALK inhibitor–naive advanced ALK-positive NSCLC: Final results of phase 3 ALTA-1L trial. Journal of Thoracic Oncology. 2021:2091-108 (Solomon B, Mok T, Kim D, Wu Y, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. The New England journal of medicine. 2014:2167-77 (Solomon B, Bauer T, Mok T, 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 Respiratory Medicine. 2023:354-66. (30)	OS and PFS in 1L Targeted literature review	Section 8.1.2	8.2.2.2.3
Novello S, Mazieres J, Oh I, de Castro J, Migliorino M, Helland A, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Annals of Oncology. 2018:1409-16 (31)	OS and PFS in 2L	Targeted literature review	8.2.2.2.4

Nakamichi S, Horinouchi H, Asao T, Goto Y, Kanda S, Fujiwara Y, et al. Comparison of radiotherapy and chemoradiotherapy for locoregional recurrence of non-small cell lung cancer developing after surgert. Clinical Lung Cancer. 2017 (32)	OS and PFS in non-metastatic recurrence	Targeted literature review	8.2.2.2.2
Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. *J Thorac Oncol*. 2013 (33)	Utility value after recurrence	Targeted literature review	10.2

6. Efficacy

6.1 Efficacy of alectinib compared to platinum-based chemotherapy regimens for patients with ALK-positive early NSCLC

6.1.1 Relevant studies

ALINA (BO40336) is a phase III, global, multicenter, open-label, randomized, study comparing the efficacy and safety of alectinib versus platinum-based chemotherapy as adjuvant therapy in patients with completely resected, stage IB–IIIA, ALK-positive NSCLC. The primary endpoint of the study is investigator-assessed DFS (INV-DFS). Overall survival (OS) and safety were secondary endpoints while time to CNS recurrence or death (CNS-DFS) was an exploratory endpoint.

Patients aged ≥18 years with completely resected (negative margins), histologically-confirmed, Stage IB-IIIA NSCLC, as per the Union Internationale Contre le Cancer/ American Joint Committee on Cancer 7th edition (UICC/AJCC 7th edition) (34), with documented ALK-positive disease as assessed by an FDA-approved and Conformité Européenne (CE)-marked test and meeting all required eligibility criteria, were enrolled in ALINA. Eligible patients were stratified by extent of disease (stage IB [tumors ≥4 cm] vs. stage II vs. stage IIIA) and race (Asian vs. non-Asian).

Patients with Stage IB NSCLC with tumors ≥4 cm per the UICC/AJCC 7th edition classification have been shown to experience more modest benefit from adjuvant chemotherapy treatment than patients with Stage II−IIIA NSCLC; this fact was taken into consideration for recruitment capping, stratification, and statistical analysis of the primary endpoint (se details below).

Screening and randomization occurred 4 to 12 weeks after patients had undergone complete surgical resection (lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy). Patients were randomized in a 1:1 fashion to receive either alectinib 600 mg orally twice a day (BID) or four 21-days cycles of one of the following platinum-based chemotherapy combinations:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1.

In case of intolerability to a cisplatin-based regimen, carboplatin was administered instead of cisplatin. Alectinib and platinum-based chemotherapy were administered until the completion of the treatment period that is 24 months for alectinib and four 21-days cycles for chemotherapy regimens, until recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first. Patients who completed a study treatment regimen or discontinued treatment prior to disease recurrence continued to be followed until disease recurrence. Data collection continues for each patient until death or study closure, whichever occur first. After disease recurrence, patients were treated at the discretion of the investigator according to local clinical practice. No crossover was allowed between the two arms.

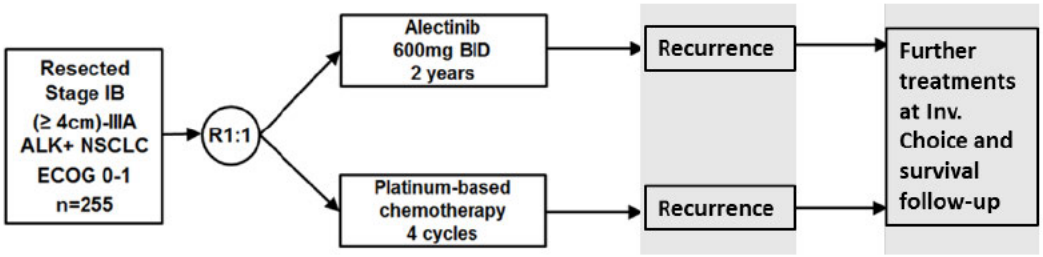


Figure 2: ALINA (BO40336) study design. ALK+ - anaplastic lymphoma kinase-positive; NSCLC – non-small cell lung cancer; ECOG - Eastern Cooperative Oncology Group; BID – twice a day.

A total of 257 patients were randomized and included in the ITT population (130 in the alectinib arm and 127 in the chemotherapy arm). A total of 231 patients had stage II–IIIA NSCLC (116 patients in the alectinib arm and 115 in the chemotherapy arm). The safety-evaluable population included 248 patients who underwent randomization and received any amount of study treatment (128 in the alectinib arm and 120 in the chemotherapy arm) (Table 7).

Table 7: Number of patients in the in the alectinib and chemotherapy arm in ITT population, stage II-IIIA subpopulation and safety-evaluable population.

	Alectinib n=130	Chemotherapy n=127	All Patients n=257
Intent-to-treat patients	130	127	257
Stage II-IIIA patients	116	115	231
Safety-evaluable patients (Treatment Received)	128	120	248

In this application a pre-specified interim analysis with CCOD of June 26, 2023, is presented. The pre-specified interim analysis of INV-DFS was conducted at the CCOD, where 59 DFS events (67%) for the stage II-IIIA subpopulation and 65 DFS events for the ITT

population were observed. The pre-specified DFS interim analysis was conducted by an independent Data Monitoring Committee (iDMC) and the stopping boundaries for both populations were crossed at which point the analysis became the primary analysis for the study. Data has been presented at the 36. Deutscher Krebskongress, February 2024 (35) and published by Wu Y-L et al. in New England Journal of Medicine, April 2024 (9).

Table 8: 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 period
ALINA, NCT03456076 (9)	Phase III, global, multicenter, open-label, randomized, study of alectinib versus platinum-based chemotherapy as adjuvant therapy	Patients will receive alectinib for max. 24 months follow by a follow-up period. Start: August 16, 2018 Estimated completion: November 19, 2026 CCOD: June 26, 2023	Patients with completely resected, stage IB□IIIA, ALK-positive NSCLC	Alectinib 600 mg orally twice daily until completion of treatment period (24 months) or recurrence of disease, unacceptable toxicity, withdrawal of consent or death, whichever occurs first.	Platinum-based chemotherapy: Cisplatin 75 mg/m^2 on Day 1 every 21 days IV intravenously (IV) until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. in combination with either of the following: Vinorelbine 25 mg/m^2 IV on Days 1 and 8 Q21D until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. Gemcitabine 1250 mg/m^2 on Days 1 and 8 Q21D IV until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. Pemetrexed 500 mg/m^2 Day 1 Q21D until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. For participants who experience unacceptable toxicity with cisplatin, carboplatin is used.	INV-DFS [Time Frame: from the date of randomization until the first DFS event, up to approximately 5 years] OS [Time Frame: From the date of randomization until death due to any cause up to approximately 8 years] Plasma Concentration of Alectinib [Time Frame: Predose (2 hours) at Baseline, Week 3, 6, 9, 12, 24, 36, 48, 60, 72, 84, and 96] Plasma Concentration of Alectinib metabolite [Time Frame: Predose (2 hours) at Baseline, Week 3, 6, 9, 12, 24, 36, 48, 60, 72, 84, and 96] Percentage of participants with adverse advent [Time Frame: From the date of randomization up to approximately 2 years]

6.1.2 Comparability of studies

ALINA (BO40336) is a head-to-head study which provide a direct comparison of alectinib and platinum-based chemotherapy regimens.

6.1.2.1 Comparability of patients across studies

The ITT population was evenly balanced between male patients (47.9%) and female patients (52.1%), with a median patient age of 56.0 years (range: 26−87 years). Most patients (76.3%) were <65 years of age. All patients had a baseline ECOG performance status (PS) of 0 (53.3%) or 1 (46.7%), and most had never smoked (59.9%) (36).
Patient demographics and baseline characteristics were generally well balanced between the alectinib and chemotherapy arms in the ITT population. Compared with the chemotherapy arm, the alectinib arm had a higher proportion of female patients (57.7% in the alectinib arm vs. 46.5% in the chemotherapy arm) and never-smokers (64.6% in the alectinib arm vs. 55.1% in the chemotherapy arm) (Table 9) (36).

Similar results were observed in the stage II-IIIA subpopulation (36).

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (36).

ALINA (BO40335)						
	Alectinib, ITT population n=130	**Chemotherapy, ITT population n=127**	**All patients, ITT population n=257**	**Alectinib, subpopulation stage II-IIIA n=116**	**Chemotherapy, subpopulation stage II-IIIA n=115**	**All patients, subpopulation stage II-IIIA n=231**
Median age, years (min-max)	54.0 (26-80)	57.0 (33-87)	56.0 (26-87)	54.0 (26-80)	57.0 (33-87)	56.0 (26-87)
Age group – n (%)						
< 65	103 (79.2%)	93 (73.2%)	196 (76.3%)	93 (80.2%)	84 (73.0%)	177 (76.6%)
≥ 65	27(20.8%)	34 (26.8%)	61 (23.7%)	23 (19.8%)	31 (27.0%)	54 (23.4%)
Gender – n (%)						
Female	75 (57.7%)	59 (46.5%)	134 (52.1%)	66 (56.9%)	53 (46.1%)	119 (51.5%)
Male	55 (42.3%)	68 (53.5%)	123 (47.9%)	50 (43.1%)	62 (53.9%)	112 (48.5%)
Race						
Asian	72 (55.4%)	71 (55.9%)	143 (55.6%)	68 (58.6%)	68 (59.1%)	136 (58.9%)
Non-Asian	58 (44.6%)	56 (44.1%)	114 (44.4%)	48 (41.4%)	47 (40.9%)	95 (41.1%)
ECOG PS at baseline						
0	72 (55.4%)	65 (51.2%)	137 (53.3%)	63 (54.3%)	61 (53.0%)	124 (53.7%)
1	58 (44.6%)	62 (48.8%)	120 (46.7%)	53 (45.7%)	54 (47.0%)	107 (46.3%)
Tobacco use history						

ALINA (BO40335)						
	Alectinib, ITT population n=130	**Chemotherapy, ITT population n=127**	**All patients, ITT population n=257**	**Alectinib, subpopulation stage II-IIIA n=116**	**Chemotherapy, subpopulation stage II-IIIA n=115**	**All patients, subpopulation stage II-IIIA n=231**
Never	84 (64.6%)	70 (55.1%)	154 (59.9%)	76 (65.5%)	63 (54.8%)	139 (60.2%)
Current	5 (3.8%)	3 (2.4%)	8 (3.1%)	5 (4.3%)	3 (2.6%)	8 (3.5%)
Previous	41 (31.5%)	54 (42.5%)	95 (37.0%)	35 (30.2%)	49 (42.6%)	84 (36.4%)
Initial diagnosis staging per AJCC 7th edition						
Stage IB	14 (10.8%)	12 (9.4%)	26 (10.1%)	N/A	N/A	N/A
Stage II	47 (36.2%)	45 (35.4%)	92 (35.8%)	47 (40.5%)	45 (39.1%)	92 (39.8%)
Stage IIIA	69 (53.1%)	70 (55.1%)	139 (54.1%)	69 (59.5%)	70 (60.9%)	139 (60.2%)
Primary tumor stage per AJCC 7th edition						
T1a	30 (23.1%)	37 (29.1%)	67 (26.1%)	30 (25.9%)	36 (31.3%)	66 (28.6%)
T1b	21 (16.2%)	22 (17.3%)	43 (16.7%)	21 (18.1%)	22 (19.1%)	43 (18.6%)
T2a	59 (45.4%)	47 (37.0%)	106 (41.2%)	46 (39.7%)	38 (33.0%)	84 (36.4%)
T2b	4 (3.1%)	10 (7.9%)	14 (5.4%)	4 (3.4%)	8 (7.0%)	12 (5.2%)
T3	15 (11.5%)	8 (6.3%)	23 (8.9%)	14 (12.1%)	8 (7.0%)	22 (9.5%)
T4	1 (0.8%)	3 (2.4%)	4 (1.6%)	1 (0.9%)	3 (2.6%)	4 (1.7%)
Regional lymph node stage						
N0	21 (16.2%)	18 (14.2%)	39 (15.2%)	8 (6.9%)	10 (8.7%)	18 (7.8%)
N1	45 (34.6%)	43 (33.9%)	88 (34.2%)	44 (37.9%)	40 (34.8%)	84 (36.4%)
N2	64 (49.2%)	66 (52.0%)	130 (50.6%)	64 (55.2%)	65 (56.5%)	129 (55.8%)

ALINA (BO40335)						
	Alectinib, ITT population n=130	**Chemotherapy, ITT population n=127**	**All patients, ITT population n=257**	**Alectinib, subpopulation stage II-IIIA n=116**	**Chemotherapy, subpopulation stage II-IIIA n=115**	**All patients, subpopulation stage II-IIIA n=231**
Nodal assesment						
Mediastinal lymph node dissection (MLND)	108 (83.1%)	105 (82.7%)	213 (82.9%)	-	-	-
Lymph node (LN) sampling conduction	19 (14.6%)	15 (11.8%)	34 (13.2%)	-	-	-
MLND and LN sampling not performed	3 (2.3%)	7 (5.5%)	10 (3.9%)	-	-	-
Histology						
Squamous	6 (4.6%)	3 (2.4%)	9 (3.5%)	5 (4.3%)	2 (1.7%)	7 (3.0%)
Non-Squamous	124 (95.4%)	124 (97.6%)	248 (96.5%)	111 (95.7%)	113 (98.3%)	224 (97.0%)
Surgical procedure						
Lobectomy	126 (96.9%)	117 (92.1%)	243 (94.6%)	-	-	-
Sleeve lobectomy	0	1 (0.8%)	1 (0.4%)	-	-	-
Bilobectomy	2 (1.5%)	5 (3.9%)	7 (2.7%)	-	-	-
Pneumonectomy	2 (1.5%)	4 (3.1%)	6 (2.3%)	-	-	-

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

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (22)	Value used in health economic model (9)
Age (Median, average)	64.6, 61.6 years	54.9 year
Gender (female)	56.5 %	52.1 %
Patient weight (average)	No available	69.63 kg
Patient height (average)	No available	165.80

6.1.4 Efficacy – results per ALINA

In the following section, a summary of the key efficacy findings for ALINA (BO40336) is presented.

Data on the following efficacy endpoints have been extracted:

- Disease-free survival (DFS)
- Overall survival (OS)
- Time to central nervous system recurrence or death (CNS-DFS)

For each outcome, data is presented for the ITT population and the subpopulation with stage II-IIIA disease.

Disease assessments were conducted at baseline and every 12 weeks for the first 2 years, every 24 weeks for years 3 through 5, and then annually until the occurrence of disease recurrence, death, loss to follow-up, withdrawal of consent, or study closure, whichever occurred first.

Disease-free survival

The primary endpoint in ALINA was DFS as assessed by the investigator in patients with completely resected stage IB-IIIA, ALK-positive NSCLC. DFS was first tested in the subpopulation of patients with stage II-IIIA. If alectinib significantly prolonged DFS in this subpopulation, then DFS would be tested in the ITT population.

DFS was defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC as determined by the investigator through use of an integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status or death from any cause, whichever occurs first. DFS as a surrogate for OS

is an accepted endpoint for drug approval by both the EMA and the FDA, as demonstrated with the approval of immune checkpoint inhibitors for adjuvant treatment of several solid tumors, including melanoma, renal cell carcinoma and muscle-invasive bladder cancer (37). DFS is the endpoint in most studies in early NSCLC (38).

Values of DFS are Kaplan-Meier estimates with 95% CI computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.

In the stage II-IIIA subpopulation, 14 patients (12.1%) in the alectinib arm and 45 patients (39.1%) in the chemotherapy arm had experienced disease recurrence or death. The primary endpoint of INV-DFS was met at the pre-specified interim analysis.

The stratified HR was 0.24 (95% CI: 0.13, 0.45), which corresponds to a 76% relative risk reduction of disease recurrence or death with alectinib compared to chemotherapy.

The median DFS was not reached in the alectinib arm and was 44.4 months (95% CI: 27.8, NE) in the chemotherapy arm.

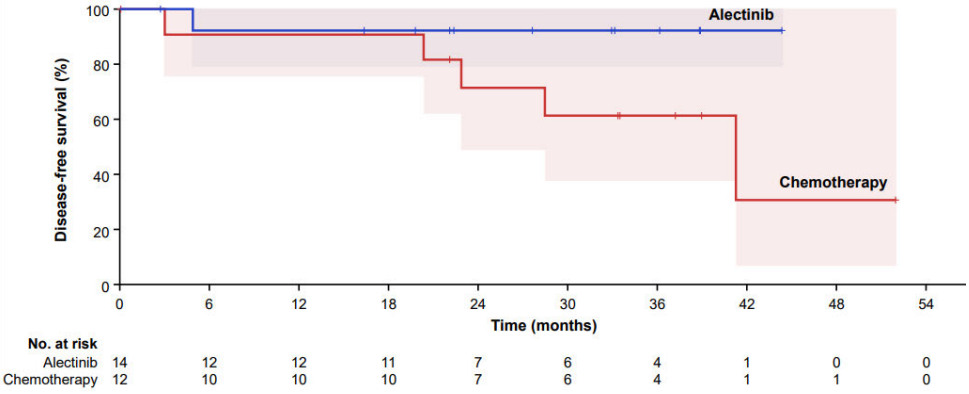


Figure 3: Kaplan-Meier plot of disease-free survival in Subgroup of patients with Stage IB.

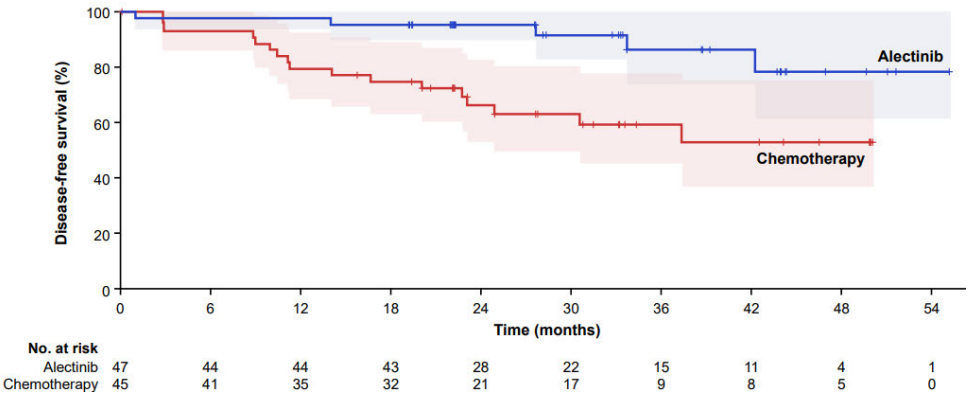


Figure 4 Kaplan-Meier plot of disease-free survival in Subgroup of patients with Stage II.

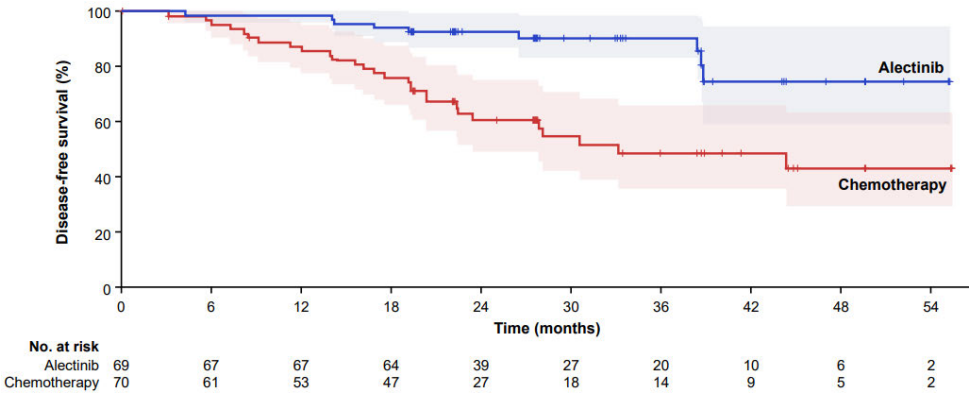


Figure 5 Kaplan-Meier plot of disease-free survival in Subgroup of patients with Stage IIIA.

Table 11 Summary Table of Disease-Free Survival in Subgroups of Patients (39).

DFS by disease stage	Alectinib	Chemotherapy
Stage IB, n	14	12
DFS HR* (95% CI)	0.21 (0.02, 1.84)	
2-year DFS rate (95% CI), %	92.3 (77.8, 100)	71.6 (44.2 98.9)
3-year DFS rate (95% CI), %	92.3 (77.8, 100)	61.4 (31.5, 91.3)
Stage II, n	47	45
DFS HR* (95% CI)	0.24 (0.09, 0.65)	
2-year DFS rate (95% CI), %	95.6 (89.5, 100)	66.3 (51.7, 81.0)
3-year DFS rate (95% CI), %	86.3 (72.8, 99.9)	59.5 (43.5, 75.4)
Stage IIIA, n	69	70
DFS HR* (95% CI)	0.25 (0.12, 0.53)	
2-year DFS rate (95% CI), %	92.7 (86.4, 98.9)	60.7 (47.9, 73.5)
3-year DFS rate (95% CI), %	90.3 (82.7, 97.9)	48.6 (33.8, 63.4)

*Unstratified analysis. Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

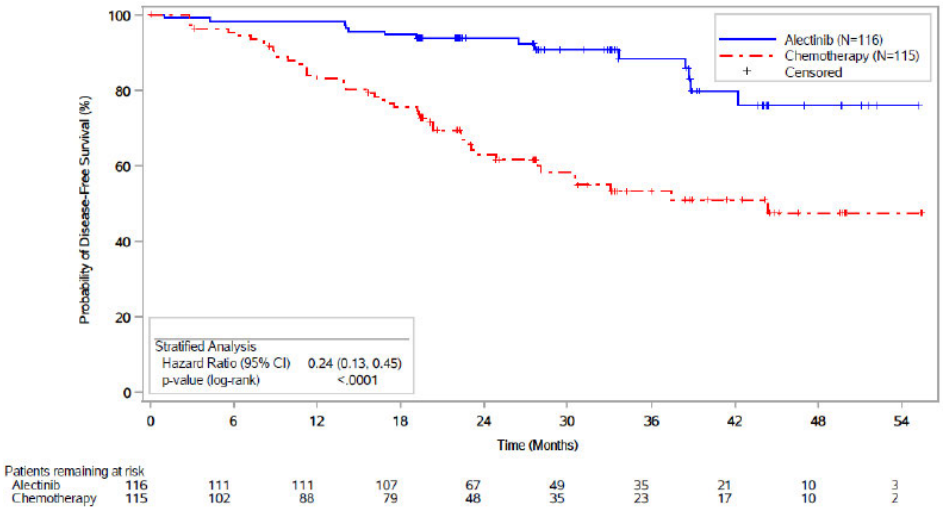


Figure 6: Kaplan-Meier plot of disease-free survival in the subpopulation of patients with stage II-IIIA disease.

The Kaplan-Meier curves began to separate at approximately 3 months after randomization in favor of the alectinib arm and the separation was maintained thereafter. A higher proportion of patients were alive and disease-free in the alectinib arm when compared to the chemotherapy arm at 2 years (93.8% [95% CI: 89.36, 98.25] vs. 63.0% [95% CI: 53.33, 72.68], respectively), and at 3 years (88.3% [95% CI: 80.83, 95.83] vs. 53.3% [95% CI: 42.34, 64.16], respectively).

Following, this analysis as alectinib significantly prolonged DFS in the stage II−IIIA subpopulation, DFS was tested in the ITT population.

In the ITT population, 15 patients (11.5%) in the alectinib arm and 50 patients (39.4%) in the chemotherapy arm had experienced disease recurrence or death. The primary endpoint of INV−DFS was met at the pre-specified interim analysis. The stratified HR was 0.24 (95% CI: 0.13, 0.43), which corresponds to a 76% relative risk reduction of disease recurrence or death with alectinib compared to chemotherapy.

The median DFS was not reached in the alectinib arm and was 41.3 months (95% CI: 28.5, NE) in the chemotherapy arm.

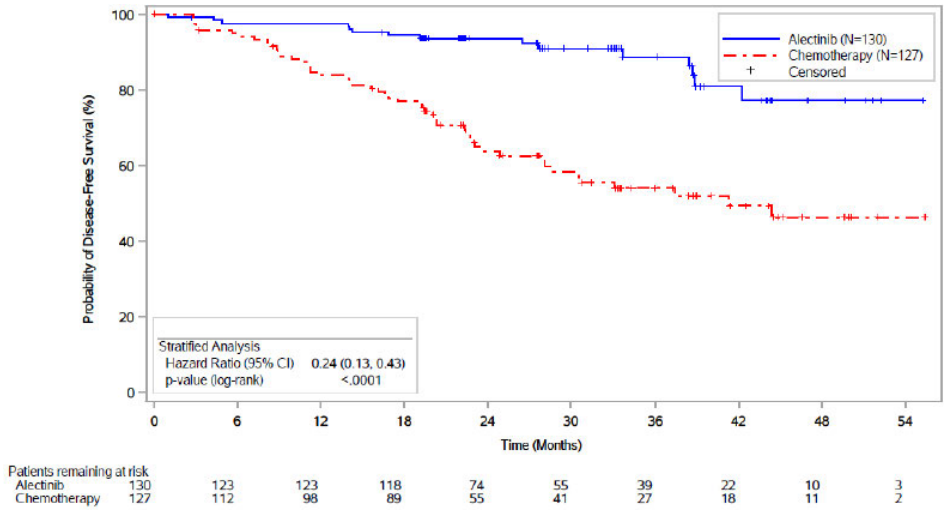


Figure 7: Kaplan-Meier plot of disease-free survival in the ITT population (stage IB-IIIA).

The Kaplan-Meier curves began to separate at approximately 3 months after randomization in favor of the alectinib arm and the separation was maintained thereafter. A higher proportion of patients were alive and disease-free in the alectinib arm when compared to the chemotherapy arm at 2 years (93.6% % [95% CI: 89.38, 97.91] vs. 63.7% [95% CI: 54.59, 72.90], respectively), and at 3 years (88.7% [95% CI: 81.76, 95.63] vs. 54.0% % [95% CI: 43.73, 64.21], respectively).

Conclusively, a significant DFS benefit was observed with alectinib vs chemotherapy in both the ITT population and stage II-IIA subpopulation.

Overall survival

OS defined as the time from randomization to death from any cause was a secondary endpoint in ALINA. OS are Kaplan-Meier estimates with 95% CI computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Data for the secondary endpoint of OS was immature with a low event-to-patient ratio at the CCOD with the median OS not being reached.

In the stage II-IIA subpopulation, there were 2 deaths (1.7%) in the alectinib arm vs. 2 deaths (1.7%) in the chemotherapy arm. The stratified HR was 0.96 (95% CI: 0.14, 6.82).

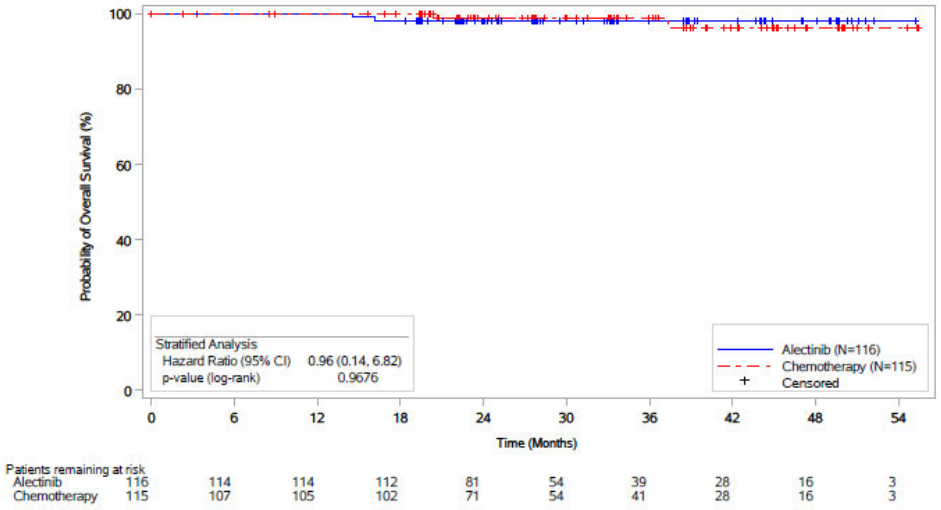


Figure 8: Kaplan-Meier plot of overall survival in the subpopulation (stage II-IIA).

In the ITT population, there were 2 deaths (1.5%) in the alectinib arm vs. 4 deaths (3.1%) in the chemotherapy arm. [redacted]. The stratified HR was 0.46 (95% CI: 0.08, 2.52) (36).

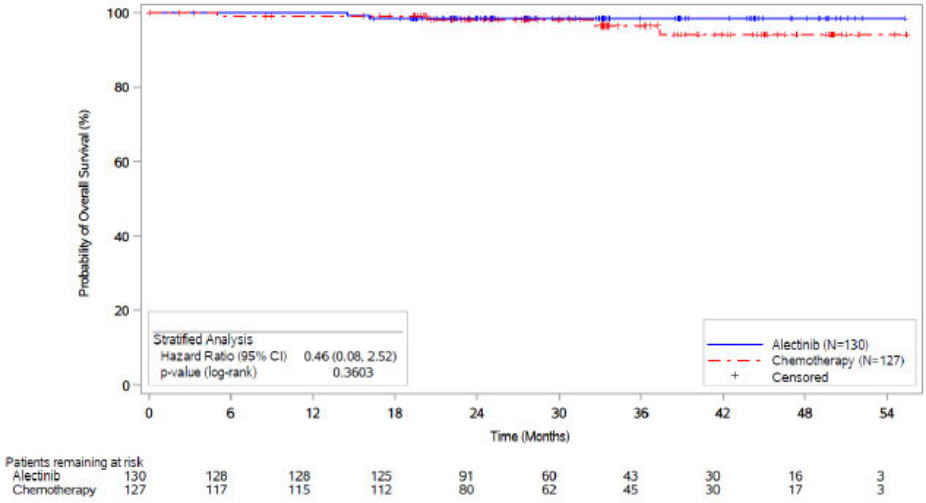


Figure 9: Kaplan-Meier plot of overall survival in the ITT population (stage IB-IIA).

Conclusively, OS was immature at the interim analysis with CCOD June 26, 2023.

Correlation between DFS and OS

Using three different models the surrogacy relationship between DFS and OS was explored. The following models have been used: linear regression, Daniel and Hughes model and bivariate random effect meta-analysis (40). The analysis included data from 29 clinical studies (40). In the analysis it is concluded that early benefits observed on DFS is a good way to predict an OS benefit as well (40). In addition West et al showed in a retrospective observational study that post-surgery real world DFS was significantly correlated with OS in patients with early-stage NSCLC (41). The study was based on data from the SEER-medicare linked data from the United States. Patients was diagnosed with stage IB-IIIA NSCLC from 2007-2019 and who underwent surgery for primary lung cancer with or without adjuvant chemotherapy and who did not receive chemotherapy in the neoadjuvant setting or adjuvant radiotherapy was included. The statistical comparisons in the study were performed with the t-test for continuous variables and the chi-square test for categorical variables for both cohorts, respectively. Using Kaplan-Meier curves OS was described and compared between the recurrence and non-recurrence cohorts with the log-rank test (41). For each landmark time point recurrence was associated with significantly shorter OS than for the cohort without recurrence. The study concludes that recurrence is associated with a significant higher risk of death than the recurrence free cohort

Time to central nervous system recurrence or death (CNS-DFS)

The exploratory endpoint of time to CNS recurrence or death was defined as the time from randomization to the first documented recurrence of disease in the CNS or death from any cause, whichever occurred first. Patients who were not reported as experiencing disease recurrence in the CNS or death were to be censored at the date of the last disease assessment. The same methodology used for DFS was applied for CNS-DFS.

In the subpopulation of patients with stage II-IIA disease, CNS-DFS showed clinically meaningful prolongation of CNS-DFS with alectinib compared to chemotherapy. A higher proportion of 16 (13.9%) patients in the chemotherapy arm had experienced CNS recurrence or death compared to 5 patients (4.3 %) in the alectinib arm, with a stratified HR of 0.24 (95% CI: 0.09, 0.65). A higher proportion of patients were alive and disease-free in

the CNS in the alectinib arm compared to the chemotherapy arm at 2 years (98.18% [95% CI: 95.69, 100.00] vs. 85.01% [95% CI: 77.36, 92.66], respectively), and at 3 years (95.02% [95% CI: 90.07, 99.97] vs. 80.15% [95% CI: 70.42, 89.89], respectively).

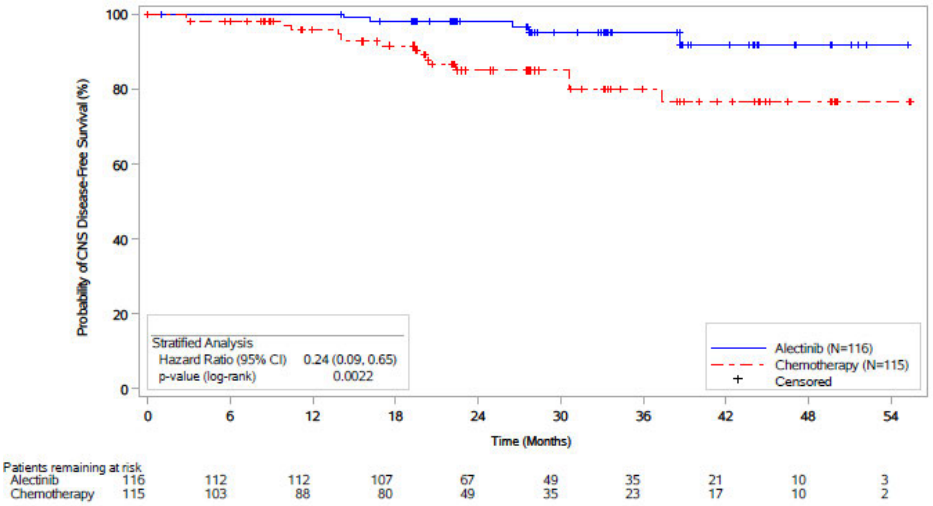


Figure 10: Kaplan-Meier plot of time to CNS recurrence or death, in the subpopulation (stage II-IIA).

In the ITT population, CNS-DFS showed clinically meaningful prolongation of CNS-DFS with alectinib compared to chemotherapy. A higher proportion of 18 patients (14.2%) in the chemotherapy arm had experienced CNS recurrence or death compared to 5 patients (3.8%) in the alectinib arm, with a stratified HR of 0.22 (95% CI: 0.08, 0.58). 4 and 18 patients had CNS recurrence in the alectinib arm and chemotherapy arm, respectively, while 1 and 4 patients died in the alectinib arm and chemotherapy arm, respectively. A higher proportion of patients were alive and disease-free in the CNS in the alectinib arm compared to the chemotherapy arm at 2 years (98.4% [95% CI: 96.11, 100.00] vs. 85.8% [95% CI: 78.83, 92.82], respectively), and at 3 years (95.5% [95% CI: 90.99, 99.99] vs. 79.7% [95% CI: 70.44, 89.03], respectively).

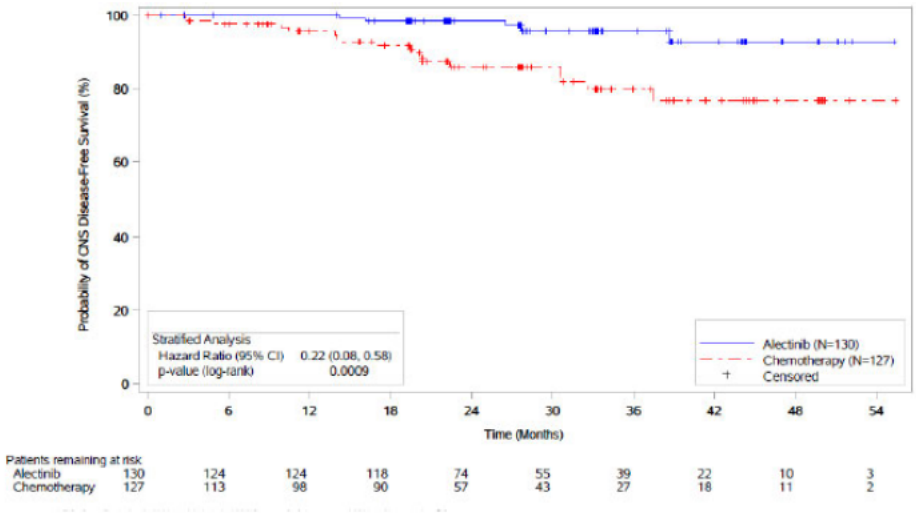


Figure 11: Kaplan-Meier plot of time to CNS recurrence or death in the ITT population (stage IB-IIA).

Conclusively, alectinib demonstrated improved CNS-DFS benefit in the ITT population and the stage II-IIA subpopulation as compared with the chemotherapy.

7. Comparative analyses of efficacy

ALINA (BO40336) is a head-to-head study which provide a direct comparison of alectinib and platinum-based chemotherapy regimens.

7.1.1 Results from the comparative analysis

Comparative results for both the ITT and stage II-IIIA subpopulation in ALINA (BO40336) are presented below (Table 12) (36).

Table 12 Results from the comparative analysis of alectinib vs. platinum-based chemotherapy for patients with ALK-positive early NSCLC

Outcome measure	Alectinib (N=130) ITT population	Chemotherapy (N=127) ITT population	Result
Median DFS	NE (95% CI: NE, NE)	41.3% (95% CI: 28.5, NE)	Stratified HR: 0.24 (95% CI: 0.13, 0.43)
2 year DFS rate	93.6% (95% CI: 89.38, 97.91)	63.7% (95% CI: 54.59, 72.90)	N/A
3 year DFS rate	88.7% (95% CI: 81.76, 95.63)	54.0% (95% CI: 43.73, 64.21)	N/A
OS	NE (95% CI: NE, NE)	NE (95% CI: NE, NE)	Stratified HR: 0.46 (95% CI: 0.08, 2.52)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Outcome measure	Alectinib (N=130) ITT population	Chemotherapy (N=127) ITT population	Result
2 year CNS-DFS rate	98.4% (95% CI: 96.11, 100.00)	85.8% (95% CI: 78.83, 92.82)	N/A
3 year CNS-DFS rate	95.5% (95% CI: 90.99, 99.99)	79.7% (95% CI: 70.44, 89.03)	N/A

Outcome measure	Alectinib (N=116) Stage II-IIIA subpopulation	Chemotherapy (N=117) Stage II-IIIA subpopulation	Result
Median DFS	NE (NE, NE)	44.4% (27.8, NE)	0.24 (0.13, 0.45)
2 year DFS rate	93.8% (95% CI:89.36, 98.25)	63.0% (95% CI:53.33, 72.68)	N/A
3 year DFS rate	88. 3% (95% CI:80.83, 95.83)	53.3% (95% CI:42.34, 64.16)	N/A
OS	NE (95% CI: NE, NE)	NE (95% CI: NE, NE)	Stratified HR: 0.96 (95% CI: 0.14, 6.82).
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
2 year CNS-DFS rate	98.18% (95% CI: 95.69, 100.00)	85.01% (95% CI: 77.36, 92.66)	N/A
3 year CNS-DFS rate	95.02% (95% CI: 90.07, 99.97)	80.15% (95% CI: 70.42, 89.89)	N/A

8. Modelling of efficacy in the health economic analysis

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

8.1.1 Extrapolation of efficacy data – Adjuvant treatment

The treatment regimens and proportion of patients treated with each regimen in the alectinib and chemotherapy arms are informed with evidence from ALINA. Patients in the alectinib arm were only treated with alectinib whereas those in the chemotherapy arm were treated with one of three cisplatin-based regimens but could substitute carboplatin for cisplatin if required. For simplicity, all patients who switched from cisplatin to carboplatin in the trial were assumed to initiate treatment on carboplatin within the model. Table 13 provides an overview of the adjuvant treatment assumptions utilised in the model.

Table 13 Adjuvant Treatment (ALINA; Safety-Evaluable Patients; CCOD June 26, 2023)

Treatment	Intervention Arm	Control Arm		
		Option 1	Option 2	Option 3
Market Share	**100.0%**	**19.2%**	**0.8%**	**80.0%**
Drug 1	**Alectinib (N = 128)**	**Cisplatin (N = 23)**	**Cisplatin (N = 1)**	**Cisplatin (N = 96)**
Administration	Oral	Intravenous	Intravenous	Intravenous
Dose size	8 x 150 mg capsules	75 mg/m^2	75 mg/m^2	75 mg/m^2
Treatment duration	24 months	4 cycles	4 cycles	4 cycles
Time between doses	1 day	3 weeks	3 weeks	3 weeks
Days of dose received	n/a	Day 1	Day 1	Day 1
Drug 2	**n/a**	**Vinorelbine (N = 23)**	**Gemcitabine (N = 1)**	**Pemetrexed (N = 96)**
Administration	n/a	Intravenous	Intravenous	Intravenous
Dose Size	n/a	25 mg/m^2	1250 mg/m^2	500 mg/m^2
Treatment duration	n/a	4 cycles	4 cycles	4 cycles
Time between doses	n/a	3 weeks	3 weeks	3 weeks
Days of dose received	n/a	Days 1, 8	Days 1, 8	Day 1
Drug 3	**n/a**	**Carboplatin (N = 2)**	**Carboplatin (N = 0)**	**Carboplatin (N = 12)**
Proportion who switched from Cisplatin to Carboplatin	n/a	8.7%	0.0%	12.5%
Administration	n/a	Intravenous	Intravenous	Intravenous
Dose Size	n/a	150 mg·AUC	150 mg·AUC	150 mg·AUC
Treatment duration	n/a	4 cycles	4 cycles	4 cycles
Time between doses	n/a	3 weeks	3 weeks	3 weeks
Days of dose received	n/a	Day 1	Day 1	Day 1

8.1.2 Extrapolation of efficacy data – Treatment after recurrence

An SLR (attached to the submission) was conducted on the treatment patterns of patients with ALK-positive advanced NSCLC to identify evidence that could assist it in informing the treatment patterns assumed within the model. Specifically, the SLR aimed to consolidate information on:

- the proportion of patients who receive treatment after experiencing recurrence by health state;
- the four most commonly used treatment options that are used to treat recurrence by health state.

The SLR was conducted as ALINA does not systematically collect data on treatments received by patients after experiencing recurrence, thus, limiting its reliability. The SLR identified 23 studies that provide evidence on the matter but all studies identified came with major limitations. None of the studies focused solely on patients who experienced recurrence nor separate patients with de novo diagnosed locally advanced and metastatic NSCLC. Therefore we investigated local Danish guidelines together with discussions with a clinical expert (28) to gain a better understanding of treatment patterns after non-metastatic and metastatic recurrence.

8.1.3 Extrapolation of efficacy data – Non-metastatic recurrence

The SLR did not identify any studies studying treatment patterns after non-metastatic recurrence. Table 14 summarizes the insights gained from discussions with the clinical expert together with local guidelines on what proportion of patients receive treatment after non-metastatic recurrence following adjuvant treatment with platinum-based chemotherapy, and if we can expect the market shares to differ for patients who are treated with adjuvant alectinib versus chemotherapy.

Table 14 Non-metastatic recurrence treatment

Proportion of Patients who receive Treatment	Treatment	Comment
[redacted]	[redacted]	[redacted]

The CEA informs the proportion of patients who receive treatment with the highest of the range (80%) and considers chemoradiotherapy as the only treatment option in the non-metastatic recurrence health state. Additionally, chemoradiotherapy as the only non-metastatic treatment option was deemed appropriate by HTA bodies within the CEA for adjuvant atezolizumab in a similar indication (CADTH, 2022; NICE, 2022).

Table 15 Definition of Treatment after Non-Metastatic Recurrence

Proportion of Patients who receive Treatment (28)	80%
Treatment Regimen by Option	**Option 1**
Market Share – Alectinib Arm	100%
Market Share – Chemotherapy Arm	100%
Drug 1	Cisplatin
Administration	Intravenous
Dose Size	75 mg/m^2
Treatment duration	4 cycles
Time between doses	3 weeks
Days of dose received	Day 1
Drug 2	Pemetrexed
Administration	Intravenous
Dose Size	500 mg/m^2
Treatment duration	4 cycles
Time between doses	3 weeks
Days of dose received	Day 1
Radiotherapy Inclusion	Yes
Treatment dose (Gy)	66
Dose per fraction (Gy)	2
Fractions per week	5

8.1.4 Extrapolation of efficacy data – Metastatic recurrence

The SLR did not identify any studies studying treatment patterns after non-metastatic recurrence. Table 16 summarizes the insights gained from discussions with the clinical expert together with local guidelines on what proportion of patients receive treatment after non-metastatic recurrence and if we can expect the market shares to differ for patients who are treated with adjuvant alectinib versus chemotherapy.

Table 16 Metastatic recurrence treatment

Line of treatment	Proportion of Patients who receive Treatment	Treatment	Comment
1st Line	[redacted]	[redacted]	[redacted]
2nd Line	[redacted]	[redacted]	[redacted]

After disease progression during treatment with an ALK-positive inhibitor, a different ALK-positive inhibitor should be used. If disease progression is seen shortly after completion of the two year ALK-positive inhibitor treatment, a TKI re-challenge will be initiated with the same treatment if it's been tolerated by the patient (28).

Table 17 Definition of First-Line Metastatic Treatment

Treatment Regimen by Option	Option 1	Option 2	Option 3	Option 4
Market Share – Alectinib Arm (relapse within 24 months)	0%	0%	100%	0%
Market Share – Alectinib Arm (relapse after 24 months)	0%	0%	100%	0%
Market Share – Chemotherapy Arm	0%	0%	100%	0%
Drug 1	Alectinib	Crizotinib	Brigatinib	Lorlatinib
Administration	Oral	Oral	Oral	Oral
Dose size	8 x 150 mg capsules	2 x 250 mg tablets	1 x 180 mg tablet	4 x 25 mg tablets
Treatment duration	Unlimited	Unlimited	Unlimited	Unlimited
Time between doses	1 day	1 day	1 day	1 day

Table 18 Definition of Second-Line Metastatic Treatment

Treatment Regimen by Option	Option 1	Option 2	Option 3
Market Share – Alectinib Arm	100%	0%	0%
Market Share – Chemotherapy Arm	100%	0%	0%
Drug 1	Alectinib	Ceritinib	Cisplatin
Administration	Oral	Oral	Intravenous
Dose size	8 x 150 mg capsules	5 x 150 mg tablets	75 mg/m^2
Treatment duration	Unlimited	Unlimited	Unlimited
Time between doses	1 day	1 day	21 days
Days dose received during each cycle	n/a	n/a	1
Drug 2	n/a	n/a	Pemetrexed
Administration	n/a	n/a	Intravenous
Dose Size	n/a	n/a	500 mg/m^2
No. of Cycles	n/a	n/a	Unlimited
Weeks between Cycles	n/a	n/a	21 days

Days dose received during each cycle	n/a	n/a	1

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

8.2.1 Disease-Free Survival

Figure 12 presents the Kaplan-Meier estimates of investigator-assessed DFS by treatment arms of the ALINA study. Based on the latest CCOD, this data is only available up to approximately month 50. The results from parametric survival analyses are used to project DFS to months not observed in the ALINA study. The parametric survival analysis pools patients across study arms but includes a covariate to capture what arm patients are in to model the effect of adjuvant alectinib on the location parameters of the distributions that it uses. This approach is appropriate in comparison to conducting the analysis separately by arm as we cannot conclude that the proportional hazard (PH) assumption is violated. Figure 13 presents the log-cumulative hazard plot of investigator-assessed DFS and

Figure 14 presents a Schoenfeld test which support this conclusion.

Figure 12 Kaplan-Meier Estimates – Investigator-Assessed DFS (ALINA; CCOD: June 26, 2023)

ALE=alectinib, CHT=chemotherapy

D: June 26, 2023)

Figure 14 Schoenfeld Residuals – Investigator-Assessed DFS (ALINA; CCOD: June 26, 2023)

8.2.1.1 Types of Disease-Free Events

Patients can experience non-metastatic recurrence, metastatic recurrence or death while disease-free. Table 19 presents the number of patients who experienced each type of event from ALINA for the alectinib arm, chemotherapy arm, and pooled across arms. Notable differences appear to exist across arms. The CEA informs the proportion of patients who experience each type of event based on the arm specific data.

Table 19 Type of Disease-Free Survival Events (ALINA, CCOD: June 26, 2023)

DFS Event	Alectinib Arm	Chemotherapy Arm	Pooled Across Arms
Total Events	14	50	64
Death	0 (0.00%)	1 (2.00%)	1 (1.56%)
Non-metastatic Recurrence	9 (64.28%)	22 (44.00%)	31 (48.43%)
Metastatic Recurrence	5 (35.72%)	27 (54.00%)	32 (50.01%)

8.2.2 Extrapolation of efficacy data

8.2.2.1 Extrapolation of DFS

Figure 15 and Figure 16 presents the projected INV-DFS using a series of parametric distributions. A decision on which parametric distribution to use is based on the fit of each projection to the observed data and the clinical validity of the long-term projections. Table 20 presents the Akaike Information (AIC) and Bayesian Information Criterion (BIC) scores for the different models where a lower score indicates a better fit. The scores indicate that the model assuming that INV-DFS follows a log-logistic distribution appears to provide the best fit to the observed data. In order to confirm the clinical validity of the long-term projections, an SLR was conducted on the efficacy and safety of early-stage NSCLC interventions with an expectation to capture evidence on longer-term DFS. A summary of the evidence that the SLR identified can be found in Appendix D. It shows that the proportion of stage IB-IIIA patients who were treated with chemotherapy and continue to be disease-free at 5 years appears to vary between 23-59%. Given that these studies do not focus on ALK-positive patients, discussions were held with TAEs. The discussions concluded that in the absence of evidence, it cannot be determined what proportion of patients will be disease-free in the long-term. Thus, the choice of projection is based on the AIC and BIC, leading to the use of the log-logistic model Figure 17.

Figure 15 Alectinib arm parametric distributions

Projected Investigator-Assessed DFS by Parametric Survival Model (ALINA; CCOD: June 26, 2023)

Figure 16 Chemotheraphy arm parametric distributions

Projected Investigator-Assessed DFS by Parametric Survival Model (ALINA; CCOD: June 26, 2023)

Figure 17 Projected Investigator-Assessed DFS with Log-Logistic Parametric Survival Model (ALINA; CCOD: June 26, 2023)

ALE=alectinib, CHT=chemotherapy

Table 20 AIC and BIC Scores of Parametric Survival Models of Investigator-Assessed DFS (ALINA; CCOD: June 26, 2023)

Distribution	AIC (Rank)	BIC (Rank)
Exponential	712.1 (6)	719.2 (2)
Weibull	709.9 (3)	720.5 (4)
Log-logistic	707.8 (1)	718.5 (1)
Log-normal	711.1 (5)	721.7 (5)

Gompertz	712.4 (7)	723.0 (6)
Generalised Gamma	710.6 (4)	724.8 (7)
Gamma	709.2 (2)	719.9 (3)

8.2.2.1.1 Adjustments to Disease-Free Survival

Cure adjustment

The median follow-up of ALINA is around 32 months. As most recurrences occur within 5 years, the DFS projections outlined in the previous section can underestimate long-term DFS (42). In order for the CEA to deal with this issue, it allows patients to be considered cured (i.e. not experience recurrence or disease related death) if they are disease-free for five years (28).

An SLR was conducted on the conditional DFS of patients who underwent resection for early-stage NSCLC in an attempt to identify evidence that could assist in informing what proportion of patients may continue to experience recurrence or disease-related death after being disease-free for some time. The SLR identified one study that shows that conditional 5-year DFS for 3 years is 91% for patients with disease stage IB or less and 83% for patients with disease stage II or greater (43).

Mortality adjustment

The CEA uses Danish lifetables from the DMC guidance (28). It can adjust the probabilities to account for the fact that lung cancer survivors may have more comorbidities than the general population and, thus, realize a greater probability of all-cause death. To identify evidence on this matter, an SLR was conducted on the relative survival of patients who had underwent resection for early-stage NSCLC. The SLR identified one study that provides evidence on conditional 5-year relative survival and shows that it may decrease with disease stage Table 21. A limitation with this study is that it focuses on patients solely from South Korea and it is unclear what proportion of their sample are ALK-positive. Discussions were held with a Canadian board of experts to validate the evidence from which it was concluded that ALK-positive patients who are considered cured may confront a similar probability of death as an age- and sex-adjusted individual from the general population (44). As patients with ALK-positive NSCLC are typically non-smokers, the TAEs considered these patients less likely to develop comorbidities in comparison to patients with other types of lung cancer. Thus, the CEA assumes that patients who are considered cured after year 5 confront a similar probability of death as someone from the general population. The CEA also applies this probability of death to non-cured patients across all health states if it leads to a higher proportion of them transitioning to death to avoid the situation where the estimates indicate that more individuals die in the general population than in the population of interest (45).

Table 21 Mortality Adjustment

Study	Country	Results
(Shin, et al., 2021)(46)	South Korea	Conditional relative survival - 5-year survival conditional on 5 years disease-free after surgery Stage I (year 5): 90% Stage II (year 5): 78% Stage III (year 5): 61%
TAEs	n/a	Conditional relative survival - 5-year survival conditional on 5 years disease-free after surgery TAE 1: 100% TAE 2: 100% TAE 3: <100%

Figure 18 Projected Investigator-Assessed DFS with Log-Logistic Parametric Survival Model and Cure and Mortality (ALINA; CCOD: June 26, 2023)

8.2.2.2 Extrapolation of PFS & OS

8.2.2.2.1 Progression after recurrence

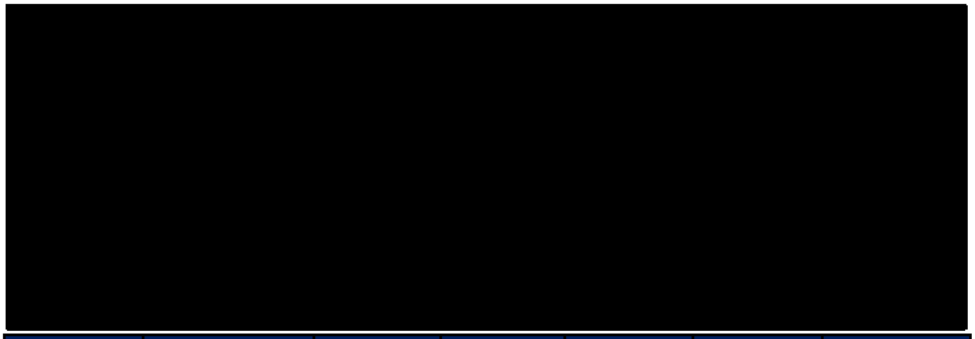
An SLR was conducted on the efficacy and safety of interventions for ALK-positive NSCLC to identify evidence that could assist it in informing the progression free-survival (PFS) and OS of patients who do or do not treat after relapsing. This is because ALINA does not systematically collect data on disease progression after first recurrence. As the study does not have access to the individual patient data (IPD) of the studies that it has identified with the SLRs, it must produce approximated datasets by digitising the Kaplan-Meier estimates of PFS and OS and transforming them to IPD (47). Alike the analysis of DFS, the results from parametric survival analyses are used to produce the output that it needs to project the outcomes across time. While several analyses are conducted, where the outcomes of interest follow several distributions, the CEA uses the results from the analyses that assume that the outcomes follow an exponential distribution to model PFS and OS. This restricts the transition probabilities to being time-invariant. However, the CEA uses the abovementioned mortality adjustment if it leads to a higher proportion of patients transitioning to death.
An advantage of the former restriction is that it simplifies the CEA. As there is a continuous flow of patients into the non-metastatic and metastatic recurrence health states, the analysis would have had to consist of several tunnel states to allow the transitions to be time-variant. A limitation of this restriction is that if it is not appropriate from a statistical or clinical standpoint, it can lead to the analysis incorrectly modelling the amount of time that a patient remains in these health states. However, a recent comparison of these approaches concluded that significant differences in the transition probabilities appear at months when most patients have already experienced an event, thus, limiting any potential bias.

8.2.2.2.2 Non-metastatic Recurrence

The SLR did not identify any studies that study the PFS of patients after non-metastatic recurrence or with locally advanced NSCLC who received chemoradiotherapy. Thus, the study pragmatically reviewed the Canadian adaptation of the cost-effectiveness analysis of adjuvant atezolizumab for the treatment of early-stage NSCLC to identify sources that it could use (48). It identified a study on the PFS of patients with stage I-III NSCLC after complete resection who experienced locoregional recurrence and were treated with chemoradiotherapy (32). A limitation of this study is that it does not focus on ALK-positive NSCLC patients treated with adjuvant therapy, and uses a sample of patients who

are from Japan. Figure 19 presents the projected PFS. Based on the AIC/BIC, the log-normal parametric survival model provides the best fit of modelled to observed PFS despite the use of the exponential model.
The SLR did not identify any studies that study the PFS or OS of patients who do not receive any treatment. Thus, the study pragmatically reviewed the Canadian adaptation of the cost-effectiveness analysis of adjuvant atezolizumab for the treatment of early-stage NSCLC in an attempt to identify sources that it could use. It identified a study that studies the OS of patients with stage I-III NSCLC after complete resection who do not receive any active treatment after non-metastatic and metastatic recurrence (49). As this study only presents OS and not PFS for these patients, the CEA uses it to inform the OS of patients with non-metastatic recurrence who do not receive treatment, preventing them from being able to transition to subsequent health states Figure 20. Based on the AIC/BIC, the log-normal parametric survival model provide the best fit of modelled to observed OS despite the use of the exponential model.

Figure 19 Progression-Free Survival after Non-Metastatic Recurrence by Treatment Option (Chemotherapy)



Criterion	Exponential	Weibull	Log-Normal	Gen. Gamma	Log-Logistic	Gompertz
AIC						
BIC						
Reference: (Nakamichi, et al., 2017) (32)						

The CEA cannot include the results of the generalized gamma model as statistical models did not converge.

Figure 20 Progression-Free Survival after Non-Metastatic Recurrence by Treatment Option (No treatment)

Criterion	Exponential	Weibull	Log-Normal	Gen. Gamma	Log-Logistic	Gompertz
AIC						
BIC						
Reference: (Wong, et al., 2016) (49)						

The CEA cannot include the results of the generalized gamma model as statistical models did not converge.

8.2.2.2.3 Metastatic Recurrence (First-Line)

The SLR identified four studies that study the PFS of first-line metastatic treatment with alectinib (29, 50-52). The first of the four studies is used as it is does not focus solely on an Asian population and the CEA has access to the IPD (Figure 21). Depending on whether one uses the AIC or BIC, the generalized gamma and log-normal parametric survival models appear to provide the best fit of modelled to observed PFS despite the use of the exponential model.

The SLR identified ten studies that study the PFS of first-line metastatic treatment with crizotinib (29, 30, 50-57). The CEA only considers four studies that do not focus solely on an Asian population and do not comprise of ALK-negative patients. Table 22 presents these studies' patient baseline characteristics and shows that patients across them are similar. It is because of this that the CEA does not base the choice of which study to use to inform PFS on the comparability of the patients in these studies to those in ALINA. Rather, the CEA bases the choice on which study has the greatest median follow-up to limit any uncertainty in the PFS projections. As such, the CEA uses Solomon et al. (2023) (30) Figure 22. Based on the AIC/ BIC, the log-logistic parametric survival model appears to provide the best fit of modelled to observed PFS despite the use of the exponential model.

The SLR identified one study each that studies the PFS of first-line metastatic treatment with brigatinib (53) and lorlatinib (30)

Figure 23 and Figure 24, respectively. Based on the AIC/BIC, the log-normal and gompertz parametric survival models provide the best fit of modelled to observed PFS for brigatinib and lorlatinib despite the use of the exponential model to model both treatments.

The SLR did not identify any studies that study the PFS or OS of patients who do not receive any treatment. Thus, the CEA also uses Wong et al. (2016) (49) to inform the OS of patients with first-line metastatic recurrence who do not receive treatment (Figure 25). Depending on whether one uses the AIC or BIC, the generalized gamma and log-normal parametric survival models provide the best fit of modelled to observed OS despite the use of the exponential model.

Table 22 Patient Characteristics of Studies considering First-Line Metastatic Treatment with Crizotinib (Clinical SLR [Advance-Stage NSCLC]; Search: September, 2023)

Characteristic	(Camidge, et al., 2019)(29)	(Camidge, et al., 2021)(53)	(Solomon, et al., 2014)(55)	(Solomon, et al., 2023)(30)
Age (median)	54	60	52	56
Gender (Male)	42%	41%	40%	38%
Race (White)	n.r.	n.r.	53%	49%
Race (Asian)	46%	64%	45%	44%
Race (Others)	54%	36%	2%	1%
Smoking Status (Never)	65%	54%	62%	64%
Smoking Status (Former)	32%	41%	33%	29%
Smoking Status (Current)	3%	5%	6%	6%
Tumor Histology (Adenocarcinoma)	94%	99%	94%	95%
Performance (ECOG 0-1)	93%	96%	94%	94%
Performance (ECOG 2)	7%	4%	6%	6%

Figure 21 Alectinib Progression-Free Survival on First-Line Metastatic Treatment

[redacted]

Criterion	Exponential	Weibull	Log-Normal	Gen. Gamma	Log-Logistic	Gompertz
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reference: ALEX (Investigator Assessed PFS, ITT, Intervention Arm, CCOD: November 30, 2018) (29)						

Figure 22 Crizotinib Progression-Free Survival on First-Line Metastatic Treatment

Criterion	Exponen-tial	Weibull	Log-Nor-mal	Gen. Gamma	Log-Lo-gistic	Gompertz
AIC						
BIC						
Reference: (Solomon, et al., 2023) (30)						

Figure 23 Brigatinib Progression-Free Survival on First-Line Metastatic Treatment

Criterion	Exponen-tial	Weibull	Log-Nor-mal	Gen. Gamma	Log-Lo-gistic	Gompertz
AIC						
BIC						
Reference: (Camidge, et al., 2021) (53)						

Figure 24 Lorlatinib Progression-Free Survival on First-Line Metastatic Treatment

Criterion	Exponential	Weibull	Log-Nor-mal	Gen. Gamma	Log-Lo-gistic	Gompertz
AIC						
BIC						
Reference: (Solomon, et al., 2023) (30)						

The CEA cannot include the results of the generalized gamma model as the survival analysis could not produce the results.

Figure 25 No treatment Progression-Free Survival on First-Line Metastatic Treatment

Criterion	Exponen-tial	Weibull	Log-Nor-mal	Gen. Gamma	Log-Lo-gistic	Gompertz
AIC						
BIC						
Reference: (Wong, et al., 2016) (49)						

8.2.2.2.4 Metastatic Recurrence (Second-Line)

The SLR identified three studies that study the OS of second-line metastatic treatment with alectinib (31, 58, 59). The CEA does not consider Hotta et al. (2022) as this study only focuses solely on an Asian population. While Yang et al. (2023) and Novello et al. (2018) focus on global populations that previously treated with crizotinib and other systemic anti-cancer treatment, the CEA informs OS with the latter of the two studies as it has access to the IPD and does not need to produce an approximated dataset (Figure 26). Depending on whether one uses the AIC or BIC, the log-logistic, log-normal and exponential parametric survival models provide the best fit of modelled to observed OS.

The SLR identified one study that studies the OS of second-line metastatic treatment with ceritinib but does not present the Kaplan-Meier estimates (60). The CEA estimates the monthly transition probability as such [median month OS = 18.1; $\lambda = \ln(0.5)/-(18.1) = 0.038$], however, it is currently left out of the model as the current model structure only allows for the inclusion of estimates from a parametric survival analysis.

The SLR identified three studies that study the OS of second-line metastatic treatment with chemotherapy (31, 58, 59). A limitation of these sources is that the studies do not focus on patients previously been treated with alectinib, brigatinib or lorlatinib. With these limitations in mind, the CEA proceeds with the use of Novello et al. (2018) (31) as it has access to the IPD and does not need to produce an approximated dataset to conduct analysis (

Figure 27). Based on the AIC/BIC, the gompertz parametric survival model provides the best fit of modelled to observed OS despite the use of the exponential model.
The CEA uses Wong et al. (2016) (49) to inform the OS of patients not on treatment (Figure 25).

Figure 26 Alectinib OS on Second-Line Metastatic Treatment

[redacted]

Criterion	Exponential	Weibull	Log-Normal	Gen. Gamma	Log-Logistic	Gompertz
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reference: ALUR (ITT, Intervention Arm, CCOD: October, 2018) (31)						

Figure 27 Cisplatin + Pemetrexed Overall Survival on Second-Line Metastatic Treatment

Criterion	Exponential	Weibull	Log-Normal	Gen. Gamma	Log-Logistic	Gompertz
AIC						
BIC						
Reference: ALUR (ITT, Control Arm, CCOD: October, 2018) (31)						

8.2.2.2.5 Type of progression free events.

Patients who have non-metastatic or metastatic recurrence (first-line) can experience further disease progression or death while they are progression-free. The CEA allows this to differ by treatment option and uses the same sources to do this that inform the PFS. However, as summarised in Table 23 only one study includes information on the type of progression event a patient experiences (progression or death). Thus, the CEA uses the ALEX study to inform the proportion of patients who experience progression versus death as their progression-free event in the non-metastatic and metastatic (first-line) recurrence health states.

Table 23 Types of Progression-Free Survival Events

Non-Metastatic Recurrence					
PFS Event	**Chemoradiotherapy**				
Total Events	14				
Death	Not reported				
Progression	Not reported				
Reference	(Nakamichi, et al., 2017)(32)				
Metastatic Recurrence (First-Line)					
PFS Event	**Alectinib**	**Crizotinib**	**Brigatinib**	**Lorlatinib**	**Pooled**
Total Events	81	92	73	49	-
Death	9 (11.1%)	Not reported	Not reported	Not reported	-
Progression	72 (88.9%)	Not reported	Not reported	Not reported	-
Reference	ALEX (ITT, Intervention Arm, CCOD: November 30, 2018)*(29)	(Solomon, et al., 2023)	(Camidge, et al., 2021)(53)	(Solomon, et al., 2023)(30)	-

8.2.2.2.6 Summarized Overall survival in the model

Figure 28: Modelled overall survival in the economic model.

8.2.3 Calculation of transition probabilities

Figure 29: Markov trace alectinib

Figure 30: Markov trace Themotherapy

Table 24 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence – Alectinib	Parametric extrapolation based on the ALINA study (log-logistic as base case)	(9)
	Recurrence – Chemotherpy	Parametric extrapolation based on the ALINA study (log-logistic as base case)	
	Non-metastatic recurrence - Treatment	Contant fraction of recurrence based on the ALINA study (64.3% for alectinib and 44.0% for chemotherapy)	
	Metastatic recurrence – No treatment	Contant fraction of recurrence based on the ALINA study (35.7% for alectinib and 54.0% for chemotherapy)	
	Death	Contant fraction of recurrence based on the ALINA study (0.0% for alectinib and 2.0% for chemotherapy)	
Non-metastatic recurrence - treatment	Metastatic recurrence - Treatment	Transition probability calculated based on Nakamichi et al. (2017) using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(32)
	Metastatic recurrence – No treatment	Transition probability calculated based on Wong et al. (2016) using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(49)
	Death	Assumption that patients are not dying from this stage, but rather progress before death	Assumption
Metastatic recurrence (1L) - Alectinib	Metastatic recurrence (2L)	Transition probability calculated based on the ALEX study using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(29)
Metastatic recurrence (1L) – Lorlatinib	Metastatic recurrence (2L)	Transition probability calculated based on Solomon et al. (2023) using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(8)
Metastatic recurrence (1L) – Brigatinib	Metastatic recurrence (2L)	Transition probability calculated based on Camidge et al. (2021) using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(53)
Metastatic recurrence (1L) – Crizotinib	Metastatic recurrence (2L)	Transition probability calculated based on Solomon et al. (2023) using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(8)
Metastatic recurrence (1L) – No treatment	Metastatic recurrence – No treatment	Transition probability calculated based on Wong et al. (2016) using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(49)

Metastatic recurrence (1L) – All	Death	Constant proportion of patients [redacted] with progression as event versus death based on the ALEX study. Applied for all ALK-TKI treatments	(29)
Metastatic recurrence (2L) – Alectinib	Death Death Death	Transition probability calculated based on the ALUR study using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(31)
Metastatic recurrence (2L) – Chemotherapy		Transition probability calculated based on the ALUR study using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	
Metastatic recurrence (2L) – No treatment		Transition probability calculated based on Wong et al. (2016) using an exponential distribution due to the nature of a markov model. Transition probability: [redacted]	(49)

8.3 Presentation of efficacy data from [additional documentation]

Described above

8.4 Modelling effects of subsequent treatments

Described above

8.5 Other assumptions regarding efficacy in the model

Described above

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

Table 25 Estimates in the model

	Modelled average [DFS]	Modelled median [DFS] (reference in Excel)	Observed median from relevant study
Alectinib	[redacted]	[redacted]	Table 27
Chemotheraphy	[redacted]	[redacted]	Table 27

Table 26 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	DFS [months]	Non-metastatic recurrence [months]	Metastatic Recurrence First-Line [months]	Metastatic Recurrence Second-Line [months]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotheraphy	2.59	135.8	7.8	20.5	12.6

More details in section 8.6.1 and 8.6.2

8.6.1 Adjuvant treatment duration

Patients discontinue adjuvant treatment if they experience recurrence, death or discontinue treatment for other reasons (e.g. intolerable toxicity, adverse events). The CEA uses evidence from ALINA to inform the discontinuation of adjuvant alectinib and chemotherapy. For the control arm, it uses data on this matter from the drug (i.e. gemcitabine, pemetrexed or vinorelbine) combined with cisplatin and carboplatin as patients in the control arm could switch from cisplatin to carboplatin. Table 27 provides an overview of this evidence.

Table 27 Proportion of Patients discontinuing Treatment after each Month/Cycle (ALINA; Safety-Evaluable Patients; CCOD: June 26, 2023)

Alectinib			
Month 1	[redacted]		
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
Month 7			
Month 8			
Month 9			
Month 10			
Month 11			
Month 12			
Month 13			
Month 14			
Month 15			
Month 16			
Month 17			
Month 18			
Month 19			
Month 20			
Month 21			
Month 22			
Month 23			
Month 24			
Control Arm*			
Regimen	**Cisplatin containing Regimen**	**Carboplatin containing Regimen**	**Gemcitabine/Pemetrexed/ Vinorelbine**

	(N = 119)	(N = 14)	(N = 120)
Cycle 1	6.7%	14.3%	2.5%
Cycle 2	7.6%	50.0%	0.8%
Cycle 3	4.2%	28.6%	6.7%
Cycle 4	81.5%	7.1%	90.0%

*The CEA informs treatment discontinuation with section 4.6.1.2 of the ALINA CSR (36). This evidence is not conditional on the treatment regimen received, it is generated by pooling all patients who received each drug.

8.6.2 Treatment after recurrence duration

Patients who receive treatment after recurrence can discontinue treatment before completing treatment also for reasons other than disease-progression or death. The CEA allows this to differ by treatment option and uses the same sources to do this that inform the PFS, as ALINA does not collect information on treatment discontinuation for patients on subsequent treatment after the earliest recurrence preventing its use. Table 28 presents the median number of months on treatment which the CEA uses to cap the number of months that a patient can receive treatment for (while presented to one decimal place, the CEA rounds them). Unfortunately, for chemoradiotherapy, the source does not provide any evidence on treatment discontinuation and, therefore, only allows patients to discontinue treatment if they experience an event. It should be noted that while the CEA can allow metastatic treatment discontinuation to be informed by the projection of time-to-off treatment into the future, it currently does not have this functionality as not all sources provided Kaplan-Meier estimates on this matter. A limitation with the approach used is that some patients may have remained on treatment after the median cut-offs biasing downwards the treatment costs

Table 28 Treatment Discontinuation with Treatment after Recurrence

Non-Metastatic Recurrence	Median Number of Months on Treatment	Reference
Chemoradiotherapy	Not reported	(Nakamichi, et al., 2017)(32)
Metastatic Recurrence (First-Line)	**Median Number of Months on Treatment**	**Reference**
Alectinib	27.0	(Camidge, et al., 2019)(29)
Crizotinib	9.6	(Solomon, et al., 2023)(30)
Brigatinib	34.9	(Camidge, et al., 2021)(53)
Lorlatinib	33.3	(Solomon, et al., 2023)(30)
Metastatic Recurrence (Second-Line)	**Median Number of Weeks on Treatment**	**Reference**
Alectinib	20.1	(Novello, et al., 2018)(31)
Ceritinib	30.3	(Shaw, et al., 2017)(60)
Cisplatin + Pemetrexed	6.0	(Novello, et al., 2018)(31)

9. Safety

9.1 Safety data from the clinical documentation

The safety-evaluable population included 248 patients who received any study treatment: 128 in the alectinib arm and 120 in the chemotherapy arm. Among safety-evaluable patients, the median duration of safety follow-up, defined as time from first study drug administration to the end of the adverse event (AE) reporting period, was 24.8

months (range: [redacted]) in the alectinib arm, and 3.7 months (range: [redacted]) in the chemotherapy arm. The median duration of exposure to alectinib was 23.9 months (range: [redacted]) while the median duration of exposure to chemotherapy was 2.1 months (range: [redacted]. When evaluating the safety data, it is important to take the significant difference of median exposure to treatment between the two arms into account (36).

All AEs were reported during treatment and until date of study completion or discontinuation, CCOD, 28 days after last dose of alectinib or 28 days after the end of the last cycle of chemotherapy (i.e., a maximum of 25 months for patients randomized to the alectinib arm and 4 months for patients randomized to the chemotherapy arm). Consequently, the period in which AEs were collected for the alectinib arm was substantially longer than the chemotherapy arm.

Table 29 provides an overview of safety events in the safety-evaluable population. As ALINA (BO40336) is still ongoing, data is based on the period up until the CCOD of June 26, 2023.

Table 29 Overview of safety events. The median duration of treatment was 23.9 months in the alectinib group and 2.1 months in the chemotherapy group (36).

	Alectinib (N=128) (source)	Chemotherapy (N=120) (source)	Difference, % (95 % CI)
Number of adverse events, n	1685	978	698 / NA (NA;NA)
Number and proportion of patients with ≥1 adverse events, n (%)	126 (98.4%)	112 (93.3%)	14 / 5.1% (NA;NA)
Number of serious adverse events*, n	20	16	4 / NA (NA;NA)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	17 (13.3%)	10 (8.3%)	7 / 5% (NA;NA)
Number of CTCAE grade ≥ 3 events, n	50	67	-17 / NA (NA;NA)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	38 (29.7%)	37 (30.8%)	1 / -1.1% (NA;NA)
Number of adverse reactions, n	-	-	-
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	-	-	-
Number and proportion of patients who had a dose reduction, n (%)**	47 (36.7%)	24 (20.0%)	23 / 16.7 % (NA;NA)
Number and proportion of patients who discontinue treatment regardless of reason*, n (%)**	18 (14.1%)	12 (10.0%)	6 /4.1 % (NA;NA)

Number and proportion of patients who discontinue treatment due to adverse events, n (%)	7 (5.5%)	14 (11.7%)	-7 / **-6.2 %** (NA;NA)

Overall, the frequency of serious AEs (SAE) was low in both treatment arms. Most SAEs were Grade 3 or less in severity and had resolved by the CCOD. The proportion of patients who experienced at least one SAE was 13.3% (17 patients) in the alectinib arm and 8.3% (10 patients) in the chemotherapy arm. The only SAE with a notable difference (> 2% between the arms) was appendicitis (3.1% [4 patients] in the alectinib arm and 0 patients in the chemotherapy arm). [redacted]. SAEs by System Organ Class (≥2% of patients) and SAEs by PT (≥1% of patients) are listed in Table 30 (36).

Table 30 Serious adverse events (All AEs were reported during treatment and until date of study completion or discontinuation, CCOD, 28 days after last dose of alectinib or 28 days after the end of the last cycle of chemotherapy).

Adverse events	Alectinib (N=128)		Chemotherapy (N=120)	
	Number of patients with adverse events	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**
Adverse event, n (%)	17 (13.3%)	20	10 (8.3%)	16
The most frequent SAEs by SOC (≥2% of patients)				
Infections and infestations	11 (8.6%)	11	2 (1.7%)	2
Gastrointestinal disorders	2 (1.6%)	2	4 (3.3%)	8
The most frequent SAEs by PT (≥1% of patients)				
Appendicitis	4 (3.1%)	-	0	-
Pneumonia	3 (2.3%)	-	1 (0.8%)	-
Nausea	0	-	2 (1.7%)	-
Neutrophil count decrease	0	-	2 (1.7%)	-
Acute myocardial infarction	2 (1.6%)	-	0	-

In Table 31 below grade 3-4 adverse events occurring in at least 10% of patient from the ALINA study is presented (9). No grade 5 events were observed.

Table 31 Adverse events used in the health economic model that appear in more than 10 % of patients

Adverse events	Alectinib (N=128)	Chemotherapy (N=120)		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)				
Investigations	**13 (10.2%)**	**14 (11.7%)**	Wu et al (9)	Direct head-to-head study
Neutrophil count decreased	0 (0%)	12 (10.0%)		
Blood creatine phosphokinase increased	8 (6.2%)	1 (0.8%)		
White blood cell count decreased	0 (0%)	4 (3.3%)		
Alanine aminotransferase increased	2 (1.6%)	0 (0%)		
Blood bilirubin increased	2 (1.6%)	0 (0%)		
Aspartate aminotransferase increased	1 (0.8%)	0 (0%)		
Blood creatinine increased	1 (0.8%)	0 (0%)		
Liver function test increased	1 (0.8%)	0 (0%)		
Blood and lymphatic system disorders	**0 (0%)**	**12 (10.0%)**		
Neutropenia	0 (0%)	10 (8.3%)		
Anaemia	0 (0%)	1 (0.8%)		
Febrile neutropenia	0 (0%)	1 (0.8%)		
Leukopenia	0 (0%)	1 (0.8%)		
Gastrointestinal disorders	**4 (3.1%)**	**9 (7.5%)**		
Nausea	0 (0%)	5 (4.2%)		
Constipation	1 (0.8%)	1 (0.8%)		

Diarrhoea	1 (0.8%)	0 (0%)
Vomiting	0 (0%)	2 (1.7%)
Abdominal pain	0 (0%)	1 (0.8%)
Epigastric discomfort	0 (0%)	1 (0.8%)
Regurgitation	0 (0%)	1 (0.8%)
Stomatitis	1 (0.8%)	0 (0%)
Infections and infestations	**1 (0.8%)**	**1 (0.8%)**
Appendicitis	1 (0.8%)	0 (0%)
Urinary tract infection	0 (0%)	1 (0.8%)
General disorders and administration site conditions	**1 (0.8%)**	**5 (4.2%)**
Asthenia	0	3 (2.5%)
Fatigue	1 (0.8%)	2 (1.7%)
Metabolism and nutrition disorders	**1 (0.8%)**	**2 (1.7%%)**
Hypertriglyceridaemia	1 (0.8%)	0
Decreased appetite	0	1 (0.8%)
Type 2 diabetes mellitus	0	1 (0.8%)
Respiratory, thoracic and mediastinal disorders	**1 (0.8%)**	**1 (0.8%)**
Cough	1 (0.8%)	0
Pneumonitis	1 (0.8%)	0
Pulmonary embolism	0	1 (0.8%)
Skin and subcutaneous tissue disorders	**2 (1.6%)**	**0 (0%)**
Rash	1 (0.8%)	0 (0%)
Rash maculo-papular	1 (0.8%)	0 (0%)

For adverse events applied in subsequent lines in the health economic model. See next section and appendix E.

In Table 32 below subsequent treatments for both treatment arms in ALINA is described.

Table 32 Subsequent Treatments In Patients with Disease Recurrence (ITT Population) (39).

Number of patients with disease recurrence, n (%)	Alectinib (n=15)	Chemotherapy (n=49)
Patients receiving any post-recurrence treatment	13 (86.7)	43 (87.8)
Systemic therapy	13 (86.7)	38 (77.6)
ALK TKI	7 (46.7)	37 (75.5)
Alectinib	4 (26.7)	29 (59.2)
Brigatinib	4 (26.7)	4 (8.2)
Crizotinib	0	4 (8.2)
Lorlatinib	0	2 (4.1)
Ceritinib	0	1 (2.0)
Chemotherapy	6 (40.0)	2 (4.1)
Other anti-cancer therapy	1 (6.7)	1 (2.0)
Immunotherapy	1 (6.7)	1 (2.0)
Radiotherapy	5 (33.3)	9 (18.4)
Surgery	1 (6.7)	3 (6.1)

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

The CEA does not consider grade 1-2 adverse events as these are events that are defined by mild to moderate symptoms which may not require any intervention. It only considers grade 3-5 treatment emergent adverse events as these are events that are treatment related and produce severe to life threatening symptoms that may require an invasive or emergency intervention. Table 56 (in Appendix E) presents the adverse events used in the health economic model. These are identified through an SLR described in Appendix J. The CEA uses this data to calculate a monthly probability of experiencing each event while on treatment together with an estimate on total follow-up.

$$P(adverse\ event_x) = 1 - e^{-occurence_x / follow-up}$$

x is the adverse event, occurence is the number of times it occurred, and follow-up is follow-up in months. The CEA uses the same sources to inform the adverse events realized

by patients on metastatic treatment after recurrence that it uses to inform PFS, as ALINA does not collect information on this matter for patients on subsequent treatment after earliest contributing event. Unfortunately, for chemoradiotherapy, Nakamichi et al. (2017) do not provide any evidence on adverse events. Thus, the CEA informs the AEs of these patients with the AEs of the control arm of ALINA as both patients receive 4 cycles of cisplatin-based chemotherapy. A limitation of this approach is that it may not account for the AEs that are caused by the radiotherapy. However, it is deemed appropriate in the absence of reliable evidence. The CEA uses the same formula above to calculate a monthly probability of experiencing each of the events. A limitation with the use of these studies is that they did not present any evidence on the occurrence of grade 3-5 treatment emergent adverse events. Instead, they presented evidence on the number of patients who experienced each grade 3-5 adverse event. Data on SAE for subsequent treatment lines in the health economic model is presented in appendix E.

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

Table 33 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
SF-36	ALINA (BO40336)	Clinical effectiveness
EQ-5D-5L	ALINA (BO40336)	Utilities/Clinical effectiveness
EQ-5D-VAS	ALINA (BO40336)	Clinical effectiveness

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

HRQoL was an exploratory endpoint in ALINA (BO40336) to document the impact of alectinib compared with platinum-based chemotherapy on patients' quality of life and daily function as measured using. It was measured using the Short Form-36 version 2 (SF-36v2) health survey. SF-36v2 was the primary instrument for collection HRQoL, and is therefore carefully described below. In addition til SF-36v2 HRQoL was also measure using EQ-5D, which is also presented as a supplement.

Patients randomized to the chemotherapy arm could receive four 21-day cycles of treatment whereas patients randomized to the alectinib arm could continue to receive treatment up to Week 96. Due to this difference in the treatment schedules, Patient-Reported Outcomes (PRO) comparisons between arms were only made up to and including Week 12. The analysis presented here is focused on the ITT population. However, similar results were observed in the subpopulation with stage II-IIIA disease.

10.1.2 Data collection

In ALINA (BO40336), HRQoL was measured using the SF-36v2 health quesionaire. SF-36v2 assesses functional health and well-being across 8 domains and 2 aggregated summary scores: the physical (PCS) and mental (MCS) component summary scores. Patients in ALINA (BO40336) completed the SF-36v2 at baseline, every 3 weeks to Week 12, then every 12 weeks until disease recurrence, withdrawal of consent, death, or Week 96 (or equivalent post-chemotherapy follow-up visit) – the same is the case for EQ-5D. SF-36v2 was scored using norm-based scoring relative to the 2009 US general population (mean ± standard deviation: 50 ± 10), with higher scores indicating better health. Within-group minimal important differences (MIDs) were used as benchmarks for each domain, MCS and PCS.

Table 34 Pattern of missing data and completion – SF36v2 and EQ-5D-5L VAS

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)	
			Alectinib			
		SF-36	EQ-5D		SF-36	EQ-5D
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Chemotherapy			
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.1.3 HRQoL results

SF-36v2 assesses functional health and well-being across 8 domains and 2 aggregated summary scores: the physical (PCS) and mental (MCS) component summary scores. Below the summary scores, PCS and MCS together with EQ-5D, are presented. However, illustrations and tables of the domains are presented in Appendix F.

Figure 31: SF-36v2 - Mental component summary

Figure 32: SF-36v2 - Physical Component Summary

Figure 33: EQ-5D-VAS

Figure 34: EQ-5D-VAS

Table 35 HRQoL SF-36v2 - summary statistics MCS and PCS

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Mental Component Summary (MCS)					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]			N/A
Week 36	[redacted]	[redacted]			N/A
Week 48	[redacted]	[redacted]			N/A
Week 60	[redacted]	[redacted]			N/A
Week 72	[redacted]	[redacted]			N/A
Week 84	[redacted]	[redacted]			N/A
Week 96	[redacted]	[redacted]			N/A
Physical Component Summary (PCS)					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]			N/A
Week 36	[redacted]	[redacted]			N/A
Week 48	[redacted]	[redacted]			N/A
Week 60	[redacted]	[redacted]			N/A
Week 72	[redacted]	[redacted]			N/A
Week 84	[redacted]	[redacted]			N/A
Week 96	[redacted]	[redacted]			N/A
		[redacted]			
	VAS	**5L**	**VAS**	**5L**	
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [redacted]
Week 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [redacted]

Week 24	[redacted]	[redacted]	[redacted]	N/A
Week 36	[redacted]	[redacted]	[redacted]	N/A
Week 48	[redacted]	[redacted]	[redacted]	N/A
Week 60	[redacted]	[redacted]	[redacted]	N/A
Week 72	[redacted]	[redacted]	[redacted]	N/A
Week 84	[redacted]	[redacted]	[redacted]	N/A
Week 96	[redacted]	[redacted]	[redacted]	N/A

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

10.2.1 HSUV calculation

ALINA administered the EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L) with different frequencies for patients in the intervention and control arms. For the intervention arm, the questionnaire was administered at baseline, every 3 weeks through week 12, and every 12 weeks thereafter until recurrence, withdrawal of consent, death or week 96 and additionally at the safety and disease follow-up visits. For the control arm, it was administered at baseline, every 3 weeks through week 12 and at the safety and disease follow-up visits. Responses were converted to health state utility values (HSUV) between 0 (death) and 1 (perfect health) with the use of a Denmark-specific algorithm (Jensen et al 2021) (61). Figure 35 descriptively summarizes the HSUVs.

Figure 35 Graphical Display of Utilities per (Jensen et al 2021) (61)

The CEA uses a linear mixed-effects model with normal random subject effects to evaluate the effect of baseline health state utility values (mean subtracted), treatment with alectinib, being off treatment, and being off treatment conditional on treatment with alectinib on a patients HSUV while being disease-free. Table 36 presents the results of the mixed-effects model, which shows that all factors have a statistically significant effect, with the exception of being off treatment conditional on treating with alectinib.

Table 36 Health State Utility Values – Mixed-Effects Model Danish tariffs (ALINA; CCOD: June 26, 2023)

Variable	Estimate	S.E.	T-Value
Intercept	[redacted]	[redacted]	[redacted]
Baseline Utility			
Alectinib			
Off-Treatment			
Alectinib*Off-Treatment			

Age and gender adjusted utility values for the Danish general population has been used according to the DMC guidance.

Table 37 summarizes the results from the mixed-effects model. The CEA uses the estimates to inform the HSUV of disease-free patients conditional on treatment received and whether they are on or off treatment.

Table 37 Health State Utility Values – Summary Danish tariffs (ALINA; CCOD: June 26, 2023)

Variable	Estimate	S.E.
Alectinib – On-Treatment	[redacted]	[redacted]
Alectinib – Off-Treatment		
Chemotherapy – On Treatment		
Chemotherapy – Off-Treatment		

10.2.2 Mapping

N/A

10.2.3 Disutility calculation

Disutilities has not been used in the health economic analysis.

10.2.4 HSUV results

Table 38 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Alectinib – On-Treatment	[redacted]	EQ-5D-5L	DK	More info in section 10.2.1
Alectinib – Off-Treatment	[redacted]	EQ-5D-5L	DK	More info in section 10.2.1
Chemotherapy – On Treatment	[redacted]	EQ-5D-5L	DK	More info in section 10.2.1
Chemotherapy – Off-Treatment	[redacted]	EQ-5D-5L	DK	More info in section 10.2.1
Non-Metastatic Recurrence	[redacted]	EQ-5D	UK	More info in section 10.2.1
Metastatic progression	[redacted]	EQ-5D	UK	More info in section 10.2.1

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

The CEA uses external sources to inform the health-state utility values of patients after experiencing non-metastatic recurrence, metastatic recurrence and further metastatic progression as ALINA does not administer the EQ-5D-5L questionnaire after recurrence. An SLR was conducted on the health related quality of life of patients with locally advanced or metastatic NSCLC. The SLR identified one relevant study (62). Table 39 presents the results that the CEA includes. The CEA only uses the estimates of the intercept and stage IV covariates to calculate the health state utility values associated with these health states as it appears that the other factors do not have a statistically significant effect on the HSUV of patients with advanced NSCLC. This results in use of HSUV values of 0.77 and 0.71 for patients who are in the non-metastatic and metastatic recurrence health states. This is not used in our base-case.

Table 39 Health State Utility Values – Non-Metastatic Recurrence, Metastatic Recurrence (first-line) and Metastatic Recurrence (second-line) (62)

Variable	Estimate	S.E.	P-Value
Intercept	[redacted]	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]	[redacted]
Progression (first-line)	[redacted]	[redacted]	[redacted]
Progression-free (second-line)	[redacted]	[redacted]	[redacted]
Progression (second-line)	[redacted]	[redacted]	[redacted]

In addition to the use of the above utility values, the CEA restricts the utility values of all patients to not be higher than the age and sex adjusted utility values of the general population.

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Non-Metastatic Recurrence	[redacted]	EQ-5D	UK	More info see above
Metastatic progression	[redacted]	EQ-5D	UK	More info see above

10.2.5 Study design

N/A. See above

10.2.6 Data collection

N/A. See above

10.2.7 HRQoL Results

N/A. See above

10.2.8 HSUV and disutility results

N/A. See above

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

Costs and resource use vary depending on the administered treatment and health states. The model includes drug costs, administration costs, subsequent therapy costs, Disease management costs, and AE costs. The costs included are consistent with the limited societal perspective as described in the DMC guidelines (28). Drug costs are estimated from Medicinpriser.dk, where administration costs, disease management costs, and AE costs are based on the Danish diagnose relative group (DRG) tariffs 2024.

For all pharmaceuticals administered in the model, pharmacy purchase prices (PPP) have been used. Drug acquisition costs are applied to patients in each health state. For intravenous therapies, the CEA assumes perfect vial sharing, and uses the cheapest vial size per mg. This simplification is conservative as it is expected that it would affect the results in favor of chemotherapy.

Table 41 Medicine costs used in the model

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Average duration of treatment
Alectinib	150 mg	224	33,270	21.72 Months
Cisplatin plus Vinorelbine	1 mg/ml	50 ml	100	11.29 Weeks
	1 mg/ml	100 ml	200	
	10 mg/ml	1 ml	245	
	10 mg/ml	5 ml	1,240	
Cisplatin plus Gemcitabine	1 mg/ml	50 ml	100	12.00 Weeks
	1 mg/ml	100 ml	200	
	40 mg/ml	25 ml	1,000	
	40 mg/ml	50 ml	1,200	
Cisplatin plus Pemetrexed	1 mg/ml	50 ml	100	11.31 Weeks
	1 mg/ml	100 ml	200	
	25 mg/ml	4 ml	1,650	
	25 mg/ml	20 ml	8,250	
Carboplatin plus Vinorelbine	10 mg/ml	15 ml	295	12.00 Weeks
	10 mg/ml	45 ml	226	
	10 mg/ml	1 ml	245	

	10 mg/ml	5 ml	1,240	
Carboplatin plus Gemcitabine	10 mg/ml	15 ml	295	12.00 Weeks
	10 mg/ml	45 ml	226	
	40 mg/ml	25 ml	1,000	
	40 mg/ml	50 ml	1,200	
Carboplatin plus Pemetrexed	10 mg/ml	15 ml	295	10.42 Weeks
	10 mg/ml	45 ml	226	
	25 mg/ml	4 ml	1,650	
	25 mg/ml	20 ml	8,250	

11.2 Medicine costs – co-administration

N/A.

11.3 Administration costs

The unit costs for the mode of administration were obtained from DRG tariffs 2024 and are applied to the administration cost in the model and presented in Table 42.

Table 42 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	Every day	0	-	-
IV	Once per administration	1311.00	17MA98	MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnose: DC384:Kræft i lungehinde: BWAA: Medicingivning intravenøst

11.4 Disease management costs

The CEA accounts for CT scan costs that are associated with follow-up care. The frequency at which CT scans are administered differs for patients who are disease-free and have experienced non-metastatic recurrence or metastatic recurrence. In the adjuvant treatment stage the patient is scanned every 3rd month for the first two years. Then every six months between year three and four and one scan year five. After disease progression the patient is followed up every three months. This involves one doctors visit and one CT scan (28).

The pathology department always tests for next generation sequencing NGS and PD-L1 status on all resected patients with higher status than pT1cN0M0, which means all patients that are candidates for adjuvant ALK therapy. This is in clinical practice today and leads to no additional cost.

If a patient relapses shortly after the two year treatment period with an ALK inhibitor a TKI re-challenge will be initiated.

Table 43 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Conformal 3-dimensional radiotherapy	Once per week for 7 weeks	32,520.00	27MP02	DRG 2024
Intensity modulated radiotherapy	Not used in the model	2,709.00	27MP04	DRG 2024
Computerised Tomography Scan	Every 3rd month for the first two years. Then every 6 months between year three and four. One scan year five(28)	2,585.00	30PR06	DRG 2024
Doctors visit	Every CT scan(28)	2111	16MA98	DRG 2024
ALK testing	Before surgery	0	-	Already standard clinical practise(28)

11.5 Costs associated with management of adverse events

The CEA calculates the monthly probability of experiencing adverse events across health states and treatment options (see section 9 for more details). This allows it to identify the proportion of patients who experience each AE while on treatment. To calculate the cost of managing adverse events, the CEA applies the costs reported in Table 44 to the proportion of patients who experienced them. For less costly events the CEA assumes that the management of the remaining adverse events impose a cost equal to the cost of a general practitioner consultation visit (DRG 13MA98) at the cost of 2111 DKK as of the latest DRG for 2024.

Table 44 Cost associated with management of adverse events

Adverse Event	Reference	Unit Cost in DKK (LC)
Abdominal pain	16MA98	2111
Abdominal pain upper	16MA98	2111
Acute kidney injury	16MA98	2111
Alanine aminotransferase increased	07MA14	31847
Amylase increased	16MA98	2111
Anaemia	16PR02	4218
Angina pectoris	16MA98	2111
Aphasia	16MA98	2111
Appendicitis	06MP17	54961
Arthralgia	16MA98	2111
Aspartate aminotransferase increased	07MA14	31847

Asthenia	16MA98	2111
Atrial flutter	16MA98	2111
Back pain	16MA98	2111
Biliary tract infection	16MA98	2111
Blood alkaline phosphate increased	16MA98	2111
Blood bilirubin increased	16MA98	2111
Blood CPK	16MA98	2111
Blood creatine increased	16MA98	2111
Blood creatine phosphokinase increased	23MA03	5103
Blood lactate dehydrogenase increased	16MA98	2111
Bronchitis	16MA98	2111
Cerebrovascular accident	16MA98	2111
Chest pain	16MA98	2111
Chronic kidney disease	16MA98	2111
Cognitive disorder	16MA98	2111
Cognitive effects	16MA98	2111
Confusional state	16MA98	2111
Constipation	16MA98	2111
Cough	16MA98	2111
Creatinine renal clearance decreased	16MA98	2111
C-reactive protein increased	16MA98	2111
Decreased appetite	16MA98	2111
Deep vein thrombosis	16MA98	2111
Dehydration	16MA98	2111
Depression	16MA98	2111
Depressed level of consciousness	16MA98	2111
Diarrhoea	16MA98	2111
Dysphagia	16MA98	2111
Dyspnea	16MA98	2111
Electrocardiogram Qt prolonged	16MA98	2111
Electrocardiogram T-wave inversion	16MA98	2111
Embolism	01SP01	6661
Epigastric discomfort	16MA98	2111
Epilepsy	16MA98	2111
Faecaloma	16MA98	2111
Fatigue	01PR02	3308
Febrile neutropenia	04MA07	45583
Gamma-glutamyltransferase increased	16MA98	2111
Gastrointestinal obstruction	16MA98	2111
Gastrointestinal perforation	16MA98	2111
General physical health deterioration	16MA98	2111
Glutamyltransferase increased	16MA98	2111
Headache	16MA98	2111
Hepatic enzyme increased	16MA98	2111
Hyperbilirubinaemia	16MA98	2111
Hypercholesterolaemia	16MA98	2111
Hyperglycaemia	16MA98	2111
Hyperlipidaemia	16MA98	2111
Hypertension	16MA98	2111
Hypertensive crisis	16MA98	2111
Hypertriglyceridaemia	16MA98	2111
Hypokalemia	16MA98	2111
Hyponatremia	16MA98	2111
Hypophosphatemia	16MA98	2111

Hypoxia	16MA98	2111
Interstitial lung disease	16MA98	2111
Jaundice	16MA98	2111
Lenticular opacities	16MA98	2111
Leukopenia	16MA98	2111
Lipase increased	16MA98	2111
Liver function test increased	07MA98	1947
Loss of consciousness	16MA98	2111
Lower respiratory tract infection	16MA98	2111
Lung infection	16MA98	2111
Lung infiltration	16MA98	2111
Lymphocyte count decreased	16MA98	2111
Lymphoedema	40PR01	1818
Malaise	16MA98	2111
Mobility decreased	16MA98	2111
Mood effects	16MA98	2111
Muscular weakness	16MA98	2111
Myalgia	08MA15	2026
Myocardial ischemia	16MA98	2111
Nausea	03MA02	8171
Neoplasm progression	16MA98	2111
Neutropenia	04MA07	45583
Neutrophil count decreased	16MA98	2111
Non-cardiac chest pain	16MA98	2111
Oedema	16MA98	2111
Pain	16MA98	2111
Pain in extremity	16MA98	2111
Pathological fracture	16MA98	2111
Pericardial effusion	16MA98	2111
Pericarditis	16MA98	2111
Peripheral neuropathy	01MA04	30685
Petit mal epilepsy	16MA98	2111
Pleural effusion	16MA98	2111
Pneumonia	16MA98	2111
Pneumonitis	04MA13	43907
Pneumothorax	16MA98	2111
Pulmonary embolism	08MA15	2026
Pyrexia	16MA98	2111
Rash	16MA98	2111
Rash maculo-papular	16MA98	2111
Regurgitation	16MA98	2111
Respiratory distress	16MA98	2111
Respiratory failure	16MA98	2111
Respiratory tract infection	16MA98	2111
Stomatitis	16MA98	2111
Syncope	16MA98	2111
Transaminases increased	16MA98	2111
Tumour flare	16MA98	2111
Typhoid fever	16MA98	2111
Type 2 diabetes mellitus	10MA03	37913
Urinary bladder rapture	16MA98	2111
Urinary tract infection	11MA07	30859
Vision disorder	16MA98	2111
Vomiting	16MA98	2111

Weight decreased	16MA98	2111
Weight increased	16MA98	2111
White blood cell count decreased	16MA98	2111

11.6 Subsequent treatment costs

For more details see section 8.

Table 45 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Average duration of treatment
Cisplatin plus Pemetrexed	1 mg/ml	50 ml	100	See Table 28
	1 mg/ml	100 ml	200	
	25 mg/ml	4 ml	1,650	See Table 28
	25 mg/ml	20 ml	8,250	
Alectinib	150 mg	224 Tablets	33,270	See Table 28
Crizotinib	250 mg	60 Tablets	30,353	See Table 28
Brigatinib	180 mg	28 Tablets	34,461	See Table 28
Lorlatinib	25 mg	30 Tablets	35,971	See Table 28
Ceritinib	150 mg	84 Tablets	20,377	See Table 28

11.7 Patient costs

Patient costs has been added to the model according to the health economic model. For each time a patient visits the hospital it is assumed that the patient will spend one hour. The cost of that one patient hour is assumed to be 188 DKK. It is assumed that a patient will not continue follow-up if assumed cured (5 years diease-free). Transportation is assumed to be 180 per visit according the DMC guidelines.

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

Other costs have not been applied.

12. Results

12.1 Base case overview

Table 46 Base case overview

Feature	Description
Comparator	Platinum-based chemotherapy
Type of model	Cohort level Semi-Markov model
Time horizon	40 years (life time)
Treatment line	Adjuvant
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L ALINA (BO40336) CCOD: June 26, 2023 (9). Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Administration costs Disease management costs Costs of adverse events Subsequent treatment costs Patient costs
Dosage of medicine	Fixed and based on weight
Average time on treatment	Intervention: 21.72 Months Comparator: 11.29 Weeks
Parametric function for PFS	Intervention: Log-logistic Comparator: Log-logistic
Parametric function for OS	See section 8.2.2.2.4
Inclusion of waste	No
Average time in model health state	Alectinib (Discounted years)
Disease-free survival	13.416
Non-Metastatic recurrence 2L	0.308
Metastatic recurrence 1L	0.491

Metastatic recurrence 2L	0.273

12.1.1 Base case results

Table 47 Base case results, discounted estimates

	Alectinib	Chemotherapy	Difference
Drug acquisition costs	757.585	53.448	704.137
Drug administration costs			0
Adverse event costs	2.152	2.025	2.152
Monitoring costs	51.486	66.133	-14.647
Subsequent treatment	270.484	625.059	-354.575
Patient time and transport costs	7.646	8.340	-694
Total costs	1.089.353	755.005	334.348
Life years gained (DFS)	14,5	10,2	4,3
Total QALYs	11,6	8,1	3,57
Incremental costs per life year gained		**78,299**	
Incremental cost per QALY gained (ICER)		**93,699**	

12.2 Sensitivity analyses

To identify key model drivers and the influence of parameter uncertainty, one-way deterministic sensitivity analyses (DSA) are conducted using alternate values for model parameters. To test the impact of applying different assumption, scenario analyses are conducted for the key model parameters.

To test the robustness of results with respect to uncertainty in the model input parameters, a probabilistic sensitivity analysis (PSA) is performed using a Monte Carlo simulation. In this analysis, each parameter subject to parameter uncertainty is assigned a probability distribution, and cost-effectiveness results associated with the simultaneous selection of random values from the distribution of each of these parameters were generated. The process was repeated for 1,000 iterations and results of the PSA were plotted on the cost-effectiveness plane (or scatter plot) and were used to calculate cost-effectiveness acceptability curves (CEACs), highlighting the probability of cost-effectiveness over various willingness to pay thresholds.

12.2.1 Deterministic sensitivity analyses

Impact on the ICER of the range of some key parameters is presented in Figure 36 below. The tornado diagram presents the relative impact some key influential model parameters have on the list-price ICER (93,9322 DKK per QALY).

Figure 36 Univariate sensitivity analysis - Alectinib vs Chemotherapy - Inc. cost-utility ratio (Base case: DKK 93,669 DKK/QALY)

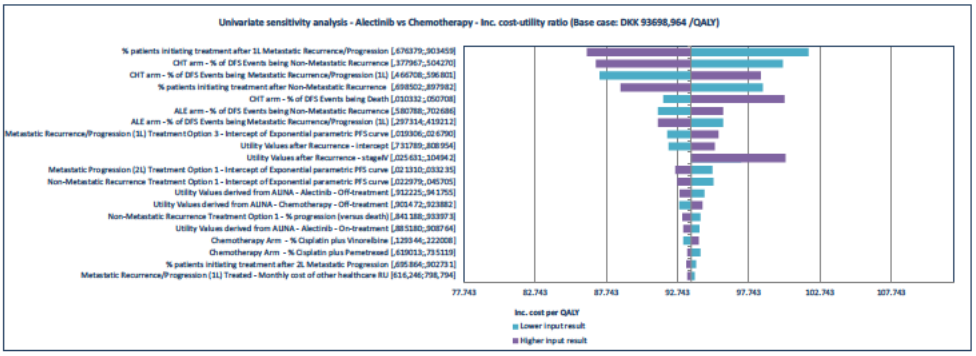


Table 48 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					
% patients initiating treatment after 1L Metastatic Recurrence/Progression	+/-10%	Important assumption	375,810 DKK 299,648 DKK	3.69 3.47	101,926 DKK 86,381 DKK
CHT arm - % of DFS Events being Non-Metastatic Recurrence	+/-10%	Important assumption	358,008 DKK 309,825 DKK	3.59 3.55	100,117 DKK 87,013 DKK
CHT arm - % of DFS Events being Metastatic Recurrence/Progression (1L)	+/-10%	Important assumption	356.102 DKK 306.394 DKK	3.59 3.55	98,587 DKK 87,265 DKK
% patients initiating treatment after Non-Metastatic Recurrence	+/-10%	Important assumption	356,256 DKK 313,194 DKK	3.61 3.53	98,719 DKK 88,744 DKK
CHT arm - % of DFS Events being Death	+/-10%	Important assumption	341,386 DKK 332,026 DKK	3.45 3.60	100,261 DKK 91,754 DKK
ALE arm - % of DFS Events being Non-Metastatic Recurrence	+/-10%	Important assumption	343,038 DKK 325,332 DKK	3.58 3.56	95.928 DKK 91.377 DKK
ALE arm - % of DFS Events being Metastatic Recurrence/Progression (1L)	+/-10%	Important assumption	325,332 DKK 343,038 DKK	3.56 3.58	91.377 DKK 95.928 DKK

Additional analysis presented above in the tornado diagram, as scenario analysis and in the model.

12.2.2 Scenario analysis

Scenario analyses are performed to explore how changing some of the key model parameters will impact the model results.

Table 49 below summarizes the main scenario results. Based on the various parameter settings explored in the scenario analyses, the resulting ICERs are differentiating in Alectinib being cost-effective compared to Platinum based chemotheraphy (i.e., max ICER ranging between 69,827 DKK to 321,992 DKK)

Table 49 Scenario analysis

Parameter	Inc. cost per QALY (DKK)	DKK Δ ICER vs base case
Base case	93,699	
Assumptions		
Time horizon: 10 years	294,545	200,846
Time horizon: 15 years	172,082	78,383
Time horizon: 20 years	127,940	34,241
Time horizon: 25 years	107,403	13,704
Time horizon: 30 years	98,986	5,287
Time horizon: 35 years	95,033	1,334
DFS distribution		
Exponential	84,110	-9,589
Weibull	71,350	-22,349
Log-normal	124,375	30,676
Generalized Gamma	88,727	-5,427
Gompertz	70,270	-23,429
Gamma	76,031	-17,668
TTOT distribution		
Exponential	108,246	14,577
Weibull	102,870	9,201

Log-normal	107,376	13,707
Generalized Gamma	130,985	37,616
Gompertz	117,005	23,336
Gamma	98,537	4,868
Treatment effect		
DFS data pooled across arms	81,300	-12,369
Treatment effect decrease after 24 months and is zero at month 60	204,460	110,791

12.2.3 Probabilistic sensitivity analyses

The cost-effectiveness plane and incremental cost-effectiveness plane, illustrating the QALYs and costs and the incremental QALYs and costs, respectively, are presented in Figure 38 and Figure 39 below using list prices. This represents the joint distribution of costs and effect for the intervention (Alectinib), and the comparator included in the model (Platinum Based Chemotheraphy) and the incremental results between these. All of simulated ICERs are located in the Nord East quadrant, indicating the intervention to be costlier and more effective than the comparator.

Figure 37 Cost-Effectiveness Plane

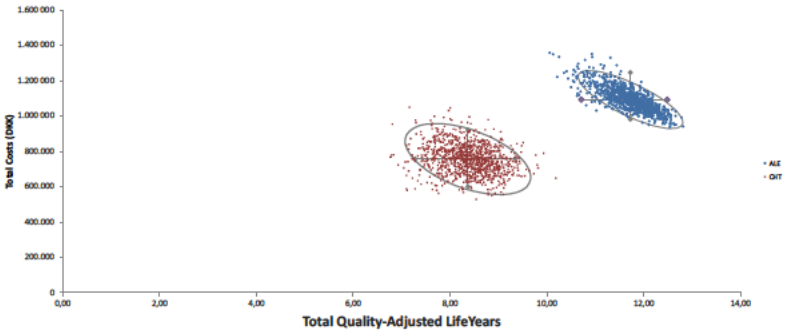


Figure 38 Incremental Cost-Effectiveness Plane

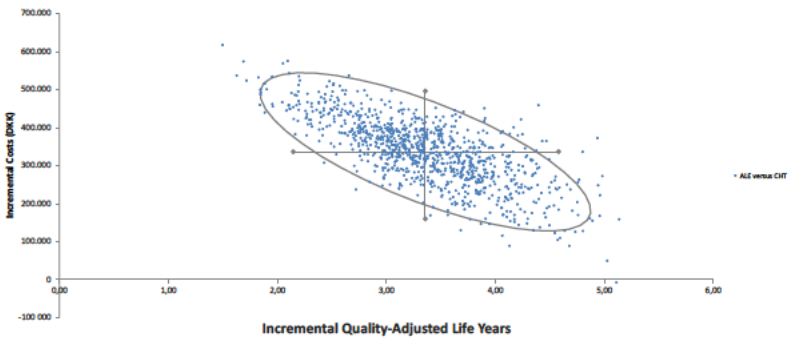
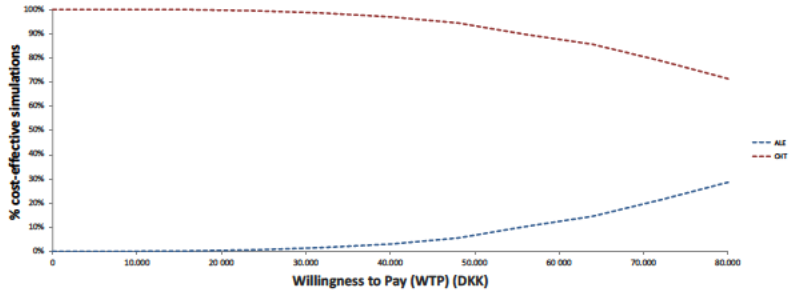


Figure 39 Cost-Effectiveness Acceptability Curve



13. Budget impact analysis

13.1 Number of patients: 8 (assumed Market share 100%)

Table 50 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		
Adjuvant Alectinib	8	8	8	8	8
Platinum-based chemotherapy	0	0	0	0	0
			Non-recommendation		
Adjuvant Alectinib	0	0	0	0	0
Platinum-based chemotherapy	8	8	8	8	8

13.2 Budget impact

Table 51 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	3.460.359	6.889.116	7.333.744	7.845.523	8.343.888
The medicine under consideration is NOT recommended	1.021.705	2.044.863	3.158.491	4.239.614	5.140.368
Budget impact of the recommendation	**2.438.655**	**4.844.253**	**4.175.252**	**3.605.910**	**3.203.520**

14. List of experts

In this application Morten Suppli, Medical doctor specializing in Clinical Oncology at Rigshospitalet consulted Roche during the application.

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Appendix A. Main characteristics of studies included

Table 52 Main characteristic of studies included

Trial name: ALINA (BO40366)	NCT number: NCT03456076
Objective	To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in adjuvant treatment of ALK-positive NSCLC.
Publications – title, author, journal, year	• Final manuscript will be published April 2024 in NEJM. • ALINA: efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC); R Shah et al.; Presented at 36TH GERMAN CANCER CONGRESS, 21-24 February 2024. • ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC); BJ Solomon et al.; Presented at ESMO, October 2023. (8) • ALINA: A phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC); BJ Solomon et al.; Journal of Clinical Oncology, 2019. (63)
Study type and design	ALINA (BO40336) is phase III, open-label, randomised study. Enrolled patients were randomised 1:1 via an interactive voice or Web-based response system (IxRS) and stratified by extent of disease (Stage IB [tumors ≥4 cm] vs. Stage II vs. Stage IIIA) and race (Asian vs. non-Asian). No crossover was allowed. First Patient Enrolled: 16 Aug 2018 Last patient Enrolled: 8 Dec 2021 CCOD: 26 June 2023 ALINA is still ongoing and is expected to be completed in 2026.
Sample size (n)	257
Main inclusion criteria	• Age ≥18 years • Complete resection of histologically confirmed Stage IB (tumor ≥ 4 cm) to Stage IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) NSCLC as per Union Internationale Contre le Cancer / American Joint Committee on Cancer, 7th edition, with negative margins, at 4-12 weeks before enrollment

	• If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred • Documented ALK-positive disease according to an FDA-approved and CE-marked test • Eligible to receive a platinum-based chemotherapy regimen according to the local labels or guidelines • Eastern Cooperative Oncology Group Performance Status of Grade 0 or 1 • Adequate hematologic and renal function • For women of childbearing potential: agreement to remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy • For men: agreement to remain abstinent or use contraceptive measures, and agreement to refrain from donating sperm for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy. Men must refrain from donating sperm during this same period • Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures
Main exclusion criteria	• Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy • Prior adjuvant radiotherapy for NSCLC • Prior exposure to systemic anti-cancer therapy and ALK inhibitors • Stage IIIA N2 patients that, in the investigator's opinion, should receive post-operative radiotherapy treatment are excluded from the study • Known sensitivity to any component of study drug to which the patient may be randomized. This includes, but is not limited to, patients with galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption. • Malignancies other than NSCLC within 5 years prior to enrollment, except for curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, ductal carcinoma in situ, papillary thyroid cancer, or any cured cancer that is considered to have no impact on disease free survival or overall survival for the current NSCLC • Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post-major bowel resection • Liver disease characterized by aspartate transaminase and alanine transaminase >= 3 × upper limit of normal or impaired excretory

	function or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, or bleeding from esophageal varices or active viral or active autoimmune, alcoholic, or other types of acute hepatitis • Japanese patients participating in the serial/intensive PK sample collection only: administration of strong/potent CYP450 3A inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib up to Week 3 • Any exclusion criteria based on the local labels or guidelines for chemotherapy regimen • Patients with symptomatic bradycardia • History of organ transplant • 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 pose an unacceptable risk to the patients in this study, in the opinion of the Principal Investigator • 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 130 participants were enrolled in the alectinib arm. Participants received alectinib 600 mg orally twice daily until completion of treatment period (24 months) or recurrence of disease, unacceptable toxicity, withdrawal of consent or death, whichever occurs first.
Comparator(s)	Adjuvant Platinum-Based Chemotherapy 127 participants were enrolled in the chemotherapy-arm. Cisplatin 75 milligrams per square meter (mg/m^2) on Day 1 every 21 days IV intravenously (IV) until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. Vinorelbine 25 mg/m^2 IV on Days 1 and 8 Q21D until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. Gemcitabine 1250 mg/m^2 on Days 1 and 8 Q21D IV until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

	Pemetrexed 500 mg/m^2 Day 1 Q21D until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. For participants who experience unacceptable toxicity with cisplatin, carboplatin can be used.
Follow-up time	Median survival follow-up period at CCOD was 27.8 and 28.4 months in the alectinib and chemotherapy arms.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoint • Disease-free Survival (DFS), as Assessed by the Investigator [Time Frame: From the date of randomization until the first DFS event, up to approximately 5 years] Secondary endpoint • Overall Survival (OS) [Time Frame: From the date of randomization until death due to any cause up to approximately 8 years] • Plasma Concentration of Alectinib [Time Frame: Predose (2 hours) at Baseline, Week 3, 6, 9, 12, 24, 36, 48, 60, 72, 84, and 96] • Plasma Concentration of Alectinib metabolite [Time Frame: Predose (2 hours) at Baseline, Week 3, 6, 9, 12, 24, 36, 48, 60, 72, 84, and 96] • Percentage of Participants with Adverse Advent [Time Frame: From the date of randomization up to approximately 2 years] [State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results must be provided in Appendix D.] **Endpoints included in this application:** DFS as assessed by the investigator OS Safety
Method of analysis	All efficacy analyses were intention-to-treat population and stage II-IIIA population analyses. We used the Kaplan–Meier method to estimate rates of disease-free survival and overall survival.
Subgroup analyses	Stage II-IIIA population (see description in the application)

Other relevant information	N/A

Appendix B. Efficacy results per study

Table 53 Results per study

Results of ALINA (NCT: NCT03456076)											
				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		
No. of pt with DFS-events (Stage II–IIIA)	Alectinib Chemotherapy	116 115	14 (12.1%) 45 (39.1%)	N/A	N/A	N/A	N/A	N/A	N/A		
Median DFS (Stage II–IIIA)	Alectinib Chemotherapy	116 115	NE (NE, NE) 44.4 (27.8, NE)	N/A	N/A	N/A	HR: 0.24	0.13–0.45	<0.0001	Kaplan-Meier estimates with 95% CI computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.	
No. of deaths (Stage II–IIIA)	Alectinib Chemotherapy	116 115	2 (1.7%) 2 (1.7%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Median OS	Alectinib	116	NE (NE, NE)	N/A	N/A	N/A	HR: 0.96	0.14, 6.82	0.9676	Kaplan-Meier estimates with 95% CI computed using the	

Results of ALINA (NCT: NCT03456076)											
				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		
(Stage II–IIIA)	Chemotherapy	115	NE (NE, NE)							method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.	
No. of pt with CNS-DFS-events (Stage II–IIIA)	Alectinib Chemotherapy	116 115	5 (4.3%) 16 (13.9%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Median time to CNS-DFS event (Stage II–IIIA)	Alectinib Chemotherapy	116 115	NE (NE, NE) NE (NE, NE)	N/A	N/A	N/A	HR: 0.24	0.09-0.65	0.0022	Kaplan-Meier estimates with 95% CI computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.	
No. of pt with DFS-events (ITT pop.)	Alectinib Chemotherapy	130 127	15 (11.5%) 50 (39.4%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

Results of ALINA (NCT: NCT03456076)											
				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 DFS (ITT pop.)	Alectinib Chemotherapy	130 127	NE (NE, NE) 43.1 (28.5, NE)	N/A	N/A	N/A	HR: 0.24	0.13–0.43	<0.0001	Kaplan-Meier estimates with 95% CI computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression	
No. of deaths (ITT pop.)	Alectinib Chemotherapy	130 127	2 (1.5%) 4 (3.1%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Median OS (ITT pop.)	Alectinib Chemotherapy	130 127	NE (NE, NE) NE (NE, NE)	N/A	N/A	N/A	HR: 0.46	0.08-2.25	0.3603	Kaplan-Meier estimates with 95% CI computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.	
No. of pt with CNS-DFS-events (ITT pop.)	Alectinib Chemotherapy	130 127	5 (3.8%) 18 (14.2%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Median time to	Alectinib	130	NE (NE, NE)	N/A	N/A	N/A	HR: 0.22	0.08-0.58	0.0009	Kaplan-Meier estimates with 95% CI computed using the	

Results of ALINA (NCT: NCT03456076)											
				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		
CNS-DFS event (ITT pop.)	Chemotherapy	127	NE (NE, NE)							method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.	

Appendix C. Comparative analysis of efficacy

N/A.

ALINA (BO40336) is a head-to-head study which provide a direct comparison of alectinib and platinum-based chemotherapy regimens. Results are presented in Appendix B.

Appendix D. Extrapolation

All relevant methods and choices on extrapolation besides the tables below are presented in section 8.

Table 54 Disease-Free Survival ≥5 Years (Clinical SLR [Early-Stage NSCLC]; Search: September, 2023)

Study	Intervention	Disease Stage and Mutation Status	Data Cut-Off	DFS
(Shen, et al., 2014)(64)	Cisplatin + Paclitaxel + Radiotherapy	Stage IIIA-pN2	2009	5-Year: 30.3%
	Cisplatin + Paclitaxel			5-Year: 18.8%
Adaura (Wu, et al., 2022)(65)	Osimertinib	Stage IB (AJCC/UICC 7th Edition), EGFR+	2022	5-Year: 78%
	Placebo			5-Year: 53%
	Osimertinib	Stage II (AJCC/UICC 7th Edition), EGFR+		5-Year: 58%
	Placebo			5-Year: 37%
	Osimertinib	Stage IIIA (AJCC/UICC 7th Edition), EGFR+		5-Year: 49%
	Placebo			5-Year: 12%
	Osimertinib	Stage IB (AJCC/UICC 8th Edition), EGFR+		5-Year: 78%
	Placebo			5-Year: 55%
	Osimertinib	Stage II (AJCC/UICC 8th Edition), EGFR+		5-Year: 60%
	Placebo			5-Year: 37%
	Osimertinib	Stage IIIA (AJCC/UICC 8th Edition), EGFR+		5-Year: 47%
	Placebo			5-Year: 15%
(Ueda, Sakada, Kuwahara, & Motohiro, 2004)(66)	Futraful + Uracil	Stage IA-IIIA	n.r.	5-Year: 86%
	Observation			5-Year: 46%
Magrit (Vansteenkiste, et al., 2016)(67)	MAGE-A3 immuno-therapeutic	Stage IB-IIIA, Positive for MAGE-A3 expression	2014	5-Year: 51.7%
	Placebo			5-Year: 49.6%
ADJUVANT (CTONG1104) (Zhong, et al., 2018)(56)	Gefitinib	Stage IIA-IIIA, EGFR+	2020	5-Year: 32.5%
	Cisplatin + Vinorelbine			5-Year: 23.2%
(Imaizumi, 2005)(68)	Observation	Stage I	n.r.	5-Year: 66.5%
	Tegafur + Uracil			5-Year: 68.8%
	Cisplatin + UFT + Vindesine			5-Year: 81.1%
(Okuda, et al., 2018)(69)	Carboplatin + Paclitaxel	Stage II-IIIA	n.r.	5-Year: 54.2%
	S-1			5-Year: 70.4%
IMPACT (Tada, et al., 2022)(70)	Gefitinib	Stage II-IIIA, EGFR+	2020	5-Year: 31.8%
	Cisplatin + Vinorelbine			5-Year: 34.1%
WJTOG0101 (Yamaguchi, et al., 2021)(71)	Gemcitabine	Stage IB-IIIA	2005	5-Year: 55%
	Tegafur + Uracil			5-Year: 50%

(Park, et al., 2005) (72)	Cisplatin + Mitomycin C + Vinblastine	Stage I	2003	5-Year: 88.8% 10-Year: 76.8%
	Cisplatin + Mitomycin C + Vinblastine			5-Year: 64.8% 10-Year: 54.8%
EVAN (Yue, et al., 2022)(73)	Erlotinib	Stage I-IV, EGFR+	n.r.	5-Year: 48.2%
IALT (Arriagada, et al., 2010)(74)	Cisplatin-based chemotherapy	Stage I-III	2005	5-Year: 39.4%
	Observation			5-Year: 34.3%
(Felip, et al., 2010)(75)	Carboplatin + Paclitaxel	Stage IA (>2cm)-Stage III (N1)	2019	5-Year: 36.6%
	Observation			5-Year: 34.1%
(Ou, et al., 2010)(76)	Carboplatin + Vinorelbine or Carboplatin + Paclitaxel	Stage IIIA	2009	5-Year: 17.9%
	Observation			5-Year: 14.7%
CALGB9633 (Strauss, et al., 2008)(77)	Carboplatin + Paclitaxel	Stage IB	n.r.	5-Year: 52% 6-Year: 51%
	Observation			5-Year: 48% 6-Year: 46%
(Roselli, et al., 2006)(78)	Cisplatin + Etoposide	Stage IB	n.r.	5-Year: 55% 10-Year: 34%
	Observation			5-Year: 20% 10-Year: 9%
HOT0703 (Fukumoto, et al., 2020)(79)	Cisplatin + Gemcitabine	Stage IB-IIIA	2017	5-Year: 40.6%
	Carboplatin + Gemcitabine			5-Year: 59%

Table 55 Summary of assumptions associated with extrapolation of DFS

Method/approach	Description/assumption
Data input	ALINA (BO40336) CCOD: June 26, 2023 (9)
Model	All standard parametric distributions have been tested.
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Log-Logistic
Function with best BIC fit	Log-Logistic
Function with best visual fit	Log-Logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Log-Logistic

Validation of selected extrapolated curves (external evidence)	See Table 54
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Log-Logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes. 95% of patients are considered cured after 5 years follow up (28).

Appendix E. Serious adverse events

MedDRA System Organ Class MedRA Preferred Term	Alectinib (N=128)	Chemotherapy (N=120)
Total number of patients with at least one adverse event	17 (13.3%)	10 (8.3%)
Overall total number of events	20	16
Infections and infestations		
Total number of patients with at least one adverse event	11 (8.6%)	2 (1.7%)
Total number of events	11	2
Appendicitis	4 (3.1%)	0
Pneumonia	3 (2.3%)	1 (0.8%)
Influenza	1 (0.8%)	0
Lower respiratory tract infection	1 (0.8%)	0
Pneumonia viral	1 (0.8%)	0
Urinary tract infection	0	1 (0.8%)
Urosepsis	1 (0.8%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	2 (1.6%)	4 (3.3%)
Total number of events	2	8
Nausea	0	2 (1.7%)
Abdominal pain	0	1 (0.8%)
Colitis	0	1 (0.8%)
Epigastric discomfort	0	1 (0.8%)
Gastritis erosive	1 (0.8%)	0
Ileus paralytic	1 (0.8%)	0
Pancreatitis acute	0	1 (0.8%)
Regurgitation	0	1 (0.8%)
Vomiting	0	1 (0.8%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	2 (1.6%)	1 (0.8%)
Total number of events	2	1
Dyspnoea	1 (0.8%)	0
Pneumonitis	1 (0.8%)	0
Pulmonary embolism	0	1 (0.8%)
Cardiac disorders		
Total number of patients with at least one adverse event	2 (1.6%)	0
Total number of events	2	0
Acute myocardial infarction	2 (1.6%)	0
Investigations		
Total number of patients with at least one adverse event	0	2 (1.7%)
Total number of events	0	2
Neutrophil count decreased	0	2 (1.7%)
Reproductive system and breast disorders		
Total number of patients with at least one adverse event	2 (1.6%)	0
Total number of events	2	0
Benign prostatic hyperplasia	1 (0.8%)	0
Uterine prolapse	1 (0.8%)	0
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	0	1 (0.8%)
Total number of events	0	1
Febrile neutropenia	0	1 (0.8%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	0	1 (0.8%)
Total number of events	0	1
Fatigue	0	1 (0.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Bladder cancer	1 (0.8%)	0
Vascular disorders		
Total number of patients with at least one adverse event	0	1 (0.8%)
Total number of events	0	1
Embolism	0	1 (0.8%)

Table 56 Adverse events applied in the health economic model

Occurrence of Adverse Events	Non-Metastatic Recurrence			
	Chemoradiotherapy			
Reference	ALINA; Safety-Evaluable Patients; Control Arm; CCOD: June 26, 2023			
	Metastatic Recurrence (First-Line)			
	Alectinib	Crizotinib	Brigatinib	Lorlatinib
Median Follow-Up Duration	27.8 months	29.3 months	40.4 months	36.7 months
Sample Size	152	142	136	149

Definition of AEs	Number of patients with grade 3-5 adverse events reported in ≥ 2 patients (Table S4)	Number of patients with grade 3-4 adverse events that differed by more than 10 percentage points between treatment arms (Table S5)	Number of patients with treatment-emergent grade 3-5 adverse events reported in at least 2% of patients (Table 2)	Number of patients with grade 3-4 adverse events that differed by more than 10 percentage points between treatment arms (Table S5)
Alanine aminotransferase increased	7	6	6	4
Aspartate aminotransferase increased	8	5	6	3
Blood CPK	5	n.r.	n.r.	n.r.
Blood bilirubin increased	3	n.r.	n.r.	n.r.
Blood creatinine increased	2	n.r.	36	n.r.
Gamma-glutamyltransferase increased	1	n.r.	3	n.r.
Neutrophil count decreased	0	n.r.	1	n.r.
Anemia	8	4	4	5
Neutropenia	0	n.r.	2	n.r.
Pulmonary embolism	2	n.r.	3	n.r.
Pleural effusion	2	n.r.	2	n.r.
Pneumonia	4	n.r.	7	n.r.
Pneumothorax	2	n.r.	n.r.	n.r.
Urinary tract infection	4	n.r.	1	n.r.
Hyponatremia	3	n.r.	n.r.	n.r.
Hypokalemia	2	n.r.	n.r.	n.r.
Lung infection	3	n.r.	n.r.	n.r.
Bronchitis	2	n.r.	n.r.	n.r.
Nausea	1	3	3	1
Vomiting	0	2	2	1
Diarrhea	1	1	3	2
Acute kidney injury	4	n.r.	n.r.	n.r.
Confusional state	1	n.r.	n.r.	n.r.
Rash	3	n.r.	n.r.	n.r.
Death	2	n.r.	n.r.	n.r.
Hyperbilirubinemia	2	n.r.	n.r.	n.r.
Arthralgia	1	0	n.r.	1
Hypercholesterolaemia	n.r.	0	n.r.	29
Hypertriglyceridaemia	n.r.	0	n.r.	34
Oedema	n.r.	2	n.r.	6
Weight increased	n.r.	3	n.r.	30
Peripheral neuropathy	n.r.	1	n.r.	2
Cognitive effects	n.r.	0	n.r.	5
Hypertension	n.r.	1	19	17
Constipation	n.r.	1	n.r.	0
Vision disorder	n.r.	1	n.r.	0
Mood effects	n.r.	0	n.r.	2
Hyperlipidaemia	n.r.	0	n.r.	3
Decreased appetite	n.r.	4	1	0
Lipase increased	n.r.	n.r.	21	n.r.

Amylase increased	n.r.	n.r.	8	n.r.
Neoplasm progression	n.r.	n.r.	4	n.r.
Blood alkaline phosphate increased	n.r.	n.r.	4	n.r.
Dyspnea	n.r.	n.r.	3	n.r.
Hypophosphatemia	n.r.	n.r.	3	n.r.
Headache	n.r.	n.r.	3	n.r.
Upper abdominal pain	n.r.	n.r.	1	n.r.
Reference	(Camidge, et al., 2019) (29)			
	Metastatic Recurrence (Second-Line)			
	Alectinib	**Ceritinib**	**Cisplatin + Pemetrexed**	**-**
Median Follow-Up Duration	6.5 months	16.6 months	5.8 months	-
Sample Size	70	115	34	-
Definition of AEs	Number of patients with grade 3-5 adverse events occurring in more than 1 patient in either treatment arm (Table S8)	Number of patients with grade 3-4 adverse events (Appendix Table 5)	Number of patients with grade 3-5 adverse events occurring in more than 1 patient in either treatment arm (Table S8)	-
Asthenia	2	6	1	-
Pneumonia	2	6	0	-
Syncope	2	0	0	-
Fatigue	0	6	3	-
Anemia	1	n.r.	2	-
Neutropenia	0	1	4	-
Febrile neutropenia	0	0	2	-
Stomatitis	0	n.r.	2	-
Acute kidney injury	2	n.r.	0	-
Diarrhoea	n.r.	5	n.r.	-
Nausea	n.r.	9	n.r.	-
Vomiting	n.r.	9	n.r.	-
Alanine aminotransferase increased	n.r.	24	n.r.	-
Decreased appetite	n.r.	2	n.r.	-
Aspartate aminotransferase increased	n.r.	16	n.r.	-
Weight decreased	n.r.	3	n.r.	-
Blood alkaline phosphate increased	n.r.	7	n.r.	-
Abdominal pain	n.r.	1	n.r.	-
Back pain	n.r.	1	n.r.	-
Headache	n.r.	1	n.r.	-
Glutamyltransferase increased	n.r.	24	n.r.	-
Pyrexia	n.r.	2	n.r.	-
Abdominal pain upper	n.r.	1	n.r.	-
Dyspnoea	n.r.	6	n.r.	-
Non-cardiac chest pain	n.r.	1	n.r.	-

Electrocardiogram Qt prolonged	n.r.	1	n.r.	-
Hypokalaemia	n.r.	6	n.r.	-
Pain	n.r.	1	n.r.	-
Pericardial effusion	n.r.	3	n.r.	-
Pleural effusion	n.r.	3	n.r.	-
Respiratory tract infection	n.r.	1	n.r.	-
Blood lactate dehydrogenase increased	n.r.	1	n.r.	-
Dehydration	n.r.	2	n.r.	-
Muscular weakness	n.r.	2	n.r.	-
Hyperglycaemia	n.r.	6	n.r.	-
Amylase increased	n.r.	5	n.r.	-
Malaise	n.r.	1	n.r.	-
Pain in extremity	n.r.	1	n.r.	-
General physical health deterioration	n.r.	5	n.r.	-
Hyponatraemia	n.r.	2	n.r.	-
Chest pain	n.r.	1	n.r.	-
Creatinine renal clearance decreased	n.r.	1	n.r.	-
Depression	n.r.	1	n.r.	-
Dysphagia	n.r.	1	n.r.	-
Pericarditis	n.r.	1	n.r.	-
Respiratory failure	n.r.	3	n.r.	-
C-reactive protein increased	n.r.	1	n.r.	-
Cognitive disorder	n.r.	1	n.r.	-
Epilepsy	n.r.	2	n.r.	-
Lower respiratory tract infection	n.r.	1	n.r.	-
Lymphocyte count decreased	n.r.	1	n.r.	-
Myocardial ischemia	n.r.	1	n.r.	-
Transaminases increased	n.r.	1	n.r.	-
Angina pectoris	n.r.	1	n.r.	-
Aphasia	n.r.	1	n.r.	-
Atrial flutter	n.r.	1	n.r.	-
Biliary tract infection	n.r.	1	n.r.	-
Cerebrovascular accident	n.r.	1	n.r.	-
Chronic kidney disease	n.r.	1	n.r.	-
Deep vein thrombosis	n.r.	1	n.r.	-
Depressed level of consciousness	n.r.	1	n.r.	-
Electrocardiogram T-wave inversion	n.r.	1	n.r.	-
Faecaloma	n.r.	1	n.r.	-
Gastrointestinal obstruction	n.r.	1	n.r.	-
Gastrointestinal perforation	n.r.	1	n.r.	-

Hepatic enzyme increased	n.r.	1	n.r.	-
Hypertensive crisis	n.r.	1	n.r.	-
Hypoxia	n.r.	1	n.r.	-
Interstitial lung disease	n.r.	1	n.r.	-
Jaundice	n.r.	1	n.r.	-
Lenticular opacities	n.r.	1	n.r.	-
Loss of consciousness	n.r.	1	n.r.	-
Lung infiltration	n.r.	1	n.r.	-
Mobility decreased	n.r.	1	n.r.	-
Neutrophil count decreased	n.r.	1	n.r.	-
Pathological fracture	n.r.	1	n.r.	-
Petit mal epilepsy	n.r.	1	n.r.	-
Pneumothorax	n.r.	1	n.r.	-
Respiratory distress	n.r.	1	n.r.	-
Tumour flare	n.r.	1	n.r.	-
Typhoid fever	n.r.	1	n.r.	-
Urinary bladder rapture	n.r.	1	n.r.	-
Reference	(Novello, et al., 2018) (31)	(Shaw, et al., 2017) (60)	(Novello, et al., 2018) (31)	-

Appendix F. Health-related quality of life

Figure 40: SF-36v2 - Bodily pain

Figure 41: SF-36v2 – General health

Figure 42: SF-36v2 – Mental health

Figure 43: SF-36v2 – physical functioning

Figure 44: SF-36v2 – Role emotional

Figure 45: SF-36v2 – Role-Physical

Figure 46: SF-36v2 – Social functionning

Figure 47: SF-36v2 – Vitality

Table 57: Summary of SF-36v2 Domains and Component Summary Scores at Baseline, Week 12, Week 96 (Alectinib) and Disease Follow-Up Visit 7* (Chemotherapy) in ITT Population (Mean [SD])

Appendix G. Probabilistic sensitivity analyses

The usual probability distributions are used to generate the PSA. All distributions are presented in the tab PSA parameters in the model.

Table 58. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Patients off treatment every month - Alectinib	Dependent on month (described fully in PSA parameter tab)	Dependent on month (described fully in PSA parameter tab)	Dependent on month (described fully in PSA parameter tab)	Beta
Patients off treatment every month – Chemotherapy	Dependent on month (described fully in PSA parameter tab)	Dependent on month (described fully in PSA parameter tab)	Dependent on month (described fully in PSA parameter tab)	Beta
Proportion on chemotherapy	Dependent on treatment (described fully in PSA parameter tab)	Dependent on treatment (described fully in PSA parameter tab)	Dependent on treatment (described fully in PSA parameter tab)	Dirchlet
Proportion on subsequent treatment	Dependent on treatment (described fully in PSA parameter tab)	Dependent on treatment (described fully in PSA parameter tab)	Dependent on treatment (described fully in PSA parameter tab)	Dirchlet
Proportion of patients that experience a metastatic recurrence, non-metastatic recurrence, 2. Recurrence and death	Dependent on treatment and state (described fully in PSA parameter tab)	Dependent on treatment and state (described fully in PSA parameter tab)	Dependent on treatment and state (described fully in PSA parameter tab)	Beta
HSUV				
Alectinib – on treatment	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib – off treatment	[redacted]	[redacted]	[redacted]	[redacted]

Chemotherapy – on treatment	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy – off treatment	[redacted]	[redacted]	[redacted]	[redacted]
After recurrence – all treatment and recurrence types	[redacted]	[redacted]	[redacted]	[redacted]
Costs				
All AE	Dependent on AE (described fully in PSA parameter tab)	Dependent on AE (described fully in PSA parameter tab)	Dependent on AE (described fully in PSA parameter tab)	Log-normal
Resource use – Disease free	[redacted]	[redacted]	[redacted]	[redacted]
Resource use – All recurrence	[redacted]	[redacted]	[redacted]	[redacted]

Appendix H. Literature searches for the clinical assessment

N/A.

This application is based on the head-to-head study ALINA (BO40366) which compare adjuvant alectinib with with platinum-based chemotherapy in patients with resected ALK-positive NSCLC. Hence, a systematic literature review has not been performed.

Table 59 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
ALINA (BO40336)	To evaluate the efficacy of alec-tinib compared with platinum-based chemo-therapy in adju-vant treatment of ALK-positive NSCLC	Phase III, global, multicenter, open-label, ran-domized, study of alectinib ver-sus platinum-based chemo-therapy as adju-vant therapy	Patients with completely re-sected, stage IB–IIIA, ALK-pos-itive NSCLC	Alectinib: n=130 Chemotherapy: n=127	DFS (Follow-up: 30.88 months (sd: 12.71))	CNS-DFS, OS, safety (Follow-up: 30.88 months (sd: 12.71))

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

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

As part of the evidence generation strategy for atezolizumab and alectinib in the adjuvant/neoadjuvant settings, a health technology assessment (HTA)-compliant systematic literature reviews (SLRs) were conducted to identify the published evidence in early-stage NSCLC on HRQoL. These will be used in the HRQoL.

Table 60 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to 2023	28th September 2023
Medline	Ovid	1946 to 2023	28th September 2023
Evidence-Based Medicine (EBM) Reviews, incorporating:	Ovid		28th September 2023
Cochrane Database of Systematic Reviews		2005 to 2023	
American College of Physicians (ACP) Journal Club		1991 to 2023	
Database of Abstracts of Reviews of Effects (DARE)		1st quarter 2016	
Cochrane Clinical Answers		September 2023	
Cochrane Central Register of Controlled Trials (CENTRAL)		August 2023	
Cochrane Methodology Register		3rd quarter 2022	
HTA database		4th quarter 2012	
National Health Service Economic Evaluation Database (NHS EED),		1st quarter 2016	

Note: The EBM databases, DARE, NHS EED, and HTA, which are not updated to the present day, were also searched via the University of York Centre for Reviews and Dissemination (CRD) website: https://www.crd.york.ac.uk/.

The following sources were hand searched to supplement the findings of the electronic databases:

Table 61 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Hand searched	28th September 2023
Scottish Medicines Consortium	https://scottishmedicines.org.uk/	Hand searched	28th September 2023

Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cda-amc.ca/	Hand searched	28th September 2023
Pharmaceutical Benefits Advisory Committee (PBAC)	https://pbac.pbs.gov.au	Hand searched	28th September 2023
Institute of Clinical and Economical review	https://icer.org/	Hand searched	28th September 2023
Health Economics Research Centre	https://www.herc.ox.ac.uk/	Hand searched	28th September 2023
Cost-effectiveness analysis (CEA) Registry	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Hand searched	28th September 2023
Research Papers in Economics (RePEc) website (EconPapers)	https://econpapers.repec.org/	Hand searched	28th September 2023
International Network of Agencies for Health Technology Assessment (INAHTA)	https://www.inahta.org/	Hand searched	28th September 2023
National Institute for Health Research (NIHR)	https://www.nihr.ac.uk/	Hand searched	28th September 2023

Table 62 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical Oncology (ASCO)	https://www.asco.org/	Hand searched	"non(-)small cell lung cancer" AND "quality of life" "NSCLC" AND "quality of life"	28th September 2023
European Society for Medical Oncology (ESMO),	https://www.esmo.org/	Hand searched	"non(-)small cell lung cancer" AND "quality of life" "NSCLC" AND "quality of life"	28th September 2023
European Lung Cancer Congress (ELCC)	https://www.esmo.org/	Hand searched	"non(-)small cell lung cancer" AND "quality of life"	28th September 2023

			"NSCLC" AND "quality of life"	
International Association for the Study of Lung Cancer (IASLC)/World Conference on Lung Cancer (WCLC)	https://wclc20xx.iaslc.org/	Hand searched	"non(-)small cell lung cancer" AND "quality of life" "NSCLC" AND "quality of life"	28th September 2023
Professional Society for Health Economics and Outcomes Research (ISPOR)	https://www.ispor.org/	Hand searched	"non(-)small cell lung cancer" AND "quality of life" "NSCLC" AND "quality of life"	28th September 2023
Health Technology Assessment International (HTAi),	https://htai.org/	Hand searched	"non(-)small cell lung cancer" AND "quality of life" "NSCLC" AND "quality of life"	28th September 2023
Society for Medical Decision Making (SMDM)	https://smdm.org	Hand searched	"non(-)small cell lung cancer" AND "quality of life" "NSCLC" AND "quality of life"	28th September 2023

I.1.1 Search strategies

The searches were conducted in the MEDLINE and Embase (access via the OVID interface) and the Cochrane CENTRAL database on March 2021, and updated on June 2022, July 2023 and on September 2023. Selected conference websites were searched manually to make sure that all important data, even those published as abstracts only, were identified.

Table 63 Search strategy for [Embase] 1974 to september 2023

No.	Query	Results
1	exp lung non small cell cancer/ or exp non small cell lung cancer/	155009
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	458920
3	non.mp.	4211990
4	2 and 3	209604
5	NSCLC.mp.	111910
6	1 or 4 or 5	256775
7	(resectable or resected).mp.	148863

No.	Query	Results
8	(early or early-stage or early stage).mp.	2599000
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	244505
10	or/7-9	2916385
11	6 and 10	58804
12	quality adjusted life year/	35406
13	(quality adjusted or adjusted life year$).ti,ab,kw.	34123
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw.	27230
15	(illness state$1 or health state$1).ti,ab,kw.	14661
16	(hui or hui1 or hui2 or hui3).ti,ab,kw.	3124
17	(multiattribute$ or multi attribute$).ti,ab,kw.	1569
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw.	31562
19	utilities.ti,ab,kw.	15151
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw.	31368
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw.	9017
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.	46008
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	3565
24	"quality of life"/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	33318
25	"quality of life"/ and ec.fs.	61564
26	"quality of life"/ and (health adj3 status).ti,ab,kw.	20208
27	(quality of life or qol).ti,ab,kw. and "cost benefit analysis"/	6851
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	177913

No.	Query	Results
29	"cost benefit analysis"/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kw.	1229
30	"quality of life"/ and (quality of life or qol).ti.	128844
31	"quality of life"/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw.	102271
32	"quality of life"/ and health-related quality of life.ti,ab,kw.	78540
33	economic model/	3272
34	or/12-33	447976
35	11 and 34	1573
36	limit 35 to yr="2023 -Current"	91

Table 64 Search strategy for MEDLINE(R) 1946 to September 2023

No.	Query	Results
1	exp Carcinoma, Non-Small-Cell Lung/	71491
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	231718
3	non.mp.	10847634
4	2 and 3	141086
5	NSCLC.mp.	61567
6	1 or 4 or 5	151825
7	(resectable or resected).mp.	96828
8	(early or early-stage or early stage).mp.	1913404
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	134827
10	or/7-9	2103901
11	6 and 10	31571
12	Quality-Adjusted Life Years/	15834
13	(quality adjusted or adjusted life year$).ti,ab,kf.	23872
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	14826

No.	Query	Results
15	(illness state$1 or health state$1).ti,ab,kf.	8489
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1998
17	(multiattribute$ or multi attribute$).ti,ab,kf.	1342
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	20401
19	utilities.ti,ab,kf.	9540
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	17662
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	6082
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	26822
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	2397
24	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	15790
25	quality of life/ and ec.fs.	10876
26	quality of life/ and (health adj3 status).ti,ab,kf.	11878
27	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	17034
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	85992
29	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	5288
30	quality of life/ and (quality of life or qol).ti.	76568
31	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	42162
32	quality of life/ and health-related quality of life.ti,ab,kf.	45432
33	Models, Economic/	11088
34	or/12-33	237851
35	11 and 34	608

No.	Query	Results
36	limit 35 to yr="2023 -Current"	61

Table 65 Search strategy for EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 2023

No.	Query	Results
1	exp Carcinoma, Non-Small-Cell Lung/	5747
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	25282
3	non.mp.	286830
4	2 and 3	16966
5	NSCLC.mp.	11349
6	1 or 4 or 5	17961
7	(resectable or resected).mp.	9534
8	(early or early-stage or early stage).mp.	151204
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	32024
10	or/7-9	184908
11	6 and 10	6656
12	Quality-Adjusted Life Years/	1938
13	(quality adjusted or adjusted life year$).ti,ab,kf.	6061
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	4897
15	(illness state$1 or health state$1).ti,ab,kf.	1530
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	316
17	(multiattribute$ or multi attribute$).ti,ab,kf.	95
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	4641
19	utilities.ti,ab,kf.	1390
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	13112

No.	Query	Results
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	3798
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	14493
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	311
24	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	3811
25	quality of life/ and ec.fs.	1946
26	quality of life/ and (health adj3 status).ti,ab,kf.	1744
27	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	3920
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	25705
29	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	1005
30	quality of life/ and (quality of life or qol).ti.	9810
31	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	9924
32	quality of life/ and health-related quality of life.ti,ab,kf.	7641
33	Models, Economic/	414
34	or/12-33	64212
35	11 and 34	377
36	limit 35 to yr="2022 -Current"	43

The eligibility criteria applied throughout the HSUV/HRQoL SLR are summarised below.

Table 66: Eligibility criteria

CRITERIA	INCLUDE	EXCLUDE
Population	Patients with early-stage NSCLC (resectable; Stage 0/1/2/3) receiving treatment in the adjuvant or neoadjuvant treatment settings – no restriction with regard to patient age or mutation status Note: the primary population of interest was patients with Stage 2–3 resectable disease; however, studies considering patients with Stage 1–3 disease were considered eligible during the screening process to assess the extent of evidence available.	Advanced/metastatic (Stage 4) NSCLC Mixed populations where a breakdown of data for early-stage NSCLC is not provided

CRITERIA	INCLUDE	EXCLUDE
Intervention and comparators	No restriction	-
Outcomes	HSUVs (and disutilities [e.g. associated with progression or AEs]) for relevant health states (individual [patient or caregiver]) derived using the following techniques: • Generic, preference-based instruments (e.g. EQ-5D, SF-6D) • Direct methods (e.g. TTO, SG, VAS) • Mapping algorithms allowing data from disease-specific/generic measures to be mapped to preference-based HSUVs Disease-specific/generic (non-utility) HRQOL data (e.g. EORTC-QLQ-C30) (studies tagged and provided as a list)	Outcomes not listed in "include" column
Study design	Studies reporting original HSUV/HRQOL data	Reviews/editorials† Case reports Pharmacokinetic studies Animal/*in vitro* studies
Geography	No restriction; however, i8 countries (UK, France, Spain, Canada, Australia, Brazil, Germany and Italy), China, South Korea, Japan, and the US were primary territories of interest	-
Publication date	No restriction	-
Language	No restriction; English language publications or non-English language publications with an English abstract were of primary interest.	-

Abbreviations: AE, adverse event; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life questionnaire; EQ-5D, European Quality of Life-5 Dimensions; HRQoL, health-related quality of life; HSUV, health state utility value; NSCLC, non-small cell lung cancer; SF-6D, Short Form-6 dimensions; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale.
† The reference lists of any relevant review publications were checked to ensure any relevant primary studies were considered for inclusion.

The inclusion/exclusion of citations (both at the title/abstract phase and full publication review) was conducted by two independent analysts. Any disputes were referred to the project manager and resolved by consensus. Data extraction was conducted by a single analyst and quality checked for 100% of data elements by a second analyst or project lead. Disputes were referred to a third party (strategic advisor).

1.1.1 Original review (March 2021)

Electronic searches of the following databases were conducted on 18th March 2021 via the Ovid platform: Embase®, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), and EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; DARE; Cochrane Clinical Answers; Cochrane Central Register of Controlled Trials; the Cochrane Methodology Register; the HTA database; and NHS EED). The electronic databases searches were supplemented by hand searching reference lists of included studies, relevant conference proceedings (last 3 years' availability), and additional grey literature sources.

Further details of the electronic database search strategies and hand searching methodology adopted for the SLR of HSUV/HRQoL studies are provided in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively.

The electronic databases identified a total of 1,987 citations. Following removal of 264 duplicates, 1,723 citations were screened on the basis of title and abstract. A total of 95 citations were considered to be potentially relevant and

were obtained for full text review, and 104 studies reporting use of generic/disease-specific HRQoL (non-utility) instruments were isolated and tagged. At the full publication review stage, a further 52 citations were excluded and an additional 38 HRQoL studies were tagged. Hand searching yielded 22 additional relevant publications (included HSUV studies, n=12; tagged HRQoL studies, n=10). This resulted in a total of 27 publications for final inclusion in the review, all of which reported HSUVs for patients with early-stage NSCLC (full publications, n=25; conference abstracts, n=2). In addition, 142 studies reporting generic and/or disease-specific HRQoL data were tagged.

June 2022 update

Electronic searches of the following databases were conducted on 22nd June 2022 via the Ovid platform: Embase®, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), and EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; DARE; Cochrane Clinical Answers; Cochrane Central Register of Controlled Trials; the Cochrane Methodology Register; the HTA database; and NHS EED). The electronic database searches were supplemented by hand searching reference lists of included studies, relevant conference proceedings (conducted after the original search to June 2022), and additional grey literature sources.

The electronic database search identified 293 citations. After the removal of 91 duplicates from the current search and 15 duplicates from the original search (March 2021), 187 citations were screened on the basis of the title and abstract. A total of 7 publications were deemed potentially relevant and were obtained for full text review and 11 publications reporting use of generic/disease-specific HRQoL (non-utility) instruments were isolated and tagged. At the full publication review stage, a further 3 publications were excluded and 2 additional HRQoL studies were tagged. Handsearching did not yield any additional studies. This resulted in the identification of 2 HSUV publications for patients with early-stage NSCLC for final inclusion in the review update. A total of 13 studies reporting generic and/or disease-specific HRQoL data were tagged.

July 2023 update

Electronic searches of the following databases were conducted on 11th July 2023 via the Ovid platform: Embase®, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), and EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; Cochrane Clinical Answers; and Cochrane Central Register of Controlled Trials). The electronic databases searches were supplemented by hand searching reference lists of included studies, relevant conference proceedings (conducted after the June 2022 update to July 2023), and additional grey literature sources.

The electronic database search identified 369 citations. After the removal of 91 duplicates from the current search and 59 duplicates of the previous searches (March 2021 and June 2022), 219 citations were screened on the basis of the title and abstract. A total of 11 publications were deemed potentially relevant and were obtained for full text review, and 11 publications reporting use of generic/disease-specific HRQoL (non-utility) instruments were isolated and tagged. At the full publication review stage, a further 8 publications were excluded and 1 additional HRQoL study was tagged. Handsearching yielded 1 additional relevant publication (tagged HRQoL studies, n=1). This resulted in 2 new HSUV publications for patients with early-stage NSCLC being identified for final inclusion in the SLR July update 2023 (full publications, N=1; conference abstracts, N=1). A total of 13 studies reporting generic and/or disease-specific HRQoL data were tagged.

September 2023 update

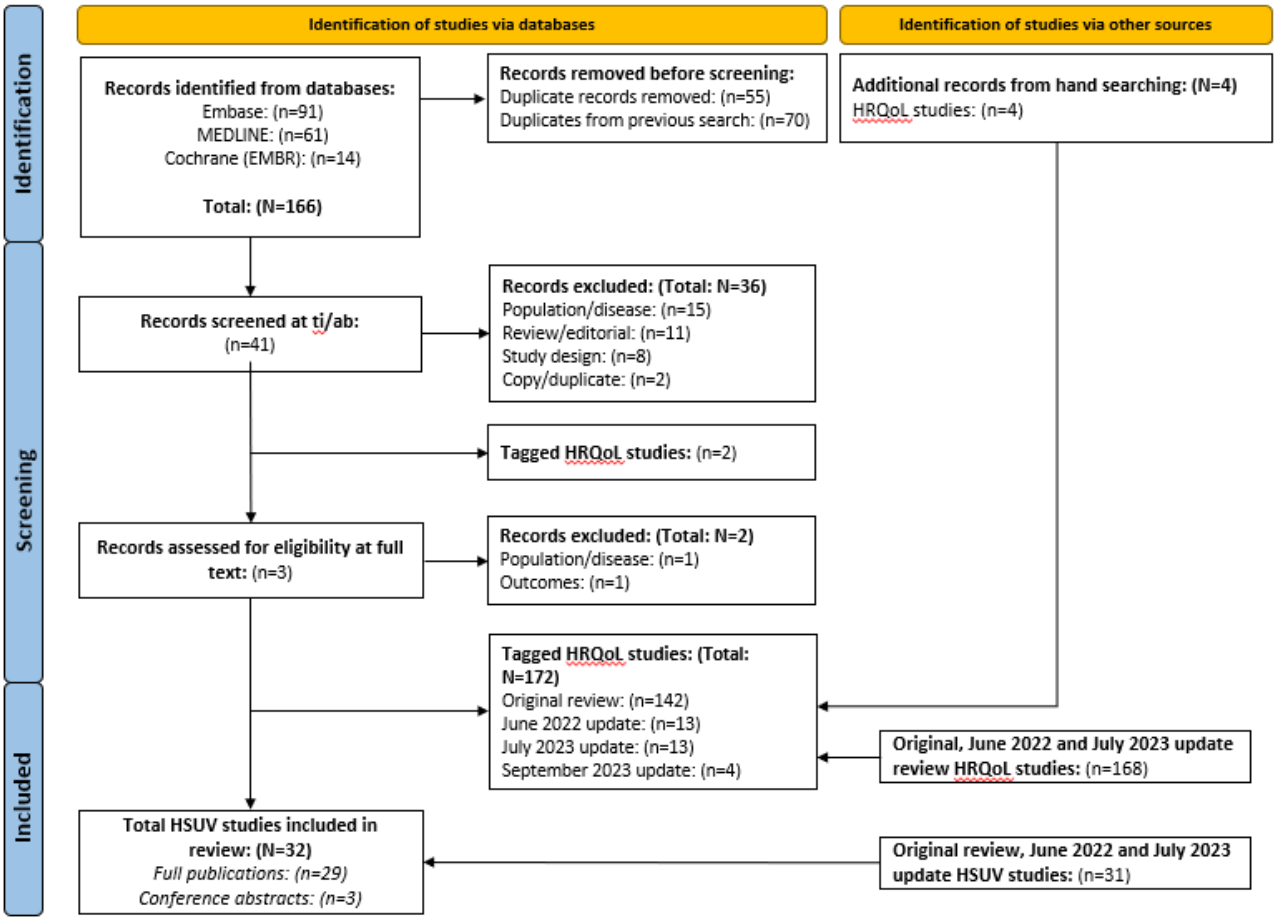
Electronic searches of the following databases were conducted on 28th September 2023 via the Ovid platform: Embase®, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), and EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; Cochrane Clini-

cal Answers; and Cochrane Central Register of Controlled Trials). The electronic databases searches were supplemented by hand searching reference lists of included studies, relevant conference proceedings (conducted after the July 2023 update to September 2023), and additional grey literature sources.

The electronic database search identified 166 citations. After the removal of 55 duplicates from the current search and 70 duplicates of the previous searches (March 2021, June 2022, and July 2023), 41 citations were screened on the basis of the title and abstract. A total of 3 publications were deemed potentially relevant and were obtained for full text review, and 2 publications reporting use of generic/disease-specific HRQoL (non-utility) instruments were isolated and tagged. At the full publication review stage, a further 2 publications were excluded. Handsearching yielded 4 additional relevant publications (tagged HRQoL studies, N=4). This resulted in 1 new HSUV publication for patients with early-stage NSCLC being identified for final inclusion in the SLR September update 2023 (full publications, N=1). A total of 6 studies reporting generic and/or disease-specific HRQoL data were tagged.

Overall summary

Across the original review (March 2021) and the June 2022, July 2023, and September 2023 updates, a total of 32 relevant HSUV studies were identified for inclusion (full publications, n=29; conference abstracts, n=3). The overall flow of studies through the review is summarised in the PRISMA flow diagram below



A summary of the 29 full publications is provided in Table 67. Colour coding has been used to indicate the following: GREEN: health states relevant to patients with Stage 2/3(A) disease; ORANGE: uncertainty in the method used to derive utilities (instrument and/or social tariff unclear); RED: intervention-specific health state where surgery +/- adjuvant chemotherapy was not used (e.g. relates to radiotherapy use); BLUE: both GREEN and RED criteria apply.

Table 67: Summary of published HSUV data associated with patients with early NSCLC (n=27)

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
Original review (N=25)					
Andreas, 2018 (80) **Multi-national (France, Germany, and UK)**	**Patients with completely resected Stage 1B–3A NSCLC (n=306)**	**Instrument: EQ-5D (version not specified) Tariff: NR**	**Patients with resected Stage 1B–3A NSCLC, disease free (n=238)**	**0.72 [0.68, 0.75]**	**Conclusions: HRQoL measures suggested a higher utility score during the period of distant metastasis and/or terminal disease than in the period of locoregional recurrence.** **Limitations:** • **Limited sample size may be a source of imprecision** • **Study data not guaranteed to be representative of all sites and physicians treating patients with Stage 1B–3A NSCLC across each country** • **External validation of medical record data not possible**
			Patients with resected Stage 1B–3A NSCLC, locoregional recurrence (n=19)	0.62 [0.51, 0.74]	
			Patients with resected Stage 1B–3A NSCLC, distant metastasis/terminal disease (n=32)	0.67 [0.55, 0.78]	
Bendixen, 2019 (81) Denmark	Patients with Stage 1 NSCLC (n=206)	Instrument: EQ-5D-3L Tariff: Danish tariff	Patients with Stage 1 NSCLC, baseline (pre-operative), VATS (n=63)	0.89 (0.13)	Conclusions: VATS is a cost-effective alternative to thoracotomy following lobectomy for Stage 1 lung cancer. Limitations: • None reported
			Patients with Stage 1 NSCLC, baseline (pre-operative), thoracotomy (n=61)	0.86 (0.15)	
			Patients with Stage 1 NSCLC, 2 weeks post-operatively, VATS (n=78)	0.78 (0.17)	

			Patients with Stage 1 NSCLC, 2 weeks post-operatively, thoracotomy (n=80)	0.73 (0.14)	
			Patients with Stage 1 NSCLC, 4 weeks post-operatively, VATS (n=78)	0.82 (0.17)	
			Patients with Stage 1 NSCLC, 4 weeks post-operatively, thoracotomy (n=73)	0.75 (0.18)	
			Patients with Stage 1 NSCLC, 8 weeks post-operatively, VATS (n=81)	0.85 (0.16)	
			Patients with Stage 1 NSCLC, 8 weeks post-operatively, thoracotomy (n=71)	0.81 (0.13)	
			Patients with Stage 1 NSCLC, 12 weeks post-operatively, VATS (n=83)	0.87 (0.14)	
			Patients with Stage 1 NSCLC, 12 weeks post-operatively, thoracotomy (n=71)	0.85 (0.14)	
			Patients with Stage 1 NSCLC, 26 weeks post-operatively, VATS (n=81)	0.86 (0.18)	
			Patients with Stage 1	0.85 (0.14)	

			NSCLC, 26 weeks post-operatively, thoracotomy (n=73)		
			Patients with Stage 1 NSCLC, 52 weeks post-operatively, VATS (n=74)	0.86 (0.16)	
			Patients with Stage 1 NSCLC, 52 weeks post-operatively, thoracotomy (n=66)	0.84 (0.18)	
Black, 2014 (82) US	Patients with Stage 1–4 NSCLC (sample size NR)	Instrument: SF-6D Tariff: NR	Patients with Stage 1A NSCLC, <12 months since diagnosis	0.696	Conclusions: no conclusions reported relating to HRQoL Limitations: • Factors relating to generalisability of results beyond the study setting were not considered
			Patients with Stage 1A NSCLC, 12+ months since diagnosis	0.718	
			Patients with Stage 1B NSCLC, <12 months since diagnosis	0.727	
			Patients with Stage 1B NSCLC, 12+ months since diagnosis	0.711	
			Patients with Stage 2 NSCLC, <12 months since diagnosis	0.600	
			Patients with Stage 2 NSCLC, 12+ months since diagnosis	0.684	
			Patients with Stage 3 NSCLC, <12 months since diagnosis	0.614	

			Patients with Stage 3 NSCLC, 12+ months since diagnosis	0.716	
			Patients with Stage 4 NSCLC, <12 months since diagnosis	0.612	
			Patients with Stage 4 NSCLC, 12+ months since diagnosis	0.623	
Blom, 2020 (83) Multi-national (review)	Patients with Stage 1–4 lung cancer (n=5,100†)	Instrument: multiple (pooled estimate) Tariff: multiple (pooled estimate)	Patients with lung cancer, all stages (n=5,100)	0.68 [0.61, 0.75]	Conclusions: the pooled HSUVs reported in this study may provide the best available stage-specific HSUVs for most countries. Limitations: • Heterogeneity across studies included in the analysis
			Patients with lung cancer, Stage 1–2 (n=1,510)	0.78 [0.70, 0.86]	
			Patients with lung cancer, Stage 3–4 (n=4,703)	0.69 [0.65, 0.73]	
Brocki, 2018 (84) Denmark	Patients at high risk for development of post-operative pulmonary complications following lung resection due to lung cancer or diagnostic lung resections (n=68)	Instrument: EQ-5D-5L Tariff: Danish tariff (assumed)	Patients with lung cancer who have undergone resection, males, baseline	0.855 (0.11)	Conclusions: post-operative inspiratory muscle training in addition to standard physiotherapy, including early mobilisation, may prevent a decline in physical activity level 2 weeks post-operatively in high-risk patients undergoing lung resection. Limitations: • Relatively small number of participants may limit the generalisability of results to the general population undergoing lung cancer surgery
			Patients with lung cancer who have undergone resection, females, baseline	0.803 (0.151)	
			Patients with lung cancer who have undergone resection, 2 weeks post-operatively, mean change from baseline	-0.127 [-0.168, -0.085]	
			Patients with lung cancer who have un-	-0.016 [-0.091, 0.060]	

			dergone resection, 2 weeks post-operatively, mean change from baseline, difference between intervention and control group		
Grutters, 2010 (85) Netherlands	Patients treated for NSCLC between 2004 and 2007 (n=245)	Instrument: EQ-5D-3L Tariff: UK tariff (assumed from reference to Dolan et al [1997] (86))	Patients with NSCLC, initial tumour Stage 1 (n=105)	0.77 (0.26)	Conclusions: results of the present study provided original data on HRQoL during survival of NSCLC; AEs were found to have a considerable impact on HRQoL. Limitations: • Some relatively small subgroups based on initial treatment modality • AEs were self-reported by respondents rather than by the physician • High proportion of patients treated with surgery indicated a relatively 'healthy' sample
			Patients with NSCLC, initial tumour Stage 2 (n=39)	0.74 (0.22)	
			Patients with NSCLC, initial tumour Stage 3 (n=99)	0.70 (0.29)	
			Patients with NSCLC, initial tumour Stage 4 (n=2)	0.86 (0.19)	
			Patients with Stage 1–4 NSCLC, recurrence (n=34)	0.61 (0.37)	
			Patients with Stage 1–4 NSCLC, no recurrence (n=177)	0.76 (0.24)	
			Patients with Stage 1–4 NSCLC, no severe AE (n=200)	0.80 (0.20)	
			Patients with Stage 1–4 NSCLC, serious AE (n=41)	0.45 (0.33)	
Ilonen, 2010 (87) Finland	Patients with Stage 1A–3B NSCLC who underwent surgery (lobectomy or bilobectomy) between May	Instrument: 15D Tariff: NR	Patients with Stage 1A–3B NSCLC undergoing lobectomy/bilobectomy, pre-operative (baseline) (n=53)	0.898	Conclusions: lobectomy and bilobectomy are associated with a significant negative long-term post-operative HRQoL in patients with NSCLC.

	2002 and November 2005 (n=53)		Patients with stage 1A–3B NSCLC undergoing lobectomy/bilobectomy, change from baseline at 3 months post-operatively (n=48)	-0.069 (p=0.001)	Limitations: • HRQoL may be overestimated as it is generally noticed that those with advanced cancer do not complete surveys when they become too ill • Seven patients (13%) lost to follow up • Study underpowered to assess impact of adjuvant or neoadjuvant therapy on HRQoL due to small patient numbers
			Patients with 1A–3B NSCLC undergoing lobectomy/bilobectomy, change from baseline at 12 months post-operatively (n=42)	-0.059 (p=0.019)	
			Patients with 1A–3B NSCLC undergoing lobectomy/bilobectomy, change from baseline at 24 months post-operatively (n=36)	-0.078 (p=0.001)	
Jang, 2009 (88) Canada	Adult patients with completely resected early-stage (T2N0, T1N1, or T2N1) NSCLC receiving adjuvant therapy (n=482)	Instrument: Q-TWiST (Method 1: arbitrary values; Method 2: EORTC-QLQ-C30, global items; Method 3: EORTC-QLQ-C30, symptom-related items;	Patients with early NSCLC, TWIST state, observation arm, Method 1	1 (NR)	Conclusions: adjuvant chemotherapy in early-stage NSCLC improves quality-adjusted survival despite chemotherapy toxicity Limitations: • Methods 2 and 3 in this study, using linearly summed QoL aggregates, were not validated methods of utility derivation, such as TTO or SG exercises, and may underestimate true utility scores
			Patients with early NSCLC, TWIST state, observation arm, Method 2	1 (NR)	
			Patients with early NSCLC, TWIST state, observation arm, Method 3	1 (NR)	
			Patients with early NSCLC, TWIST state, observation	0.75 (NR)	

		Method 4: EQ-5D-3L) Tariff: NR	arm, Method 4		
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, Method 1	1 (NR)	
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, Method 2	1 (NR)	
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, Method 3	1 (NR)	
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, Method 4	0.75 (NR)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, Method 1	0.75 (NR)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, Method 2	0.57 (0.21)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, Method 3	0.86 (0.09)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, Method 4	0.68 (NR)	
			Patients with early NSCLC, relapse state, observation	0.50 (NR)	

			arm, Method 1		
			Patients with early NSCLC, relapse state, observation arm, Method 2	0.50 (0.25)	
			Patients with early NSCLC, relapse state, observation arm, Method 3	0.83 (0.10)	
			Patients with early NSCLC, relapse state, observation arm, Method 4	0.60 (NR)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, Method 1	0.50 (NR)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, Method 2	0.50 (0.25)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, Method 3	0.83 (0.10)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, Method 4	0.60 (NR)	
Jang, 2010 (89) Canada	Outpatients with Stage 1–4 NSCLC (n=172)	Instrument: EQ-5D-3L and EORTC-QLQ-C30 mapped	Patients with NSCLC (all stages: 1–4), baseline	0.76 (0.20) [0.73, 0.78]	Conclusions: this study demonstrates the feasibility of converting QoL data into utilities for patients with NSCLC using linear modelling.
			Patients with Stage 1 NSCLC (n=34),	0.80 (0.18)	

		to EQ-5D-3L Tariff: US tariff	EQ-5D-3L (actual)		Limitations: • Relatively small sample size • Lack of a unique population to test for external validity • Population tariffs were based on a subset of the US general population, which may not appropriately represent health preferences in Canadian patients with NSCLC • High utility score may reflect a biased sample of higher performance status patients who were willing to complete the questionnaires
			Patients with Stage 1 NSCLC (n=34), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.80 (0.14)	
			Patients with Stage 2 NSCLC (n=16), EQ-5D-3L (actual)	0.78 (0.23)	
			Patients with Stage 2 NSCLC (n=16), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.80 (0.12)	
			Patients with Stage 3 NSCLC (n=36), EQ-5D-3L (actual)	0.73 (0.23)	
			Patients with Stage 3 NSCLC (n=36), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.74 (0.13)	
			Patients with Stage 4 NSCLC (n=86), EQ-5D-3L (actual)	0.75 (0.15)	
			Patients with Stage 4 NSCLC (n=86), EORTC-QLQ-C30 to EQ-5D-3L	0.77 (0.13)	

			(mapped, predicted)		
			Patients with NSCLC (all stages), relapse free, chemotherapy (n=9), EQ-5D-3L (actual)	0.76 (0.04)	
			Patients with NSCLC (all stages), relapse free, chemotherapy (n=9), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.74 (0.06)	
			Patients with NSCLC (all stages), relapse free, post-chemotherapy (n=27), EQ-5D-3L (actual)	0.76 (0.21)	
			Patients with NSCLC (all stages), relapse free, post-chemotherapy (n=27), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.76 (0.12)	
			Patients with NSCLC (all stages), relapse free, no chemotherapy (n=34), EQ-5D-3L (actual)	0.77 (0.22)	
			Patients with NSCLC (all stages), relapse free, no chemotherapy (n=34),	0.80 (0.16)	

			EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)		
Jeppesen, 2018 (90) Denmark (supplemented by data reported in Jeppesen et al [2017] (91))	Patients with a diagnosis of T1-2N0M0 (localised) NSCLC treated with SBRT (n=51)	Instrument: EQ-5D-5L Tariff: Danish tariff	Patients with localised NSCLC, baseline, SBRT + CGA	0.77 (0.19)	Conclusions: in patients with localised NSCLC treated with SBRT, a CGA did not impact the overall quality of life, the prevalence/length of unplanned admissions, or survival. Limitations: • Relatively small sample size makes results difficult to interpret • The eligibility criteria of the study did not select only a geriatric population, and this could potentially have diluted the effect of a CGA
			Patients with localised NSCLC, baseline, SBRT alone	0.71 (0.19)	
			Patients with localised NSCLC, 5 weeks' follow up, SBRT + CGA	0.75 (SE 0.03)	
			Patients with localised NSCLC, 5 weeks' follow up, SBRT alone	0.70 (SE 0.03)	
			Patients with localised NSCLC, 3 months' follow up, SBRT + CGA	0.77 (SE 0.04)	
			Patients with localised NSCLC, 3 months' follow up, SBRT alone	0.74 (SE 0.04)	
			Patients with localised NSCLC, 6 months' follow up, SBRT + CGA	0.69 (SE 0.03)	
			Patients with localised NSCLC, 6 months' follow up, SBRT alone	0.67 (SE 0.03)	
			Patients with localised NSCLC, 9	0.75 (SE 0.04)	

			months' follow up, SBRT + CGA		
			Patients with localised NSCLC, 9 months' follow up, SBRT alone	0.72 (SE 0.04)	
			Patients with localised NSCLC, 12 months' follow up, SBRT + CGA	0.75 (SE 0.04)	
			Patients with localised NSCLC, 12 months' follow up, SBRT alone	0.67 (SE 0.04)	
Khan, 2016 (92) UK	Patients with histologically confirmed Stage 1–4 NSCLC (n=98)	Instrument: EQ-5D (3L and 5L) and EORTC-QLQ-C30 mapped to EQ-5D (3L and 5L) Tariff: UK tariff (86, 93)	Patients with NSCLC, random effects model, EORTC-QLQ-C30 to EQ-5D-5L (predicted)	0.577 (0.241)	Conclusions: mapping algorithms developed from EQ-5D-5L appear to provide improved estimates of utilities compared with EQ-5D-3L in patients with NSCLC, particularly at poorer health states. Limitations: • Small sample size and relatively few health states • Inferences should be limited to a similar NSCLC population until further evidence emerges of wider applicability across tumour types • External validity was not possible in an independent data set • Insufficient numbers of events were available for reliable computation of QALYs
			Patients with NSCLC, random effects model, EQ-5D-5L (observed)	0.572 (0.224)	
			Patients with NSCLC, beta binomial model, EORTC-QLQ-C30 to EQ-5D-5L (predicted)	0.575 (0.211)	
			Patients with NSCLC, beta binomial model, EQ-5D-5L (observed)	0.572 (0.224)	
			Patients with NSCLC, LVDM model, EORTC-QLQ-C30 to EQ-	0.569 (0.217)	

			5D-5L (predicted)		• The values of the EQ-5D-5L were cross-walked from the EQ-5D-3L and are therefore subject to uncertainty
			Patients with NSCLC, LVDM model, EQ-5D-5L (observed)	0.572 (0.224)	
			Patients with NSCLC, random effects model, EORTC-QLQ-C30 to EQ-5D-3L (predicted)	0.523 (0.252)	
			Patients with NSCLC, random effects model, EQ-5D-3L (observed)	0.515 (0.308)	
			Patients with NSCLC, beta binomial model, EORTC-QLQ-C30 to EQ-5D-3L (predicted)	0.518 (0.183)	
			Patients with NSCLC, beta binomial model, EQ-5D-3L (observed)	0.515 (0.308)	
			Patients with NSCLC, LVDM model, EORTC-QLQ-C30 to EQ-5D-3L (predicted)	0.532 (0.252)	
			Patients with NSCLC, LVDM model, EQ-5D-3L (observed)	0.515 (0.308)	
Kim, 2018 (94) South Korea	Adults (aged ≥19 years) from the Korean general population on	Instrument: SG and VAS	Stage 1 lung cancer, valued by proxy respondents from the Korean general	0.48 (0.17)	Conclusions: findings indicate that a range of descriptions of lung cancer states can be feasibly evaluated in

	behalf of patients with Stage 1–4 lung cancer (n=515)	Tariff: NA	public, VAS, baseline		the South Korean population using either the VAS or SG methods. Limitations: • The number of scenarios was intentionally reduced to minimise the cognitive burden on participants • Response integrity data were not collected and it is therefore not possible to analyse characteristics relating to non-response
			Stage 1 lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.66 (0.27)	
			Stage 2 lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.38 (0.17)	
			Stage 2 lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.56 (0.28)	
			Stage 3A lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.27 (0.17)	
			Stage 3A lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.45 (0.29)	
			Stage 3B lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.20 (0.18)	
			Stage 3B lung cancer, valued by proxy respondents	0.38 (0.29)	

			from the Korean general public, SG, baseline		
			Stage 4 lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.09 (0.18)	
			Stage 4 lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.31 (0.30)	
			Pulmonary nodule, valued by proxy respondents from the Korean general public, VAS, baseline	0.66 (0.21)	
			Pulmonary nodule, valued by proxy respondents from the Korean general public, SG, baseline	0.83 (0.24)	
Koide, 2019 (95) Japan	Patients with Stage 1–3 NSCLC, who underwent VATS (n=24)	Instrument: EQ-5D-5L Tariff: Japanese tariff	Patients with Stage 1–3 NSCLC, preoperative (baseline)	0.81 (0.19)	Conclusions: QoL survey for NSCLC patients using EQ-5D-5L was simple and useful in identifying the issue faced by the medical team; it also could predict operation time and bleeding under specific circumstances. Limitations: • None reported
			Patients with Stage 1–3 NSCLC, postoperative	0.74 (0.11)	
Manser, 2006 (96) Australia	Patients with lung cancer (any stage) recruited from a	Instrument: AQoL	Patients with Stage 1 NSCLC, baseline (n=29)	0.62 [0.43-0.87]‡	Conclusions: data from this study supported the validity of the

	tertiary multi-disciplinary lung cancer clinic (n=92)	Tariff: NR	Patients with Stage 2 NSCLC, baseline (n=15)	0.60 [0.24-0.80]‡	AQoL for use in patients with lung cancer; however, there remains some uncertainty about whether the AQoL has sufficient content validity and sensitivity to different health states for use in patients with lung cancer. Limitations: • Potential selection bias and relatively small sample size • Loss to follow up in the inoperable group at 3 and 6 months • Disease-specific HRQoL questionnaire was not utilised
			Patients with Stage 3 NSCLC, baseline (n=22)	0.67 [0.52-0.87]‡	
			Patients with Stage 4 NSCLC, baseline (n=23)	0.68 [0.54-0.82]‡	
			Patients with lung cancer, inoperable (n=42), baseline	0.66 [0.52-0.82]‡	
			Patients with lung cancer, operable (n=49), baseline	0.67 [0.35-0.87]‡	
			Patients with lung cancer, all patients (n=66), 3 months' follow up	0.57 [0.49, 0.64]‡	
			Patients with lung cancer, operable (n=44), 3 months' follow up	0.55 [0.45, 0.64]‡	
			Patients with lung cancer, inoperable (n=22), 3 months' follow up	0.60 [0.49, 0.72]‡	
			Patients with lung cancer, all patients (n=59), 6 months' follow up	0.59 [0.52, 0.66]‡	
			Patients with lung cancer, operable (n=43), 6 months' follow up	0.59 [0.50, 0.68]‡	

			Patients with lung cancer, inoperable (n=16), 6 months' follow up	0.60 [0.50, 0.70]‡	
			Patients with Stage 1 NSCLC, surgical group, 6 months' follow up (n=22)	0.67 [0.54, 0.79]‡	
			Patients with Stage 2–3 NSCLC, surgical group, 6 months' follow up (n=20)	0.55 [0.40, 0.69]‡	
			Patients with Stage 1–3 (non-surgical) and Stage 4 NSCLC, 6 months' follow up (n=18)	0.56 [0.46, 0.67]‡	
Naik, 2017 (97) Canada	Adult ambulatory cancer survivors, including lung cancer (n=1,759)	Instrument: EQ-5D-3L Tariff: UK, US, and Canadian tariffs	Patients with lung cancer (n=149), Canadian tariff	0.78 (SE 0.02)	Conclusions: this work represents the first set of health utility scores for numerous cancer sites derived using Canadian preference weights; the dataset demonstrated construct validity and health utility scores varied by general socio-demographic and clinical parameters. Limitations: • Not possible to adjust for some clinical variables in regression analysis • Estimates presented may not necessarily be representative of cancer survivors in the Canadian community at large • Individuals were recruited based on a convenience sampling approach
			Patients with lung cancer (n=149), US tariff	0.80 (SE 0.01)	
			Patients with lung cancer (n=149), UK tariff	0.73 (SE 0.02)	
			Patients with local/regional lung cancer (n=89), Canadian tariff	0.78 (SE 0.02)	
			Patients with distant/metastatic lung cancer (n=60), Canadian tariff	0.77 (SE 0.03)	

Rauma, 2019 (98) Finland	Patients with localised NSCLC who underwent lobectomy at a single institution between January 2006 and January 2013 (n=180)	Instrument: 15D Tariff: NR	Patients with local NSCLC, total 15D score, VATS	0.809	Conclusion: this study reported the surprising result that patients with NSCLC undergoing VATS had worse long-term HRQoL scores in several critical dimensions, including breathing and overall 15D score. Limitations: • Retrospective study design and lack of baseline HRQoL data precluded identification of actual changes in HRQoL as a consequence of the selected surgical method • The 2-part collection of data may predispose the results to some temporal bias
			Patients with local NSCLC, total 15D score, thoracotomy	0.851	
			Patients with local NSCLC, 15D breathing dimension, VATS	0.637	
			Patients with local NSCLC, 15D breathing dimension, thoracotomy	0.719	
			Patients with local NSCLC, 15D speaking dimension, VATS	0.942	
			Patients with local NSCLC, 15D speaking dimension, thoracotomy	0.973	
			Patients with local NSCLC, 15D usual activities dimension, VATS	0.746	
			Patients with local NSCLC, 15D usual activities dimension, thoracotomy	0.821	
			Patients with local NSCLC, 15D mental function dimension, VATS	0.818	
			Patients with local NSCLC, 15D mental	0.917	

			function dimension, thoracotomy		
			Patients with local NSCLC, 15D vitality dimension, VATS	0.767	
			Patients with local NSCLC, 15D vitality dimension, thoracotomy	0.824	
Sharples, 2012 (99) UK	Patients with known/suspected NSCLC, pending results of surgical staging and potentially suitable for surgical resection, with no evidence of distant metastatic disease (n=144)	Instrument: EQ-5D-3L Tariff: UK tariff (assumed from reference to Dolan et al [1997] (86))	Patients with NSCLC, baseline (Day 0), EUS/EBUS (n=73)	0.81 (0.18)	Conclusions: taking the clinical, QoL, and health resource data together, evidence from this study suggested that lung cancer staging could commence with a combined EUS/EBUS examination, followed by surgical staging if these tests were negative. Limitations: • Limited number of comparators • The EQ-5D is a generic measure that is unlikely to illustrate changes in QoL that are specific to the disease course
			Patients with NSCLC, baseline (Day 0), surgical staging (n=71)	0.83 (0.14)	
			Patients with NSCLC, end of staging (Day 7), EUS/EBUS (n=73)	0.78 (0.23)	
			Patients with NSCLC, end of staging (Day 7), surgical staging (n=71)	0.67 (0.29)	
			Patients with NSCLC, 2 months' follow up (Day 61), EUS/EBUS (n=73)	0.64 (0.27)	
			Patients with NSCLC, 2 months' follow up (Day 61), surgical staging (n=71)	0.65 (0.26)	
			Patients with NSCLC, 6 months' follow up (Day 183),	0.68 (0.30)	

			EUS/EBUS (n=73)		
			Patients with NSCLC, 6 months' follow up (Day 183), surgical staging (n=71)	0.67 (0.31)	
Swan, 2018 (100) US	Patients with early- (1–2) or late- (3–4) stage NSCLC (n=236)	Instrument: SG, MAUT-based index, and FACT-U§ Tariff: NA	Patients with early (Stage 1–2) NSCLC, SG, baseline	0.82 (0.16)	Conclusions: FACT-U shows early evidence of validity for informing economic analysis of lung cancer treatments. Limitations: • Minorities were limited in the study sample
			Patients with early (Stage 1–2) NSCLC, MAUT-based index, baseline	0.69 (0.21)	
			Patients with early (Stage 1–2) NSCLC, FACT-U, baseline	0.83 (0.14)	
			Patients with advanced (Stage 3–4) NSCLC, SG, baseline	0.82 (0.13)	
			Patients with advanced (Stage 3–4) NSCLC, MAUT-based index, baseline	0.60 (0.2)	
			Patients with advanced (Stage 3–4) NSCLC, FACT-U, baseline	0.78 (0.14)	
Tramontano, 2015 (101) US (supplemented by data reported in Blom et al	Patients with newly diagnosed lung cancer (Stage 1–4) (n=2,396)	Instrument: EQ-5D-3L and SF-6D Tariff: NR	Patients with lung cancer, all stages, EQ-5D-3L (n=2,396)	0.78 (0.18) [0.77, 0.79]	Conclusions: this study generated a catalogue of community-weighted utilities applicable to societal perspective cost-effectiveness analyses of lung cancer interventions and compared utilities based on the EQ-5D and SF-6D.
			Patients with lung cancer, all stages, SF-6D (n=2,344)	0.68 (0.14) [NR]	
			Patients with Stage 1–2 lung cancer,	0.80 (NR) [0.79, 0.81]	

[2020] (83))			EQ-5D-3L (n=982)		Limitations: • None reported
			Patients with Stage 3–4 lung cancer, EQ-5D-3L (n=1,277)	0.77 (NR) [0.76, 0.78]	
Trippoli, 2001 (102) Italy	Patients with a diagnosis of NSCLC (n=92)	Instrument: EQ-5D-3L Tariff: NR	Patients with NSCLC (all n=92)	0.58 (0.33)	Conclusions: the EQ-5D-3L measurements obtained from these patients will aid evaluation of the cost-utility ratio for NSCLC therapies. Limitations: • No detailed data about therapeutic interventions and staging were collected during the study • No disease-specific questionnaires (e.g. EORTC-QLQ-C30, FACT-L, or the LCSS) were employed
			Patients with NSCLC, male (n=85)	0.58 (0.34)	
			Patients with NSCLC, female (n=7)	0.67 (0.16)	
			Patients with NSCLC, treatment with surgery (n=26)	0.56 (0.27)	
			Patients with NSCLC, no treatment with surgery (n=65)	0.59 (0.35)	
			Patients with NSCLC, treatment with chemotherapy (n=79)	0.59 (0.32)	
			Patients with NSCLC, no treatment with chemotherapy (n=13)	0.57 (0.39)	
			Patients with NSCLC, treatment with radiotherapy (n=21)	0.53 (0.30)	
			Patients with NSCLC, no treatment with radiotherapy (n=70)	0.60 (0.34)	
			Patients with NSCLC, metastasis present (n=59)	0.53 (0.36)	

			Patients with NSCLC, metastasis absent (n=32)	0.68 (0.24)	
			Patients with NSCLC, age <65 years' old (n=46)	0.64 (0.31)	
			Patients with NSCLC, age >65 years' old (n=46)	0.54 (0.34)	
			Patients with NSCLC, time since diagnosis <12 months (n=67)	0.61 (0.34)	
			Patients with NSCLC, time since diagnosis >12 months (n=21)	0.50 (0.30)	
Vogel, 2019 (103) US	Patients with Stage 1–3 NSCLC receiving definitive chemo-radiation (n=43)	Instrument: EQ-5D (version not specified) Tariff: NR	Patients with Stage 1–3 NSCLC, pre radiation	0.86	Conclusions: CCI was associated with multiple HRQoL outcomes in patients with locally advanced (Stage 1–3) NSCLC treated with definitive chemoradiation. Limitations: • Relatively small sample size and highly-selected patient population • Confounding factors that may not have been adjusted for in analyses, including education level, income, and physical activity
			Patients with Stage 1–3 NSCLC, post-radiation	0.83	

Witlox, 2020 (104) Netherlands	Patients with Stage 3 NSCLC (n=174)	Instrument: EQ-5D-3L Tariff: Dutch tariff	Patients with Stage 3 NSCLC, prophylactic cranial irradiation arm, baseline	0.80	Conclusions: a statistically significant or clinically relevant impact of prophylactic cranial irradiation on HRQoL was not observed in this study in patients with Stage 3 NSCLC. Limitations: • Patients who developed symptomatic brain metastases may have dropped out of the analysis and thus HRQoL might be potentially overestimated overall • The NVALT-11/DLCRG-02 trial was not powered to detect a statistically significant difference between the study arms, as HRQoL was a secondary endpoint
			Patients with Stage 3 NSCLC, observation arm, baseline	0.79	
Wolff, 2018 (105) Netherlands	Patients with stage I NSCLC treated with either SBRT or surgery (N=302)	**Instrument:** EORTC-QLQ-C30 mapped to EQ-5D-3L (published algorithm by Longworth et al [2014] (106)) **Tariff:** UK tariff (assumed from reference to Dolan et al [1997] (86))	Patients with stage I NSCLC, treatment difference at baseline, SBRT versus surgery	0.071 [0.017, 0.128]	Conclusions: this study shows that there is no clinically meaningful difference in health utility between patients with surgically treated early-stage NSCLC and patients treated with SBRT. Limitations: • It was not possible to study the impact of treatment toxicities on health utility • Fourteen patients were censored at the start of adjuvant treatment or when a recurrence was detected
			Patients with stage I NSCLC, mean 1-year treatment difference, SBRT versus surgery	0.026 [-0.028, 0.080]	

Yang, 2014 (107) Taiwan	Patients with NSCLC and free from other malignancies during the period from January 2005 to December 2011 (N=518)	**Instrument:** EQ-5D-3L **Tariff:** Taiwanese tariff	Patients with stage I NSCLC, performance status 0–1, operable (N=275)	0.86 (0.17)	Conclusions: the utility gained from surgical operation for operable lung cancer is substantial, even after adjustment for lead-time bias. Limitations: • QoL and survival of patients might be affected by major chronic diseases • QoL measurements from some individuals were performed repeatedly • The estimation of QALE would have been more accurate if the QoL of every patient in the cohort repeatedly during the follow-up period
			Patients with stage II NSCLC, performance status 0–1, operable (N=275)	0.83 (0.17)	
			Patients with stage III NSCLC, performance status 0–1, operable (N=275)	0.83 (0.17)	
			Patients with stage III NSCLC, performance status 0–1, inoperable (N=243)	0.73 (0.25)	
			Patients with stage I NSCLC, performance status 0–4, operable (N=281)	0.85 (0.17)	
			Patients with stage II NSCLC, performance status 0–4, operable (N=281)	0.83 (0.17)	
			Patients with stage III NSCLC, performance status 0–4, operable (N=281)	0.83 (0.16)	
			Patients with stage III NSCLC, performance status 0–4,	0.72 (0.25)	

			inoperable (N=250)		
			Patients with operable NSCLC, performance status 0–1 (N=275), male, age ≤54 years	0.86 (0.15)	
			Patients with operable NSCLC, performance status 0–1 (N=275), male, age 55–74 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0–1 (N=275), male, age ≥75 years	0.77 (0.19)	
			Patients with operable NSCLC, performance status 0–1 (N=275), female, age ≤54 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0–1 (N=275), female, age 55–74 years	0.82 (0.17)	
			Patients with operable NSCLC, performance status 0–1 (N=275), female, age ≥75 years	0.72 (0.23)	
			Patients with operable NSCLC, performance status 0-4	0.86 (0.15)	

			(N=281), male, age ≤54 years		
			Patients with operable NSCLC, performance status 0–4 (N=281), male, age 55–74 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0–4 (N=281), male, age ≥75 years	0.77 (0.19)	
			Patients with operable NSCLC, performance status 0–4 (N=281), female, age ≤54 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0–4 (N=281), female, age 55–74 years	0.82 (0.17)	
			Patients with operable NSCLC, performance status 0–4 (N=281), female, age ≥75 years	0.72 (0.23)	
Yang, 2019 (108) Taiwan	Patients with lung cancer (any stage) visiting the author's hospital (N=1,715)	**Instrument:** EQ-5D-3L **Tariff:** Taiwanese tariff	Patients with stage I–IIIA squamous NSCLC, age <65 years (N=46)	0.88 (SE 0.02)	Conclusions: this 7-year real-world survey provided detailed EQ-5D estimates of health utility, which could be used for future cost-effectiveness analysis for treatments of lung cancer; compared with patients undergoing sec-
			Patients with stage I–IIIA non-squamous NSCLC, age <65 years (N=350)	0.90 (SE 0.01)	

			Patients with stage I–IIIA squamous NSCLC, age ≥65 years (N=68)	0.85 (SE 0.02)	ond-line chemotherapy, those receiving targeted therapy had higher utility values. Limitations: • Detailed AEs were not included in each measurement, which may have a considerable impact on QoL, in the mixed model analysis • Most participants were from outpatient departments, and thus the utility values were likely to be overestimated • QoL measurements were not performed in a predefined period
			Patients with stage I–IIIA non-squamous NSCLC, age ≥65 years (N=260)	0.86 (SE 0.01)	
			Patients with stage IIIB–IV squamous NSCLC, age <65 years (N=46)	0.84 (SE 0.03)	
			Patients with stage IIIB–IV non-squamous NSCLC, age <65 years (N=476)	0.85 (SE 0.01)	
			Patients with stage IIIB–IV squamous NSCLC, age ≥65 years (N=66)	0.73 (SE 0.03)	
			Patients with stage IIIB–IV non-squamous NSCLC, age ≥65 years (N=321)	0.81 (SE 0.01)	
June 2022 update (N=2)					
Mahal, 2021 (109) **US**	**Patients who were treated for a primary stage I–III tumour (prostate, breast, lung) with valid dates of diagnosis and death and who did not have a second cancer diagnosed before their follow-up survey (N=67 [patients with**	**Instrument: SF-6D** **Tariff: NA (study used an algorithm to calculate utilities from SF-12**	**Early era lung cancer patients (treated 1998–2003); baseline (N=67)**	**0.72 (0.14)**	**Conclusions: Older patients treated for prostate, breast, or lung cancer in the 'Late Era' reported similar outcomes of changes in HRQoL compared with 'Early Era' patients. That is, as advancements in cancer care have become more successful (and potentially more intense), the QoL of patients undergoing contemporary**
			Early era lung cancer patients (treated 1998–2003); change from baseline at follow-up (N=62)	–0.07 (0.14)	
			Late era lung cancer patients (treated 2006–	0.74 (0.14)	

	lung cancer only])	**and SF-36)**	2011); baseline (N=67)		**therapy has not been impacted. This finding perhaps highlights significant improvements in supportive care services.** **Limitations:** • **The study analysed only patients who were enrolled in the Medicare Advantage plan and thus part of the Medicare Health Outcomes Survey. It is possible that Medicare Advantage enrolees are healthier than fee-for-service beneficiaries, though others have shown equivalence** • **The researchers were unable to assess the specific treatments received by patients. The SEER-MHOS combined database does not include claims; therefore, only the SEER treatment variables were available, which are general** • **Due to limitations of the dataset, it was not possible to assess HRQoL/utilities more than 2 years after cancer treatment, and it is possible that trends in health utility changes after 2 years differ from those within 2 years** • **The study was limited by the small sample size of patients who had completed a survey both pre-cancer diagnosis and post cancer treatment**
			Late era lung cancer patients (treated 2006–2011); change from baseline at follow-up (N=62)	–0.07 (0.12)	

					• **A calliper was not used in the propensity score matching algorithm** • **There is potential for residual confounding. Many standardised mean differences presented in this study were large due to the sample size. Regression adjustment to mitigate residual imbalance was not conducted**
Sigel, 2022 (110) US	Patients with stage I NSCLC with major comorbid illness (N=15,537)	**Instrument:** SF-6D **Tariff:** NA (study used an algorithm to calculate utilities from SF-12 and SF-36)	Mean utility from SEER-MHOS data for stage I NSCLC patients (N=1,292)	0.77	Conclusions: Simulation modelling approaches were used to estimate the QALE gains associated with different treatment approaches for stage I NSCLC patients according to age, sex, tumour size and histologic subtype, and comorbidity profile. It was found that more aggressive surgical approaches were associated with the greatest projected life year gains in most scenarios, although older patients and those with greater comorbid burden often benefited equally from less aggressive strategies. These results may be useful for guiding future comparative research. Limitations: • Limitations in the available randomised data for comparison of the treatment modalities are included in this analysis. Direct experimental comparison data for segmentectomy, wedge
			Annual utility decline for participants at risk of stage I lung cancer (N=NR)	0.017	

					resection, and SBRT are even more limited • The ascertainment of comorbidity status from the cancer cohorts relied on diagnostic codes, which may have limited accuracy and could not be used to assess disease severity • The model does not reflect changes in lung cancer survival associated with sociodemographic or geographic regional differences, although US population-based data was used for much of the parameterisation • Accepted clinically meaningful differences in survival have not been well established for stage I lung cancer treatments
July 2023 update (N=1)					
Jin, 2023 (111) **China**	**Adult patients with pulmonary tumours identified as being candidates for minimally invasive lobectomy (resectable NSCLC) (N=320)**	**Instrument:** **EQ-5D-3L** **Tariff: Unclear**	**Patients with resected NSCLC, mean difference at 4 weeks**	**0.002 [-0.008, 0.012]**	**Conclusions: Both surgical modalities showed satisfactory and comparable HRQoL and postoperative pain up to 48 weeks after surgery, despite some minor statistical differences at Week 4.** **Limitations:** • **The single centre nature of the clinical trial makes it less persuasive than a multicentre study** • **No blinding to treatment assignment was incorporated into the trial, the research findings may be influ-**
			Patients with resected NSCLC, mean difference at 24 weeks	0.003 [-0.004, 0.010]	
			Patients with resected NSCLC, mean difference at 48 weeks	0.004 [-0.002, 0.011]	

					enced by the subjective feelings of the patients • **Some patients were lost to follow up at each time point, contributing to approximately 90% survey rate at Week 48**
September 2023 update (N=1)					
Patel, 2023 (112) **Multinational**	**Patients age >18 years with clinical stage I, II, or IIIa NSCLC and candidate for minimally invasive pulmonary lobectomy, as determined by the operating surgeon (N=164)**	**Instrument:** **EQ-5D-5L** **Tariff: Canadian tariff**	**Patients undergoing VATS for stage I–IIIa NSCLC; baseline (N=77)**	**0.82 (0.18)**	**Conclusions: Early results of the RAVAL trial suggest that RPL-4 is a cost-effective intervention which is associated with comparable patient-reported HU scores when compared with VATS-Lobectomy.** **Limitations:** • **HU and the resulting ICER, were measured at a short time horizon of 12-months. Longer term follow-up, and future data on mortality may influence these results in either direction**
			Patients undergoing RTS for stage I–IIIa NSCLC; baseline (N=80)	0.84 (0.10)	
			Patients undergoing VATS for stage I–IIIa NSCLC; 3-weeks post-surgery (N=76)	0.74 (0.19)	
			Patients undergoing RTS for stage I–IIIa NSCLC; 3-weeks post-surgery (N=79)	0.78 (0.17)	
			Patients undergoing VATS for stage I–IIIa NSCLC; 7-weeks post-surgery (N=71)	0.78 (0.18)	
			Patients undergoing RTS for stage I–IIIa NSCLC; 7-weeks post-surgery (N=75)	0.84 (0.14)	
			Patients undergoing VATS for stage I–IIIa NSCLC; 12-weeks post-surgery (N=73)	0.80 (0.19)	

		Patients undergoing RTS for stage I–IIIa NSCLC; 12-weeks post-surgery (N=75)	0.85 (0.10)	
		Patients undergoing VATS for stage I–IIIa NSCLC; 6-months post-surgery (N=8)	0.71 (0.20)	
		Patients undergoing RTS for stage I–IIIa NSCLC; 6-months post-surgery (N=9)	0.85 (0.12)	
		Patients undergoing VATS for stage I–IIIa NSCLC; 12-months post-surgery (N=77)	0.79 (0.22)	
		Patients undergoing RTS for stage I–IIIa NSCLC; 12-months post-surgery (N=72)	0.84 (0.11)	

Abbreviations: 15D, 15 Dimensions; AE, adverse event; AQoL, Assessment of Quality of Life; CCI, Charlson Comorbidity Index; CI, confidence interval; CGA, comprehensive geriatric assessment; EBUS, endobronchial ultrasound; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D (3L/5L), European Quality of Life-5 Dimensions (3 Level/5 Level version); EUS, endoscopic ultrasound; FACT-L, Functional Assessment of Cancer Therapy – Lung; FACT-U, Functional Assessment of Cancer Therapy - Lung Utility Index; HRQoL, health-related quality of life; HSUV, health state utility value; HU, health utility; IQR, interquartile range; LCSS, Lung Cancer Symptom Scale; LVDM, Limited Variable Dependent Mixture; MAUT, multi-attribute utility theory; NA, not applicable; NR, not reported; NSCLC, non-small cell lung cancer; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year; QoL, quality of life; RTS, robotic-assisted thoracoscopic surgery; SBRT, stereotactic body radiation therapy; SD, standard deviation; SE, standard error; SF-6D, Short Form-6 Dimensions; SG, standard gamble; TTO, time trade off; VATS, video-assisted thoracoscopic surgery; VAS, visual analogue scale.
† Individuals contributing to pooled value for all stages: Stage I-II: N=1,510; Stage III-IV: N=4,703.
‡ Median [IQR].
§ The FACT-U was constructed with two methods: (i) MAUT, where a VAS–based index was transformed to SG; and (ii) an unweighted index, where items were summed, normalised to a 0 to 1.0 scale, and the result transformed to a scale length equivalent to the VAS or SG MAUT-based model on a Dead to Full Health scale.
GREEN: health states relevant to patients with stage II/III(A) disease; ORANGE: uncertainty in the method used to derive utilities (instrument and/or social tariff unclear); RED: intervention-specific health state where surgery +/- adjuvant chemotherapy is not used (e.g., relates to radiotherapy use); BLUE: both GREEN and RED criteria apply.

In summary, the current SLR provides a comprehensive repository of the currently available published utility and HRQoL data relevant to patients with early-stage NSCLC. The evidence identified suggests that early NSCLC has a substantial impact on HRQoL that is influenced by numerous factors, including geographical location, disease stage, and treatment approach. Further studies using prospective study designs and larger patient cohorts are required to confirm these findings. The requirements of HTA body reference cases should also be taken into consideration when designing future trials, in order to generate robust HSUVs that would be considered appropriate for informing reimbursement decisions. In any case, the choice of utility inputs for future economic evaluations

should be fully justified, and estimates should be thoroughly tested through comprehensive sensitivity analysis.

I.1.2 Quality assessment and generalizability of estimates

During data extraction, the relevance of utilities and the quality of the studies generated were assessed and recorded, and the quality of any mapping algorithms examined. This process was recommended by NICE, in technical support documents (TSDs) 8-10 and enables justification of the use/non-use of different utility values or mapping algorithms in an economic model. In particular, the following issues were addressed:

- Whether response rates, loss to follow up, or missing data level were likely to threaten the validity of the utility estimate
- Whether the selection criteria yielded a population similar to that being modelled
- Whether utility incorporated decrement for quality-of-life loss from AEs
- Whether the utility met the NICE reference case (i.e. health states should be described by the patient and valued according to societal preferences using UK/English societal preferences) (113)

I.1.3 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted.]

Appendix J. Literature searches to the health economic model

J.1 External literature for input to the health economic model

Structured searches were run in the Medical Literature Analysis and Retrieval System (MEDLINE®), Excerpta Medica dataBASE (Embase®), Cochrane databases, and MEDLINE In-process via PubMed to identify literature published from 2008 to 14th September 2023 (i.e., the last 15 years). These were supplemented by grey literature searches and back-referencing of relevant review articles, and searches for relevant congress abstracts from the last 3 years (2021-September 2023). Additionally, trial registry searches were conducted to retrieve ongoing and planned trials.

J.1.1 Systematic search for Clinical Evidence on Interventions used for Locally Advanced or Metastatic NSCLC in a Population with ALK Positive Disease

The objective was to conduct a systematic literature review (SLR) of clinical evidence (efficacy and safety) associated with interventions in the treatment of locally advanced or metastatic anaplastic lymphoma kinase positive (ALK+) non-small-cell lung cancer (NSCLC).

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Via Embase.com	2008 to September 2023 (the last 15 years)	15 th September 2023
Medline	Via Embase.com	2008 to September 2023 (the last 15 years)	15 th September 2023
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Libary	2008 to September 2023 (the last 15 years)	15 th September 2023
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Libary	2008 to September 2023 (the last 15 years)	15 th September 2023

Supplementary searches

In addition to the structured search, the following supplementary searches were also conducted to identify relevant literature. The keywords used for conducting supplementary searches were as follows:

NSCLC terms: “non small cell lung cancer”, “bronchial non small cell cancer”, “bronchial non small cell carcinoma”, “lung non small cell cancer”, “lung non small cell carcinoma”, “non small cell bronchial cancer”, “non small cell lung carcinoma”, “non small cell pulmonary cancer”, “non small cell pulmonary carcinoma”, “pulmonary non small cell cancer”, “pulmonary non small cell carcinoma”, “nsclc”, “lung adenocarcinoma”, “squamous cell lung carcinoma”

Disease stage search terms: “anaplastic lymphoma kinase”, “alk+”, “alk-positive”, “anaplastic lymphoma kinase inhibitor”, “alk inhibitor”

Study design terms: “clinical trial”, “randomization”, “controlled study”, “comparative study”, “single blind procedure”, “double blind procedure”, “crossover procedure”, “placebo”, “controlled clinical trial”, “randomised controlled trial”, “randomized controlled trial”, “randomisation”, “randomization”, “randomi”, “rct”, “random allocation”, “randomly allocated”, “allocated randomly”, “placebo”, “prospective study”

Conference searches
To retrieve the latest data for completed and ongoing trials, hand-searching of the following relevant conference proceedings/databases in the last 3 years (2021–2023) was conducted:

- American Society of Clinical Oncology (ASCO) Annual Meeting
- European Society for Medical Oncology (ESMO) Congress
- American Society of Hematology (ASH)
- American Association for Cancer Research (AACR)
- World Conference on Lung Cancer (WCLC)
- ESMO Immuno-Oncology Congress
- European Lung Cancer Congress (ELCC)

The conference search was conducted between August and September 2023.
Trial registry searches
To retrieve relevant information from ongoing and planned clinical trials, keyword-based searches in the following trial registries were conducted between the 26th and 27th of October 2023:

- Clinicaltrials.gov (www.clinicaltrials.gov)
- EU Clinical Trials Register (EU-CTR, www.clinicaltrialsregister.eu)
- International Clinical Trials Registry Platform Search Portal (ICTRP Search Portal, WHO search portal: http://apps.who.int/trialsearch/).

J.1.2 Example: Targeted literature search for [estimates]

In addition to the structured search, the following supplementary searches were also conducted to identify relevant literature. The keywords used for conducting supplementary searches were as follows.

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
American Society of Clinical Oncology (ASCO)		Hand searched	Between august and september 2023
European Society for Medical Oncology (ESMO)		Hand searched	Between august and september 2023
American Society of Hematology		Hand searched	Between august and september 2023
American Association for Cancer Research		Hand searched	Between august and september 2023
World Conference on Lung Cancer		Hand searched	Between august and september 2023
ESMO Immuno-Oncology		Hand searched	Between august and september 2023
European Lung Cancer Congress		Hand searched	Between august and september 2023
Clinicaltrials.gov	www.clinicaltrials.gov	Hand searched	26th and 27th of October 2023:
EU Clinical Trials Register	ww.clinicaltrialsregister.eu	Hand searched	26th and 27th of October 2023:
International Clinical Trials Registry Platform Search Portal	ICTRP Search Portal	Hand searched	26th and 27th of October 2023:
WHO search portal:	http://apps.who.int/trialsearch/	Hand searched	26th and 27th of October 2023:

In the manual search the following searches has been used:
NSCLC terms: “non small cell lung cancer”, “bronchial non small cell cancer”, “bronchial non small cell carcinoma”, “lung non small cell cancer”, “lung non small cell carcinoma”, “non small cell bronchial cancer”, “non small cell lung carcinoma”, “non small cell pulmonary cancer”, “non small cell pulmonary carcinoma”, “pulmonary non small cell cancer”,

"pulmonary non small cell carcinoma", "nsclc", "lung adenocarcinoma", "squamous cell lung carcinoma"

Disease stage search terms: "anaplastic lymphoma kinase", "alk+", "alk-positive", "anaplastic lymphoma kinase inhibitor", "alk inhibitor"

Study design terms: "clinical trial", "randomization", "controlled study", "comparative study", "single blind procedure", "double blind procedure", "crossover procedure", "placebo", "controlled clinical trial", "randomised controlled trial", "randomized controlled trial", "randomisation", "randomization", "randomi", "rct", "random allocation", "randomly allocated", "allocated randomly", "placebo", "prospective study"

Eligibility criteria

To be included in this review, publications had to meet the predefined eligibility (inclusion/exclusion) criteria based on the PICOS framework and provide relevant data to address the research questions of interest, as shown below

Table 68: Inclusion and exclusion criteria

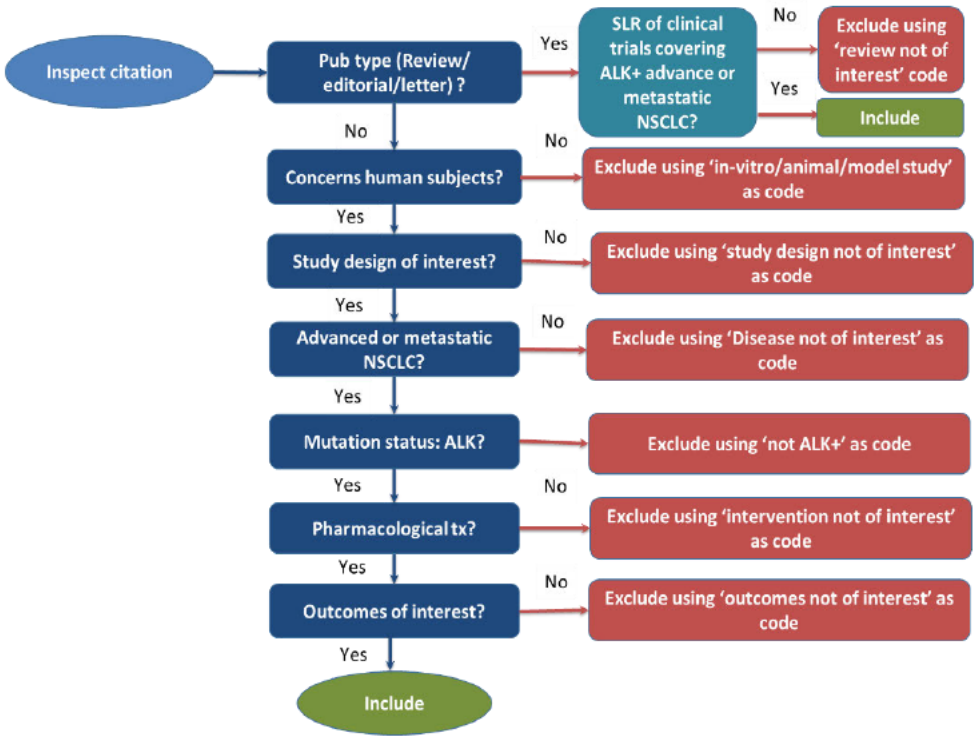
Description	Inclusion criteria	Exclusion criteria
Population	• Indication: NSCLC • Stage: Locally advanced or metastatic (Stage IIIB or IV) • Mutation: ALK+ • Line of treatment: Any	Publications reporting for following patient populations were excluded: • Children • Healthy volunteers • Cancer other than NSCLC • Stage I, Stage II and IIIa NSCLC • Mutation status other than ALK+
Intervention	• Any pharmacological intervention	• Vaccines • Herbal intervention • Non-cancerous therapy (supplements, metformin etc.)
Comparator	• Any pharmacological intervention • Placebo • Best supportive care	• Adjuvant therapy

Outcome	• Efficacy outcomes
	  ○ Progression-free survival
	  ○ Overall survival
	  ○ Overall response rate
	  ▪ Complete response
	  ▪ Partial response
	  ▪ Stable disease
	• Treatment exposure
	• Safety outcomes (Non-specific)
	  ○ Overall AEs
	  ○ Overall SAEs
	  ○ Overall TRAEs
	  ○ Safety outcomes (specific)
		• Genetic outcomes
		• Pharmacokinetic outcomes

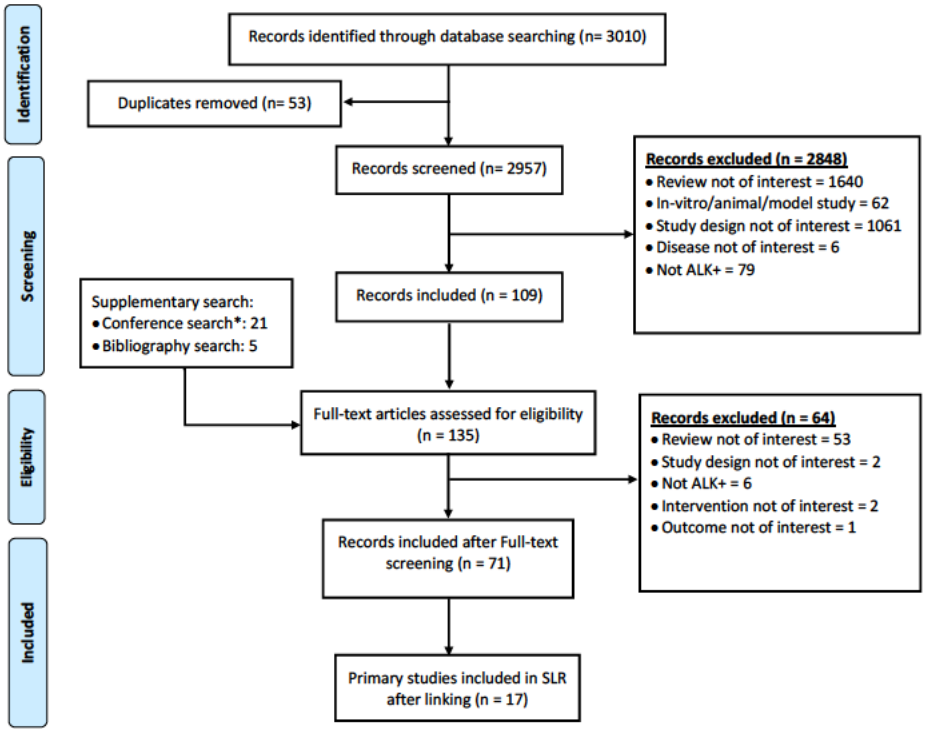
Description	Inclusion criteria	Exclusion criteria
	○ Tolerability/discontinuation • HRQoL/PROs (any scale)	
Study design	• RCTs	• Non-RCTs • Non-comparative clinical trials (single-arm trials) • Observational studies (prospective/retrospective cohort studies, cross-sectional studies) • Case reports and case series
Publication/ study type	• Primary studies (conducted in humans) • Systematic reviews published from 2018 (for citation-chasing only)	The following types of publications were excluded: • Narrative publications • Non-systematic reviews • Editorials • Letters • Expert opinion The following study types were excluded: • Animal studies • In vitro/ex vivo studies • Gene expression/protein expression studies
Publication timeframe	2008 onwards (conference proceedings from 2021 to date)	Publications prior to 2008
Language	Only English language articles	Non-English articles

AE=Adverse event; ALK+=Anaplastic lymphoma kinase positive; HRQoL=Health-related quality of life; NSCLC=Non-small cell lung cancer; PRO=Patient-reported outcome; RCT=Randomised controlled trial; SAE=Serious adverse event; SLR=Systematic literature review; TRAE=Treatment-related adverse event.

Implementation and reporting followed the approach recommended by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Studies were selected in two steps. Firstly, the title and the abstract of each record identified during the structured and supplementary searches were assessed for relevance as per the screening flowchart below. Secondly, full-text versions of the selected citations were examined in detail to select the final list of studies to be included. During both steps, screening was conducted by two independent reviewers, and any discrepancies were resolved by a third reviewer.



Following this approach gives 17 studies included in the SLR. The exclusion is outlined in the PRISMA diagram below.



The included studies in the SLR are presented below.

Table 69: Overview of included studies

Study identifier	NSCLC stage	Sample size	Study phase	Data collection period	Follow-up duration (median), mos	Study country	Intervention	Comparator
All/any treatment-naïve (n=6)								
PROFILE 1014	IIIB or IV	343	III	2011-2013	~46.0	Multi-national (27 countries)	CRZ	CT (PEM + [CS/CB])
ASCEND-4	IIIB or IV	376	III	2013-2015	19.7	Multi-national (28 countries)	CER	CT (PEM + [CS/CB])
ALESIA	IIIB or IV	187	III	2016-2017	61: ALC; 51.0: CRZ	Multi-national (China, South Korea, and Thailand)	ALC	CRZ
ALEX	IIIB or IV	303	III	2014-2016	48.2: ALC; 23.3: CRZ	Multi-national (29 countries)	ALC	CRZ
CROWN	IIIB or IV	296	III	2017-2019	36.7: LOR; 29.3: CRZ	Multi-national (23 countries)	LOR	CRZ
PROFILE 1029	IIIB or IV	207	III	2012-2014	22.5: CRZ; 21.6: CT	Multi-national (China, Hong Kong, Malaysia, the Republic of China, and Thailand)	CRZ	CT (PEM + [CS/CB])
All ALKi naïve ± CT (n=6)								
ALTA-1L	IIIB or IV	275	III	2016-2017	40.4: BRG; 15.2: CRZ	Multi-national (20 countries)	BRG	CRZ
Li 2021	IIIB or IV	120	Not specified	2017-2018	NR	China	ALC	CRZ
Yang 2023	IIIB or IV	264	III	2019-2020	28.48: ENV; 28.55: CRZ	China	ENV	CRZ
eXalt3	IIIB or IV	290	III	2016-2018	23.8: ENS; 20.2: CRZ	Multi-national (21 countries)	ENS	CRZ
J-ALEX	IIIB or IV	207	III	2013-2015	12.0: ALC; 12.2: CRZ	Japan	ALC	CRZ
PROFILE 1007	IIIB or IV	347	III	2010-2012	12.2: CRZ; 12.1 CT	Multi-national (21 countries)	CRZ	CT (PEM/DTX)
All ALKi pretreated ± CT (n=4)								

Study identifier	NSCLC stage	Sample size	Study phase	Data collection period	Follow-up duration (median), mos	Study country	Intervention	Comparator
ALUR	IIIB or IV	107	III	NR	NR	Multi-national (13 countries)	ALC	CT (PEM/DTX)
AS-CEND-5	IIIB or IV	231	III	2013-2015	16.5	Multi-national (20 countries)	CER	CT (PEM/DTX)
ALTA-3	IIIB or IV	248	III	2019-2021	15.9: BRG; 16.9: ALC	Multi-national (17 countries)	BRG	ALC
ALTA	IIIB or IV	222	II	2014-2015	19.6: BRG 90 mg (QD); 28.3: BRG 180 mg (QD)	Multi-national (18 countries)	BRG (90 mg, QD)	BRG (180 mg, QD)
Treatment (any) naïve + pretreated (any) [n=1]								
AS-CEND-8	IIIB or IV	306	I	2015-2017	19.6: all randomised and 14.3: treatment-naive patients	Multi-national (18 countries)	CER (450 mg, fed)	CER (600 mg, fed); CER (750 mg, fasted)

Some of the studies have multiple publications. An overview of studies and articles are presented below

Table 70: List of included studies (categorised according to prior treatment)

S. No.	Study identifier (Author year)	NCT ID	Linked publication(s) or citations	Type of publication
All/any treatment-naïve				
1	**PROFILE 1014**	NCT01154140	Solomon 2016, Solomon 2018	Journal article
2	**ASCEND-4**	NCT01828099		Journal article
3	**ALESIA**	NCT02838420	Zhou 2018, Zhou 2022	Journal article
4	**ALEX**	NCT02075840	Mok 2020, Perol 2019, Gadgeel 2018, Mok 2020, Camidge 2019	Journal article
5	**CROWN**	NCT03052608	Mazieres 2022, Solomon 2022, Soo 2023, Mazieres 2021, Solomon 2022, Bearz 2022, Solomon 2022, Zhou 2021, Bearz 2022, Qing 2022, Bauer 2023, Solomon 2021, Liu 2022, Shaw	Journal article

S. No.	Study identifier (Author year)	NCT ID	Linked publication(s) or citations	Type of publication
			2020, Bearz 2023	
6	**PROFILE 1029**	NCT01639001		Journal article
All ALKi naïve ± CT				
7	**ALTA-1L**	NCT02737501	Camidge 2021, Popat 2016, Campelo 2021, Ahn 2022, Califano 2019, Camidge 2020, Camidge 2022, Popat 2021, Garcia 2022, Tiseo 2022	Journal article
8	**Li 2021**			Journal article
9	**Yang 2023**	NCT04009317	Zhang 2022	Journal article
10	**eXalt3**	NCT02767804	Selvaggi 2021	Journal article
11	**J-ALEX**	JapicCTI-132316; JO28929	Hotta 2022, Nakagawa 2020, Nishio 2018; Yoshioka 2021	Journal article
12	**PROFILE 1007**	NCT00932893	Nishio 2018, Blackhall 2014, Yamamoto 2013, Nokihara 2013	Journal article
All ALKi pretreated ± CT				
13	**ALUR**	NCT02604342		Journal article
14	**ASCEND-5**	NCT01828112	Dcaglaotti 2016, Kiura 2018	Journal article
15	**ALTA-3**	NCT03596866	Yang 2022	Journal article
16	**ALTA**	NCT02094573	Huber 2020, Lenderkin 2019, Kawata 2019, Gettinger 2021	Journal article
Treatment (any) naïve + pretreated (any)				
17	**ASCEND-8**	NCT02299505	Cho 2023, Cho 2019, Cho 2021	Journal article

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